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Asthma severity and susceptibility to air pollution

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Asthma severity and susceptibility to air pollution. T.J.N. Hiltermann, J. Stolk, S.C. van der Zee, B. Brunekreef, C.R. de Bruijne, P.H. Fischer, C.B. Ameling, P.J. Sterk, P.S. Hiemstra, L. van Bree. ©ERS Journals Ltd 1998.

ABSTRACT: Exacerbations of asthma have been associated with exposure to ozone or particles with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10}). We postulated in this study that the association of summertime air pollution (*i.e.* ozone and PM_{10}) with acute respiratory symptoms, medication use and peak expiratory flow differs among patients grouped according to asthma severity.

During the summer of 1995, effects of ambient air pollution on these parameters were studied in a panel of 60 nonsmoking patients with intermittent to severe persistent asthma. These patients were recruited from our Pulmonary Out-patient Clinic. Subgroup analysis was performed on the degree of hyperresponsiveness and lung steroid use before the start of the study, as indictors for the severity of asthma. Associations of the parameters studied with ozone, PM_{10}, nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and black smoke were evaluated using time series analysis.

Several episodes with increased summertime air pollution occurred during the 96 day study period. Eight hour average ozone concentrations exceeded the World Health Organization (WHO) Air Quality Guidelines (120 µg·m^{-3}) on 16 occasions. Daily mean levels of PM_{10} were moderately elevated (range 16–98 µg·m^{-3}). Levels of the other measured pollutants were low. There was a consistent, positive association of the prevalence of shortness of breath (maximal relative risk (RR_{max}) 1.18) with ozone, PM_{10}, black smoke and NO_2. In addition, bronchodilator use was associated with both ozone and PM_{10} levels (RR_{max} 1.16). Stratification by airway hyperresponsiveness and steroid use did not affect the magnitude of the observed associations. No associations with peak expiratory flow measurements were found.

We conclude that the severity of asthma is not an indicator for the sensitivity to air pollution.

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Epidemiological studies have shown associations between ambient air pollution and deterioration of respiratory health. In summer the most frequently reported association is the one between respiratory disease and ambient ozone levels [1, 2], but associations have also been found with other pollutants *e.g.* aerosol sulphates [3] and particles with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10}) [4]. Increased incidences of asthma attacks and reduced lung function have been noted in epidemiological studies during episodes with relatively high levels of air pollutants [2, 5–7]. Stronger associations between air pollution and hospital admissions have been reported for patients with asthma than for those with chronic obstructive pulmonary disease (COPD) [2]. Furthermore, controlled exposure studies have demonstrated that asthmatic subjects exposed to air pollutants, such as ozone, nitrogen dioxide (NO_2) and sulphur dioxide (SO_2), develop increases in airway inflammation or symptoms, and decreases in lung function [8–10]. Taken together, epidemiological and experimental data suggest that air pollution may have profound health effects in populations with pre-existing respiratory disease.

In our Pulmonary Out-patient Clinic, we observed that some asthmatics reported relatively more symptoms on hot summer days (*i.e.* days when ozone levels were relatively high), whereas other patients with similar severity of disease did not. Controlled experimental studies suggest that this clinical observation may be relevant: 1) the effect of ozone exposure on lung function varies markedly between subjects, but is highly reproducible within (healthy) subjects [11]; 2) subjects with asthma are more sensitive to bronchoconstrictor effects of SO_2 than those without asthma [12]. These studies indicate that an individual pattern of airway responsiveness to different air pollutants may exist, leading to a heterogeneous clinical response in the population. The individual susceptibility to air pollution may in part be determined by the severity of asthma. To date there is no "gold standard" parameter that ultimately reflects asthma severity [13]. Both steroid use [14, 15] and airway hyperresponsiveness [15–17] have been put forward as clinical indices that may reflect the degree of asthma severity within a population of asthmatics.

In this study we hypothesized that, in patients with intermittent to severe persistent asthma, the severity of asthma (as indicated both by the amount of steroid use and airway hyperresponsiveness) is the major predictor of symptoms of asthma on smog days during summer.

Methods

Subjects

Two hundred and seventy asthmatic patients from the Pulmonary Out-patient Clinic of the Leiden University Medical Centre were asked to complete a questionnaire in the late spring of 1995. Through this form we were informed whether they had an increase in symptoms of asthma during the summer of 1994 (26 smog days, *i.e.* 1 h maximum ozone levels Š180 μg·m^{-3}), relative to previous summers (1993 (10 smog days) and 1992 (20 smog days)). From the 149 responding subjects, 62 patients, representative of an asthma population with intermittent to severe persistent asthma (Global Initiative for Asthma (GINA) criteria), participated in a prospective study [13]. We recruited our nonsmoking subjects on the basis of a clinical history of asthma and airway hyperresponsiveness (provocative concentration of methacholine bromide causing a 20% fall in forced expiratory volume in one second (PC_{20}) <9.6 mg·mL^{-1}). Two subjects were excluded from the analysis, because they dropped out of the study within the first 14 days. All other subjects completed the study (for subject characteristics see table 1). The study was approved by the Medical Ethics Board of Leiden University Medical Centre, and informed consent was obtained from each subject.

