Increased asthma medication use in association with ambient fine and ultrafine particles

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ABSTRACT: The association between particulate air pollution and asthma medication use and symptoms was assessed in a panel study of 53 adult asthmatics in Erfurt, Germany in winter 1996/1997.

Number concentrations of ultrafine particles, 0.01–0.1 µm in diameter (NC0.01–0.1), mean 17,300·cm^{-3}, and mass concentrations of fine particles 0.01–2.5 µm in diameter (MC0.01–2.5), mean 30.3 µg·m^{-3}, were measured concurrently. They were not highly correlated (r=0.45). The associations between ambient particle concentrations and the prevalence of inhaled β2-agonist, corticosteroid use and asthma symptoms, were analysed separately with logistic regression models, adjusting for trend, temperature, weekend, holidays, and first order autocorrelation of the error.

Cumulative exposures over 14 days of ultrafine and fine particles were associated with corticosteroid use. β2-agonist use was associated with 5-day mean NC0.01–0.1 and MC0.01–2.5. The prevalence of asthma symptoms was associated with ambient particle concentrations. The results suggest that reported asthma medication use and symptoms increase in association with particulate air pollution and gaseous pollutants such as nitrogen dioxide.
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Adverse health effects of particulate air pollution, such as increases in mortality and morbidity, have been consistently observed in epidemiological studies at current concentrations [1, 2]. Asthmatics were considered a susceptible population in panel-based, time-series analyses. Small but consistent increases in respiratory symptoms and decreases in lung function were observed in asthmatic adults and children in most of the studies [3–8]. In contrast, a large European multicentre study (Pollution Effects on Asthmatic Children in Europe (PEACE)) has shown negative findings [9]. Asthma medication use has been reported to increase in association with particulate air pollution [5, 10–12].

In eastern Germany, air pollution emission has changed substantially since the unification in 1990. Domestic coal heating was replaced by controlled combustion of natural gas or oil. Industrial activity has been reduced and motor vehicle engines improved. The particle size composition in Erfurt, eastern Germany, has been monitored since 1991. Continuous measurements of ambient particulate matter <10 µm in aerodynamic diameter (PM10), fine particles <2.5 µm in aerodynamic diameter (PM2.5), size distribution of particles between 0.01–2.5 µm and gases have been conducted. In the past decade, a downward trend of particulate mass and sulphur dioxide (SO_2) has been observed, but the number concentration of ultrafine particles has remained high [13].

The current regulations of particulate air pollution in the USA and the European Union (EU) aim at the reduction of PM2.5 and PM10 concentrations. These particle fractions are inhaled and have been shown in epidemiological studies to cause adverse health effects [1, 2]. Also ultrafine particle (diameter <0.1 µm) number concentrations have been associated with a decrease of peak expiratory flow (PEF) in panel studies on asthmatic adults in Erfurt [14] and Finland [15] and an increase in symptoms in Erfurt [14]. Furthermore, an increase in mortality was found in association with the number concentration of ultrafine particles (NC0.01–0.1) [16]. These ultrafine particles are present in large numbers, but contribute little mass, therefore they are not controlled by the present regulations.

The present study aimed to verify of the results observed by PETERS et al. [14] in a larger panel of asthmatic adults and to extend the number of analysed pollutants and health endpoints. The role of ambient air pollution on the increase of medication use was specifically studied. It was hypothesised that elevated concentrations of fine particle mass and number of ultrafine particles are associated with an increase in asthma medication use prevalence. In particular, it was hypothesised that particles may affect on demand medication. Furthermore, the present study investigated whether asthma medication would prevent the reporting of wheezing and other asthma symptoms.

Materials and methods

Study design

A panel study was conducted from September 1996–March 1997 in Erfurt, an eastern German city with 200,000 inhabitants. The city is located in a valley surrounded by the Thuringian Forest. During winter, inversion might repeatedly trap the air in the valley. The main sources of ambient air pollution are a power plant, vehicle traffic and domestic heating [16].

During the study period, daily concentrations of air pollutants and meteorological data were assessed. At the same time, study participants kept a diary on their health status and medication use.

Panel study

Sixty-seven asthmatic adults, resident in Erfurt, were recruited by 14 physicians from September through to November 1996. Respiratory diseases were documented by the physician in a short questionnaire. Eligible participants had to be treated with asthma medication during the previous year, and had to be nonsmokers. Written consent was obtained from all participants.

Details on health and smoking status, as well as socio-demographic indicators of the study subjects were obtained through a questionnaire, based on the European Community (EC) respiratory health survey [17, 18].

Asthma was defined as present if the referring physician had diagnosed asthma, or if the subjects themselves in the initial questionnaire had reported asthma diagnosis together with symptoms of asthma in the last 12 months. Asthma symptoms included wheezing, shortness of breath at rest, waking up with breathing problems, or coughing without having a cold.

Asthma medication included inhaled short-acting β_2-agonists, inhaled long-acting β_2-agonists, inhaled corticosteroids, cromolyn sodium, theophylline, oral corticosteroids and N-acetylcysteine.

During the study period, the participants put down the severity of symptoms (as none, slight, severe or very severe) and their medication use (name of medication and number of units taken) in a diary every evening. Symptoms to be noted down were: wheezing, shortness of breath, attack of shortness of breath with wheezing, waking up with breathing problems, phlegm and cough. The present study reports in detail on wheezing as a predominantly lower respiratory tract symptom that is asthma related; the main results of the other symptoms are presented.

Study participants also recorded hours spent outside the study area. The diaries were sent to the research centre every 2 weeks, where they were checked for plausibility and missing values.

Persons who had participated <30 days (n=3), reported implausible values (n=1), were found to be active smokers (n=7) or were chronic obstructive pulmonary disease (COPD) patients (n=3) were excluded from the statistical analyses.

Exposure

Air pollutants and weather data were measured daily in Erfurt. The measurement site is situated in an urban area (background site), 50 m away from the vehicle traffic [14, 19]. Number concentrations of particles with a diameter between 0.01–2.5 μm were measured with a Mobile Aerosol Spectrometer (MAS) in 10 min intervals [19, 20]. The MAS consists of two instruments. The first one is a combination of a differential mobility analyser (DMA, model 3071; TSI, Aachen, Germany) and a condensation particle counter (CPC, model 3760; TSI, Aachen, Germany) covering the particle size range 0.01–0.5 μm; and the second one is an optical laser aerosol spectrometer (Model LAS-X; PMS, Leonberg, Germany), characterising particles ranging in size from 0.1–2.5 μm. The MAS provides number concentration data as a function of the particle diameter. The mass distribution was estimated on the basis of the volume distribution, assuming spherical particles and a mean density of 1,530 kg·m^{-3}.

Daily means of the number concentrations were calculated. For regression analyses, the discrete fractions of ultrafine particles (diameter 0.01–0.1 μm), accumulation mode particles (diameter 0.1–0.5 μm) and particles with a diameter between 0.5–2.5 μm were chosen [14]. Mass concentrations of fine particles (diameter <2.5 μm, MC$_{0.01–2.5}$) and of accumulation mode particles (diameter 0.1–0.5 μm, MC$_{0.1–0.5}$) were computed, based on the number concentrations as described above.

PM$_{10}$ and PM$_{2.5}$ 24-hr measurements were conducted daily with Harvard Impactors. The coarse particle mass fraction (PM$_{2.5–10}$) was calculated as the difference of these two measurements. PM$_{2.5}$ daily values highly correlated with the calculated MC$_{0.01–2.5}$ 24-hr means (r=0.97) and are therefore not reported.

Measurements of SO$_2$ (SO$_2$-monitor, Environment SA, model AF21M), according to the principle of UV-fluorescence, temperature and ambient humidity were concurrently conducted at the same site. A monitoring station run by the "Thüringer Landesanstalt für Umwelt" (Thuringian State Institute for Environment) provided data of the daily concentrations of

nitrogen dioxide (NO$_2$) (*via* chemiluminescence) and carbon monoxide (CO) (on the principle of infra-red light absorption) measured at an urban background station, ~2 km from the National Research Center for Environment and Health (GSF) measurement station.

Statistical analyses

Logistic regression models were used to estimate the association between the daily prevalence of medication use as well as symptoms and particulate air pollution controlling for time varying confounders.

Asthma medication categories "inhaled short-acting β$_2$-agonists" and "inhaled corticosteroids" (including Cromolyn sodium) were formed and coded as 0 (no use of medication) or 1 (use of medication). Daily prevalences of the medications were calculated in the subgroups of participants who, during the study period, ever reported using this medication. Severe or very severe symptoms were classified as a positive response of the respective subject on that day. The daily prevalence of each symptom was calculated based on all participants. Participants who spent >8 h outside the study area were excluded from the prevalence calculation of a day. Days for which <50% of medication use or symptom data were available were excluded from the analyses, in order to avoid an effect of the recruitment period. Figure 1 shows three respective time series of prevalences as used in the analyses. For the statistical analyses, the number of available days ranged between 131–148, due to missing days in the outcome, exposure and confounder variables.