Study design

Subjects were monitored for 3 months (July 3 to October 6 1995). During this period they were asked to use a diary to record morning and evening peak flow, respiratory symptoms, medication use and exposure to environmental tobacco smoke. To stimulate daily recording of symptoms, subjects visited the Pulmonary Out-patient Clinic every 2 weeks. On each occasion they handed in the completed form of the diary, and received a new diary for the next 2 weeks. During this visit a nasal lavage was also performed to analyse associations between inflammatory markers and environmental air pollution. These data have been presented in a separate report [18]. Before the start of the study all recruited nonsmoking subjects were screened for their atopic status and hyperresponsiveness to methacholine.

Table 1. – Baseline characteristics of the study population

	Total group
Subjects n	60
Sex M/F	33/27
Age yrs*	31 (18–55)
Passive smoking %$^{+}$	10.0 (6)
Atopic/nonatopic n	52/8
House dust mite % atopic^{+}	90 (47)
Grass pollen % atopic^{+}	69 (36)
Mugwort pollen % atopic^{+}	29 (15)
PC_{20} mg·mL$^{-1\dagger}$	0.60 (0.01–6.55)
FEV_1 % pred*	89.7 (43.5–127.6)
FVC % pred*	96.0 (38.3–133.5)
PEF % pred*	104.9 (52.1–140.0)
FEV_1/FVC*	0.80 (0.60–0.99)
Bronchodilator use %$^{+}$	85.0 (51)
Inhaled lung steroid use %$^{+}$	75.0 (45)

*: range in parenthesis; $^{+}$: percentage of group in parenthesis; †: geometric mean, and range in parenthesis. % atopic: percentage sensitized from all atopic subjects; % pred: group mean value of individual percentage predicted lung function parameter; FEV_1: forced expiratory volume in one second; PC_{20}: provocative concentration of methacholine causing a 20% decrease in FEV_1; FVC: forced vital capacity; PEF: peak expiratory flow; M: male; F: female.

Symptoms

Subjects were instructed on how to use a peak flow meter and how to fill in the diary card. The diary was based on that used in previous epidemiological studies in the Netherlands [19]. Just before night rest subjects indicated the presence and severity of selected symptoms. The subjective symptoms that were monitored included: shortness of breath, waking with breathing problems, pain on deep inspiration, asthma attacks, wheezing, cough and/or phlegm, runny or stuffed nose, fever, eye irritation, throat irritation and medication use. In addition, the patients recorded whether someone had smoked in their presence. The symptoms were rated on a symptom severity scale as follows: 0=not present; 1=minimal; and 2=moderate to severe. Medication use was subdivided into: inhaled (lung) steroid use; nasal steroid use; short acting bronchodilators; and other medication use.

Pulmonary function measurements and bronchoprovocation testing

Spirometry was performed on a dry rolling-seal spirometer (Morgan Spiroflow, Rainham, UK), according to recent standardization recommendations [20]. Inhalation challenge tests were performed by using doubling doses of methacholine bromide (Janssen Pharmaceutica, Beerse, Belgium) inhaled by the standardized 2 min tidal breathing method [21]. The response was measured by forced expiratory volume in one second (FEV_1). The tests were discontinued if FEV_1 decreased by more than 20% from baseline or when a concentration of 9.6 mg·mL^{-1} methacholine bromide (~40 mM) had been administered. Following the last methacholine dose 400 μg salbutamol was inhaled per metered dose-inhaler.

Peak flow

Peak flow (Personal Best, Healthscan Inc., Cedar Grove, NJ, USA) was measured before medication use, twice a day, when getting up in the morning and before going to bed in the evening. Every test consisted of three manoeuvres, and subjects were instructed to note each of the three readings in their diary. The largest of three readings was used in the analysis [20].

Atopic status

The atopic status of all participants was determined by measuring specific immunoglobulin (Ig)E levels to a panel of common inhalant allergens (Phadiatop; Kabi Pharmacia Diagnostics AB, Uppsala, Sweden) in the patient serum. If

this measurement indicated that a subject was atopic, the specific (IgE) response to house-dust mite (*Dermatophagoides pteronyssinus*), grass pollen (Poaceae), mugwort (*Artemisia vulgaris*) and relevant individual inhalant allergens was determined (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden).

Air pollution data

Air pollution and meteorological data were taken from the Dutch National Air Quality Monitoring Network operated by the National Institute of Public Health and the Environment (RIVM) in Bilthoven, the Netherlands, as described previously [19, 22]. Data were obtained from three stations (De Zilk, Zegveld and The Hague Centre). These stations were located in a geographical circle with a radius of 20 km, and all patients lived within this area. Since the correlation of the air pollutants between the stations was high (r≥0.88), only the pollutant levels of Zegveld were used in the analysis. Measured air pollutants were: ozone, PM_{10}, NO_2, SO_2 and black smoke. For ozone, the maximal 8 h moving average was used in the analysis of ozone, and the 24 h mean was used for all other air pollutants [8].

Analysis

The data were analysed for the whole study population and for two subgroups using the Statistical Analysis System (SAS) software (version 6.08; SAS Institute Inc., Cary, NC, USA). One subgroup was formed on the basis of PC_{20} prior to the study, and the other on the basis of steroid use before the start of the study. Medication and symptom data were first entered into the database as either present (symptom score 1 and 2) or absent (symptom score 0), and on the basis of these data the daily prevalence was calculated. Next, the association of these prevalence data with air pollution was analysed using a logistic regression model (SAS; Proc Model). The SAS/ETS %AR macro was used to specify a first-order autoregressive process for the residuals from the logistic model [22].

To identify potential trends and irregularities in the peak expiratory flow (PEF) data, the morning and evening values of each subject were plotted against the day of study. The individual daily morning to evening PEF change (ΔPEF) was analysed separately in a linear regression model with a first order autocorrelation (SAS; Proc Model, %AR macro). The associations between air pollutants and symptoms, medication use or ΔPEF were analysed using air pollution data of the day on which the symptoms were recorded (lag 0), the two previous days (lag 1 and lag 2) and the average air pollutant concentration of the previous week.

For symptoms and medication use the relative risks were calculated over "pollutant ranges", using the estimated regression slope and its standard error (SEM) [1, 19]. "Pollutant ranges" were defined as the difference between the mean and the maximal observed air pollutant concentration during the study period: for lag 0–lag 2 this was 100 $\mu g \cdot m^{-3}$ for ozone, 50 $\mu g \cdot m^{-3}$ for PM_{10}, 10 $\mu g \cdot m^{-3}$ for NO_2 and 10 $\mu g \cdot m^{-3}$ for black smoke (table 2). The "pollutant range" of the average pollutant concentration of the previous week was about half the range of that for the daily pollutant levels. Therefore, a "pollutant range" of 50 $\mu g \cdot m^{-3}$ for ozone, 25 $\mu g \cdot m^{-3}$ for PM_{10}, 5 $\mu g \cdot m^{-3}$ for NO_2, and 5 $\mu g \cdot m^{-3}$ for black smoke was used in the analysis for the weekly concentration. For the ΔPEF the same "pollutant ranges" were used as for symptoms and medication use, but because a linear regression model was used in the analysis, data were expressed as change in ΔPEF for each "pollutant range" ($L \cdot min^{-1}$), instead of as a relative risk.

Table 2. – Mean values and Pearson correlation coefficients between air pollutants and temperature

Variable	Mean range	O_3	PM_{10}	NO_2	SO_2	BS
O_3 $\mu g \cdot m^{-3}$*	80.1 (11.5–185.3)	1.00	-	-	-	-
PM_{10} $\mu g \cdot m^{-3}$	39.7 (16.4–97.9)	0.64	1.00	-	-	-
NO_2 $\mu g \cdot m^{-3}$	21.1 (6.8–42.2)	-0.13	0.18	1.00	-	-
SO_2 $\mu g \cdot m^{-3}$	4.3 (0.1–16.2)	0.30	0.37	0.49	1.00	-
BS $\mu g \cdot m^{-3}$	6.2 (0–22.0)	0.22	0.63	0.65	0.53	1.00
t_{max} °C†	22.6 (11.1–32.3)	0.82	0.70	-0.05	0.23	0.37

*: 8 h moving average; †: 1 h maximum temperature (t_{max}). All correlation coefficients significantly different from zero ($p < 0.05$), except that of nitrogen dioxide (NO_2) with ozone (O_3), PM_{10} and temperature (>0.07). PM_{10}: particles with a 50% cut-off aerodynamic diameter of 10 μm; SO_2: sulphur dioxide; BS: black smoke.

Confounders considered were trends in symptom prevalence and medication use, trends in mean morning and evening PEF, exposure to outdoor aeroallergens (data kindly provided by F.Th.M. Spieksma, Leiden, the Netherlands), exposure to environmental tobacco smoke, day of the week and daily maximum temperature (1 h average). We modelled trends in symptom prevalence by including a linear, quadratic and cubic term for day of study; for the PEF data we included a linear and quadratic term for day of study. Changes in relative risks were tested using a two-tailed unpaired t-test. When the data were not normally distributed, a Wilcoxon rank test was applied. A p-value of less than 0.05 was considered statistically significant.

Results

Subject characteristics

The population baseline characteristics are presented in table 1. All subjects had a history of asthma, and demonstrated airway hyperresponsiveness to methacholine (PC_{20} <9.6 $mg \cdot mL^{-1}$). The variation in the amount of medication use, PC_{20} and FEV_1 was large, indicative of a wide range in the severity of asthma among the subjects. Most subjects used bronchodilators on demand and inhaled steroids as maintenance medication.

Air pollution

The 8 h moving ozone maximum and the 24 h average concentration levels of PM_{10}, NO_2 and black smoke during the study period are shown in figure 1. In table 2 a summary of the correlations between ambient air pollution concentrations and temperature data is presented. Ozone was the most prominent air pollutant present during the study, with 16 days that exceeded the World Health Organization (WHO) guideline for the maximal 8 h moving average of 120 $\mu g \cdot m^{-3}$. PM_{10} was moderately

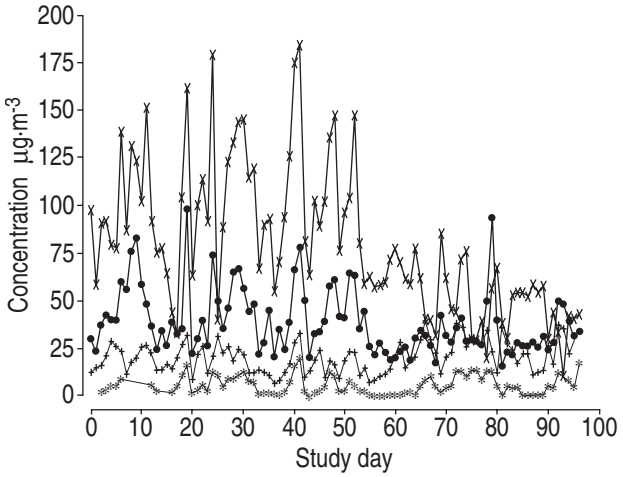

Fig. 1. – Daily ambient ozone (χ), particles with a 50% cut-off aerodynamic diameter of 10 µm (PM10) (●), NO_2 (+) and black smoke (*) during the study period. Data are presented as 8 h moving average for ozone. For PM10, NO_2, and black smoke data are presented as mean 24 h value (00:00–00:00 h). Study day 1=July 3 1995; study day 100= October 10 1995.

Table 3. – Characteristics of the population during the study period (July 3–October 7 1995)

Characteristic		
Shortness of breath %	43.4	(30–56)
Waking with breathing problems %	12.7	(4–27)
Pain on deep inspiration %	6.9	(0–16)
Cough and/or phlegm %	34.5	(27–47)
Nasal symptoms %	54.3	(34–76)
Passive smoking %	32.2	(10–44)
Bronchodilator use %	32.1	(23–42)
Inhaled lung steroid use %	65.5	(53–74)
ΔPEF L·min^{-1}	4.3	(-9.8–18.8)

Values are presented as mean, and range in parentheiss. ΔPEF: change in peak expiratory flow.

elevated (75th percentile: 47 µg·m^{-3}). The daily average concentrations of NO_2 and black smoke were all low (<43 and <23 µg·m^{-3}, respectively). The SO_2 levels were not included in the analysis, since they were negligible during the study period (<17 µg·m^{-3}, table 2). There was a relatively strong correlation between the levels of ozone and PM10 (r=0.64). Both ozone and PM10 levels were highly correlated with ambient maximal temperature (rŠ0.70, table 2).

Symptom prevalence

The range of the mean daily prevalence for most symptoms during the study period was relatively large (table 3): for bronchodilator use 23–42%; for shortness of breath 30–56%; for woken up with breathing problems 4–27%; for pain on deep inspiration 0–16%; for cough and/or phlegm 27–47%; for runny and/or stuffed nose 34–76%; and finally for inhaled lung steroid use 53–74%. The strongest associations between air pollution data and symptom prevalences were found for ozone (table 4). Significant positive associations between ozone levels and bronchodilator use (maximal relative risk (RRmax) 1.16), shortness of breath (RRmax 1.18) and pain on deep inspiration (RRmax 1.44) were found. A negative trend for cough and/or phlegm was noted when analysed with the ozone concentration of the previous day. The effects on most symptoms of the other air pollutants were smaller than those of ozone (table 5). Woken up with breathing problems was associated with PM10 (RRmax 1.24). Shortness of breath was associated with PM10, NO_2 and black smoke levels (RRmax 1.17, 1.06 and 1.11 respectively). Significant negative associations were found between nasal symptoms and PM10, NO_2 and black smoke levels (RRmax 0.77, 0.91 and 0.86, respectively). A trend toward an increase in shortness of breath was seen for the 7 day mean concentration of NO_2. Another positive trend could be demonstrated for bronchodilator use and the 7 day mean PM10 concentration. A similar trend was found for lung steroid use and previous day black smoke concentration. No associations could be demonstrated between wheezing or asthma attacks and air pollution.

Peak flow

A trend towards a significant associations could be demonstrated between ΔPEF and both ozone and black smoke levels. For all pollutants the observed association with ΔPEF was negative, although the effects were small (ð-3.2 L·min^{-1}) and no significant associations could be demonstrated (fig. 2, tables 4 and 5).

Subgroup analysis

Overall, no significant differences in the observed associations with ozone were observed when analysed in subgroups. The effect of ozone on pain during deep inspiration was stronger in the subgroup with the PC20 less than the mean (RRmax 2.23 *versus* 1.68), whereas inhaled steroid use was significant only in the subgroup that demonstrated less hyperresponsiveness at the start of the study (PC20 Š mean; RRmax 1.24, table 6). A positive association for bronchodilator use with the mean 7 day ozone concentration could be demonstrated in the PC20 < mean subgroup (RRmax 1.25), but a similar trend could be demonstrated in the subgroup with PC20 Š mean (RRmax 1.18) for ozone levels with a 2 day lag. A significant negative as-sociation for cough and/or phlegm with ozone levels with a 1 day lag (RRmax 0.79) was observed in the subgroup with PC20 < mean. In the subgroup analysis on steroid use before the start of the study, significant

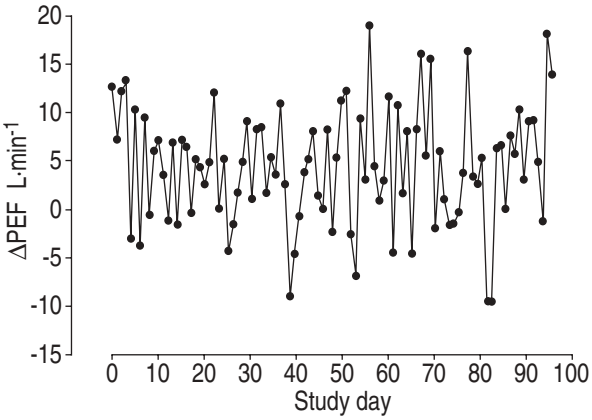

Fig. 2. – Group mean daily morning to evening peak flow change (ΔPEF) during the study period. Study day 1=July 3 1995; study day 100=October 10 1995.

Table 4. – Relative risks of ambient ozone exposure for respiratory symptoms and peak expiratory flow

	Ozone			
	lag 0	lag 1	lag 2	7 day
Bronchodilator use	1.05 (0.94–1.19)	1.09 (0.97–1.22)	1.09 (0.97–1.22)	1.16* (1.02–1.33)
Shortness of breath	1.18* (1.02–1.36)	1.06 (0.92–1.23)	1.01 (0.88–1.17)	1.05 (0.86–1.28)
Woken up with breathing problems	1.14 (0.90–1.45)	0.93 (0.73–1.19)	0.98 (0.77–1.25)	0.93 (0.65–1.33)
Pain on deep inspiration	1.44* (1.10–1.88)	1.05 (0.78–1.41)	1.14 (0.86–1.51)	1.29 (0.90–1.85)
Cough and/or phlegm	0.94 (0.83–1.07)	0.88† (0.78–1.00)	0.95 (0.83–1.08)	0.88 (0.74–1.03)
Nasal symptoms	1.01 (0.85–1.20)	0.95 (0.80–1.13)	1.06 (0.89–1.26)	0.95 (0.71–1.29)
Inhaled steroids	0.98 (0.91–1.04)	1.03 (0.97–1.10)	0.99 (0.93–1.06)	1.02 (0.88–1.17)
ΔPEF‡	-1.0 (1.9)	-0.8 (2.3)§	-3.2 (1.8)	-0.7 (1.8)

Values are presented as mean, and 95% confidence interval in parenthesis, unless otherwise indicated. lag 0, lag 1, lag 2: analysis using air pollution data from 0, 1 and 2 days prior to symptom recording, respectively; 7 day: mean 7 day concentration. Relative risks were calculated for ozone per 100 μg·m^{-3} (for lag 0–lag 2) or 50 μg·m^{-3} (for 7 day) increase. †: $p<0.10$; *: $p<0.05$; ‡: pooled ß (L·min^{-1}) from individual linear regression analysis and corresponding SEM; §: median value ±SEM ΔPEF: morning peak expiratory flow (PEF)-evening PEF.

Table 5. – Relative risk of PM_{10}, NO_2 and BS for respiratory symptoms and peak expiratory flow (PEF)

	PM_{10}			NO_2			BS		
	lag 0	lag 1	7 day	lag 0	lag 1	7 day	lag 0	lag 1	7 day
Bronchodilator use	1.03 (0.93–1.15)	0.99 (0.89–1.10)	1.12† (1.00–1.25)	0.99 (0.94–1.03)	0.99 (0.95–1.04)	1.03 (0.98–1.07)	0.97 (0.91–1.05)	1.01 (0.94–1.09)	1.01 (0.95–1.08)
Shortness of breath	1.17* (1.03–1.34)	1.08 (0.94–1.24)	1.01 (0.86–1.20)	1.06* (1.00–1.12)	1.00 (0.95–1.06)	1.05† (1.00–1.12)	1.11* (1.01–1.21)	1.07 (0.98–1.18)	1.06 (0.96–1.16)
Woken up with breathing problems	1.24* (1.01–1.54)	0.90 (0.70–1.14)	0.86 (0.63–1.18)	1.01 (0.92–1.12)	1.06 (0.96–1.16)	1.07 (0.96–1.20)	1.11 (0.95–1.29)	1.02 (0.86–1.20)	1.01 (0.85–1.19)
Pain on deep inspiration	1.12 (0.88–1.44)	0.83 (0.63–1.10)	0.87 (0.64–1.18)	1.06 (0.96–1.17)	0.96 (0.87–1.07)	1.00 (0.90–1.11)	1.13 (0.97–1.32)	0.84 (0.70–1.01)	0.90 (0.77–1.04)
Cough and/or phlegm	0.93 (0.83–1.04)	0.97 (0.86–1.09)	0.94 (0.82–1.08)	0.99 (0.94–1.04)	1.01 (0.97–1.06)	1.03 (0.98–1.08)	0.98 (0.90–1.06)	1.00 (0.92–1.08)	0.99 (0.92–1.06)
Nasal symptoms	0.98 (0.83–1.15)	0.82* (0.70–0.96)	0.77* (0.61–0.97)	0.96 (0.90–1.03)	0.92* (0.86–0.98)	0.91* (0.83–0.99)	0.98 (0.87–1.10)	0.86* (0.78–0.96)	0.91 (0.80–1.04)
Inhaled steroids	1.01 (0.95–1.07)	1.05 (0.98–1.12)	1.01 (0.89–1.14)	1.00 (0.98–1.03)	1.00 (0.98–1.03)	0.98 (0.93–1.03)	0.97 (0.92–1.02)	1.05† (1.00–1.10)	0.96 (0.90–1.03)
ΔPEF‡	-0.9 (1.5)	-0.5 (1.9)	-1.1 (2.1)	-0.2 (1.0)§	0.0 (1.1)§	-0.4 (0.9)	-1.7 (1.4)†§	-0.8 (1.6)§	-1.1 (1.3)§

Values are presented as mean, and 95% confidence interval, in parenthesis, unless otherwise stated. PM_{10}: particles with a 50% cut-off aerodynamic diameter of 10 μm; NO_2: nitrogen dioxide; BS: black smoke. Relative risks were calculated for PM_{10} per 50 μg·m^{-3} (for lag 0–lag 1) or 25 μg·m^{-3} (for 7 day) increase, for NO_2 and BS per 10 μg·m^{-3} (for lag 0–lag 1) or 5 μg·m^{-3} (for 7 day) increase; †: $p<0.10$; *: $p<0.05$; ‡: pooled ß (L·min^{-1}) from individual linear regression analysis and corresponding SEM; §: median value ±SEM For further definitions, see legend to table 4.

associations could only be demonstrated in the subgroup using less steroid medication, although the magnitude of the response was comparable between the subgroups. In the subgroup using less steroids before the start of the study, pain on deep inspiration was associated with ozone levels on the same day (RR_{max} 1.65), and cough and/or phlegm were sig- nificantly negatively associated with ozone levels of the previous week (RR_{max} 0.71). No significant associations between PEF measurements and ambient ozone exposure could be demonstrated in either subgroup.

Discussion

In the present study we observed statistically significant, positive associations between air pollution levels and lower respiratory symptoms and medication use in patients with mild to severe asthma. Stratification on airway hyperresponsiveness and steroid use did not affect the magnitude of the observed associations. These results indicate that, contrary to our primary hypothesis, the severity of asthma as assessed by steroid use or airway hyperresponsiveness does not predict the impact of air pollution on patients with asthma.

To our knowledge, this is the first epidemiological study to investigate the relationship between the severity of asthma and the sensitivity to air pollution. The relationship between increased symptom prevalence or medication use and air pollution noted in the present study is consistent with the findings of other investigators [2, 5, 19, 23]. The effects on PEF are comparable to those reported in a recent study with asthmatic children, that observed the strongest effects with ozone [23]. Furthermore, in the present study the most prominent associations between symptoms and air pollution were observed for ozone. However, positive associations could also be demonstrated for PM_{10}, and to a lesser extent for NO_2 and black smoke. The mean prevalences of symptoms and medication use were relatively high in this study (in the order of 10–60%; table 3). For this reason, the RR_{max} (comparing days with high and low exposure) cannot be very great, as the baseline risk is already high. Therefore, the relative risks reported in the present study are likely to be of clinical importance. In the present study negative associations were noted for cough and/or phlegm with

Table 6. – Relative risk of ambient ozone for respiratory symptoms and peak expiratory flow (PEF) in subgroups

	PC_{20} <mean (n=31)				PC_{20} Šmean (n=29)			
	lag 0	lag 1	lag 2	7 day	lag 0	lag 1	lag 2	7 day
Bronchodilator use	1.11 (0.93–1.34)	1.02 (0.86–1.21)	1.00 (0.84–1.19)	1.25† (1.03–1.53)	0.93 (0.76–1.13)	1.13 (0.93–1.37)	1.18† (0.97–1.43)	1.05 (0.77–1.42)
Shortness of breath	1.15 (0.95–1.40)	1.02 (0.84–1.24)	1.05 (0.86–1.27)	1.08 (0.84–1.39)	1.17 (0.96–1.42)	1.07 (0.88–1.31)	0.95 (0.78–1.15)	0.97 (0.71–1.33)
Woken up with breathing problems	1.01 (0.71–1.44)	1.08 (0.76–1.52)	0.97 (0.68–1.37)	1.04 (0.58–1.87)	1.21 (0.90–1.62)	0.86 (0.63–1.16)	0.99 (0.73–1.34)	0.88 (0.60–1.29)
Pain on deep inspiration	0.88 (0.53–1.46)	1.06 (0.65–1.73)	2.00* (1.23–3.25)	2.23† (0.99–4.99)	1.68* (1.18–2.39)	0.87 (0.58–1.29)	0.84 (0.58–1.23)	1.08 (0.62–1.90)
Cough and/or phlegm	1.04 (0.85–1.27)	0.77* (0.63–0.94)	0.96 (0.77–1.18)	0.81 (0.60–1.10)	0.89 (0.75–1.06)	0.99 (0.83–1.18)	0.96 (0.80–1.14)	0.87 (0.68–1.10)
Nasal symptoms	0.96 (0.77–1.20)	0.97 (0.77–1.21)	1.6 (0.85–1.32)	1.20 (0.85–1.70)	0.98 (0.74–1.31)	0.92 (0.69–1.22)	1.03 (0.77–1.36)	0.66* (0.43–1.00)
Inhaled steroids	1.02 (0.92–1.12)	1.04 (0.95–1.15)	0.92† (0.84–1.01)	0.99 (0.77–1.29)	0.97 (0.90–1.05)	1.02 (0.94–1.11)	1.09* (1.00–1.17)	1.24* (1.07–1.44)
ΔPEF‡	-1.4 (3.0)	0.4 (3.5)§	-5.0† (2.9)	-3.3 (2.7)	-0.8 (2.3)§	-1.4 (3.0)	-1.3 (2.2)	2.1 (2.4)
	Steroid use >mean (n=28)				Steroid use ðmean (n=32)			
	lag 0	lag 1	lag 2	7 day	lag 0	lag 1	lag 2	7 day
Bronchodilator use	1.08 (0.91–1.28)	1.13 (0.95–1.33)	1.07 (0.90–1.26)	1.13 (0.92–1.39)	1.03 (0.84–1.27)	1.02 (0.83–1.25)	1.09 (0.89–1.33)	1.22* (0.98–1.51)
Shortness of breath	1.13 (0.92–1.40)	1.16 (0.94–1.43)	0.98 (0.79–1.21)	1.14 (0.82–1.58)	1.18 (0.93–1.50)	0.94 (0.74–1.20)	0.97 (0.77–1.24)	0.94 (0.70–1.25)
Woken up with breathing problems	1.09 (0.80–1.50)	1.14 (0.84–1.55)	1.13 (0.83–1.54)	1.14 (0.69–1.88)	1.18 (0.84–1.65)	0.75* (0.53–1.05)	0.80 (0.57–1.13)	0.78 (0.52–1.17)
Pain on deep inspiration	1.28 (0.83–1.96)	1.22 (0.79–1.89)	1.42 (0.92–2.17)	1.34 (0.71–2.51)	1.65* (1.17–2.32)	0.99 (0.67–1.45)	0.91 (0.63–1.31)	1.33 (0.79–2.23)
Cough and/or phlegm	0.95 (0.77–1.18)	0.91 (0.74–1.12)	0.96 (0.78–1.19)	1.02 (0.78–1.35)	0.94 (0.75–1.18)	0.81† (0.65–1.01)	0.96 (0.77–1.20)	0.71* (0.54–0.93)
Nasal symptoms	1.07 (0.79–1.44)	1.01 (0.75–1.35)	1.33† (0.99–1.79)	1.23 (0.87–1.74)	0.98 (0.80–1.20)	0.96 (0.78–1.18)	0.86 (0.70–1.05)	0.78 (0.54–1.14)
Inhaled steroids	1.19 (0.92–1.54)	0.94 (0.74–1.20)	0.99 (0.78–1.26)	1.32 (0.73–2.41)	0.99 (0.92–1.07)	1.01 (0.94–1.09)	1.02 (0.94–1.10)	1.05 (0.91–1.21)
ΔPEF‡	-0.8 (2.5)§	-0.1 (3.7)§	-3.7 (2.3)	-1.0 (2.7)	-2.9 (2.8)	-2.3 (3.0)	-2.8 (2.8)	-0.4 (2.5)

Relative risks were calculated for ozone per 100 $\mu g \cdot m^{-3}$ (for lag 0–lag 2) or 50 $\mu g \cdot m^{-3}$ (for 7 day) increase; †: $p<0.010$; *: $p<0.05$; ‡: pooled ß ($L \cdot min^{-1}$) from individual linear regression analysis and corresponding SEM §: median ±SEM PC_{20}: provocative concentration of methacholine causing a 20% fall in forced expiratory volume in one second. For further definitions, see legend to table 4.

ozone, and for nasal symptoms with PM_{10}, NO_2 and black smoke. Of course, these data have to be regarded with caution, since for a given parameter, on the basis of chance alone, half of all associations will be in a negative direction, and 5% of the observations will be significantly associated with air pollution.

The role of several confounders has been examined, *i.e.* pollen, maximal temperature and environmental tobacco smoke. In addition to air pollutants, subjects may have also been exposed to varying concentrations of aeroallergens during the course of the study. The start of the study (July 3 1995) corresponded with the last week of the grass pollen season (May 21–July 11 1995; personal communication F.Th.M. Spieksma). During the study period there was the usual seasonal presence of outdoor airborne mugwort pollen (July 25–August 25 1995; peak August 2 1995) [24]. The peak in nasal symptom prevalence noted around day 30 of the study period (fig. 3) coincided with the mugwort pollen peak of August 2. In contrast, this mugwort pollen peak was not accompanied by changes in PEF or lower respiratory symptoms. When the association of the daily pollen counts with symptoms was analysed, a significant increase in wheezing was noted (data not shown). The pollen counts did not, however, explain the association of symptoms or medication use with air pollutants, as demonstrated by introducing pollen counts as a confounder in the model. Temperature generally showed similar positive associations with symptom

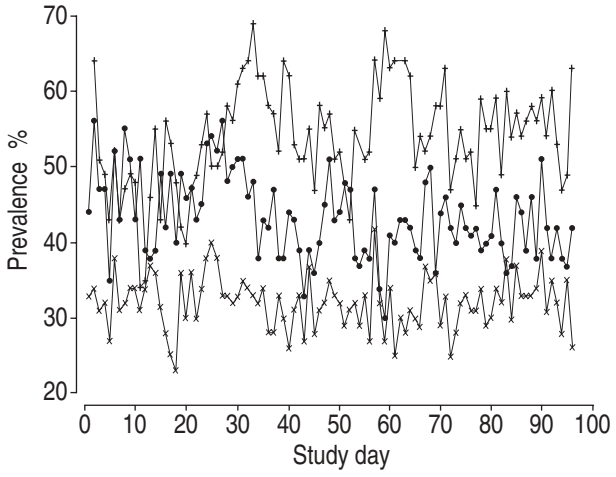

Fig. 3. – Prevalence of short acting bronchodilator use (—●—), runny and/ or stuffed nose (—+—) and shortness of breath (—x—) during the study period. Study day 1=July 3 1995; study day 100=October 10 1995.

prevalence as it did with ozone and PM10, but temperature was highly correlated with both ozone and PM10. However, it is questionable whether temperature will have been a confounder in this study. To our knowledge there is no evidence that temperature, in the range measured during the present study, has any effect on medication use or asthma symptoms [25]. Therefore, we do not think that temperature can explain our results. Exposure may have been misclassified to some extent because of the use of one monitoring station, and because subjects spend most of their time indoors. However, such misclassification is not likely to be differential, and hence, effects of air pollution will probably be somewhat underestimated, rather than overestimated because of such misclassification.

The reporting of symptoms and medication use by our patients may have been biased by several factors. First, selection bias may have occurred, since subjects with more asthmatic symptoms during smog episodes will be more willing to participate in a study. Retrospectively, this does not seem to be the case, since 50% of the participants could be classified as nonsensitive to air pollution (based on self-reported "sensitivity" prior to the study; data not shown). Subjects were motivated to participate in the study, resulting in a high percentage (Š 85% daily) of diaries being daily filled in by the participants during the entire study period. One other bias may have been introduced by the Dutch smog alert system, which reported 24 smog days during the study period (RIVM, Bilthoven, The Netherlands). Therefore, it is possible that our results are biased by the publicity on air pollution. However, COHEN *et al*. [26] did not find reported symptom differences between a well-publicized and an unpublicized air pollution episode in New York, with similar concentration levels in both episodes. In addition, the relative risks that we report on symptoms and medication use for our population are similar to those observed after ambient ozone exposure in subjects with obstructive airways disease [5]. Therefore, we do not think it likely that selection or reporting bias would have been of major influence in this study.

Since lung function measurements were performed with a low frequency at fixed time points, only effects on lung function that persisted for long time intervals could be evaluated in this study. One of the major biases in this study could have been medication use, for which we were not able to control. Introducing these variables into our model did not change our results, although both steroids and bronchodilator use may have profound modifying effects on PEF. Nevertheless, these biases may explain that essentially no associations were found between lung function measurements and air pollution, whereas we did find associations with symptoms and air pollution.

It has been suggested that subjects with more severe asthma may be more susceptible and show more severe adverse events to air pollution [27]. Recently, TAGGART *et al*. [28] demonstrated that summertime air pollution may increase bronchial hyperresponsiveness in a subgroup (63%) of asthmatic subjects, while the baseline airway hyperresponsiveness was not different between the subgroups. Furthermore, stratification of the present subjects according to airway hyperresponsiveness to methacholine did not reveal different associations with ozone between the subgroups (table 6). This indicates that bronchial hyperresponsiveness did not predict the response to air pollutants in the present study. However, airway hyperresponsiveness is variable within subjects, and can be transiently enhanced by factors such as allergen exposure, viral infections or recent exacerbations. It has been demonstrated that in longitudinal studies airway hyperresponsiveness may be an indicator of asthma severity for the group as a whole, but not for individual subjects [16]. Measurements of airway hyperresponsiveness in cross-sectional study designs (such as the present study) have more consistently demonstrated associations with indicators of asthma severity such as symptoms, medication use and peak flow variability [16]. Nevertheless, our results may be biased by the within subject variability of this measurement. Therefore, steroid use before the start of the study was assessed as well as another objective measure of asthma severity that was used for stratification [14]. Furthermore, in this analysis no significant changes in the effects of ozone exposure on symptoms and lung function were demonstrable between the group using high (>400 µg) and the group using low steroids (ð400 µg). Therefore, we are not able to demonstrate an association of two markers of asthma severity with sensitivity to air pollution. This finding is in line with several controlled clinical studies of asthmatic subjects that did not show an en-hanced responsiveness, in terms of symptoms and lung function parameters, to acute ozone exposures compared to healthy controls [8, 9, 29]. In addition, experimental exposure studies have reported an intersubject variability in the magnitude of ozone-induced effects [30, 31], while this response is highly reproducible within subjects [30]. Hence, our results further support findings of experimental exposures and clinical data and states for health effects of air pollution that it is not the severity of asthma but the differences in intrinsic responsiveness which are important.

The contribution of air pollution relative to other stimuli that may trigger exacerbations of asthma is difficult to assess. Short-term increases in symptoms can be triggered by many different irritants, including allergens, viruses, cold air, exercise, passive smoke and changes in weather. Among these stimuli, allergens [32, 33] and viruses [34] predominate. Interactions between air pollution, and viruses or allergens may have existed in this study, as has been demonstrated previously [35–38]. However, the present study was not designed to study such interactions. Taken together, the present study indicates that air pollution, as occurred during the study period, plays a role in exacerbations of asthma, although viruses and allergens are probably more important in this respect.

The results from the present study indicate that the severity of asthma is not an indicator for the responsiveness to air pollution. Therefore, it may be of value to develop tools (*e.g*. biochemical markers) to screen selected subjects for the health impact of air pollution. We speculate that, although the impact of air pollution on lung function measurements and symptoms is relatively small, it is a factor that may exacerbate asthma and contribute to the chronicity of the disease, especially in subjects sensitive to air pollution.

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