The selection of the confounders was conducted in stages [21]. Trend was considered as a linear, quadratic or cubic function, to control for an overall increase or decrease, or for seasonal variation in medication use or symptom prevalences. In addition, nonlinearity of trend was assessed using nonparametric methods. Short-term effects of meteorological factors, such as relative humidity and temperature (both as linear and quadratic terms) were considered, and 1-day lags of both were tested. Very cold days (<-10°C) were additionally adjusted with a piece-wise linear term. Dummy variables for the day of the week were included. An alternative approach distinguished between weekdays and weekends. Dummy variables for each month, Christmas holidays and periods of influenza epidemics were tested. The lack of independence caused by the repeated measures on each subject was considered in the analysis using autoregressive models [22–24]. The models were based on generalised estimating equations, and controlled for heteroscedasticity of the rates [25]. A first-order autoregressive structure was detected. The final model, initially selected for inhaled short-acting β$_2$-agonists as outcome variable, controlled for first order autoregression, trend (cubic), temperature, weekend, and Christmas holidays, it was verified for the other outcomes that were considered in the analyses. The model was selected stepwise using a combination of goodness-of-fit and change-in-estimate criteria, with a linear trend function as forced in variable.
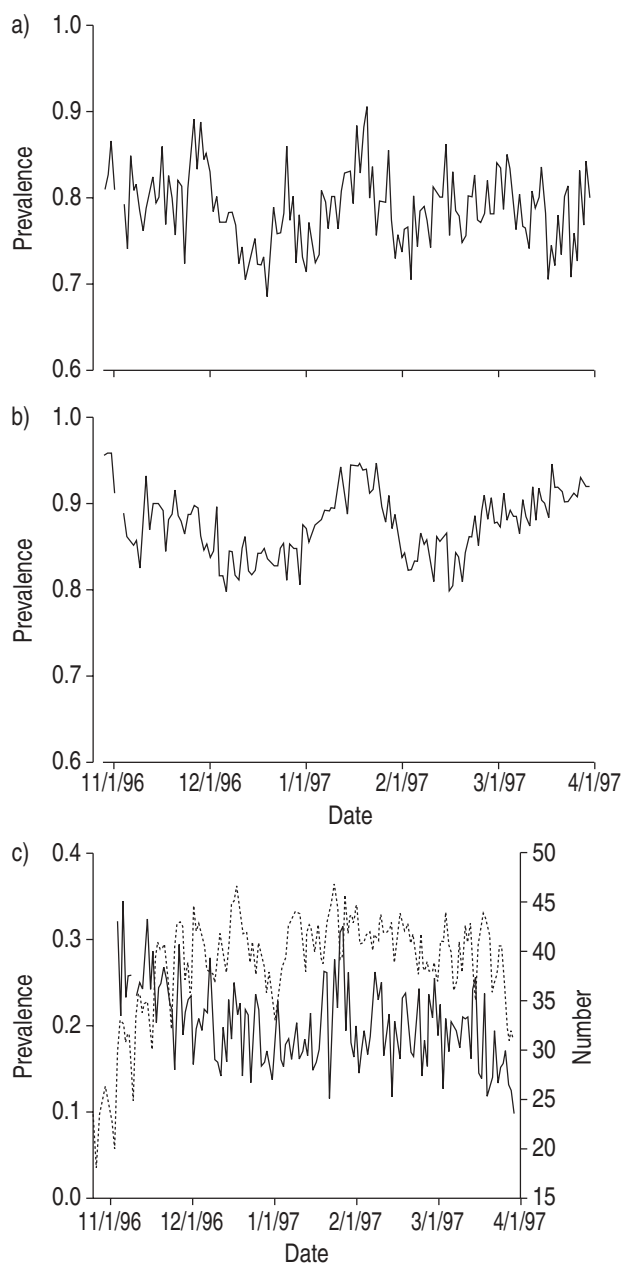

Fig. 1. – Time series of medication use and wheezing prevalence October 25, 1996–March 30, 1997, where participation was >50%. a) Short-acting β$_2$-agonist use, b) corticosteroid use, and c) wheezing (——) and participants filling out a diary (··········).

Since pollution data tend to be serially correlated and since there is a possibility of lagged or accumulated effects, the lag structure was assessed with unconstrained lag models [26]. Moving averages were used in the final models, which were calculated from the same day and the preceding days. The calculation was based on at least two-thirds of nonmissing pollutant measures. Since there was access to exposure data of 2 weeks prior to the analysis period, the number of missing values did not increase with this procedure, when compared to same day exposure measures.

Two-pollutant models were calculated for fine particles (MC$_{0.01–2.5}$) and for ultrafine particles (NC$_{0.01–0.1}$), together with the gases NO$_2$, SO$_2$ and CO. There was

not sufficient power to distinguish between measures of mass concentrations, given their high correlation. A cut-off point for the correlation coefficient was set at 0.8, to avoid extreme colinearity, which would cause disproportionately biased effect estimates.

Results

Final analyses included a total of 53 subjects, 33 were female, average age was 59.0 yrs; the range was 37–77 yrs (table 1).

All 53 study participants received asthma medication prescriptions during the study period. Mean prevalence of any medication use was 95.2%, with a minimum of 89.5% and a maximum of 100%. Most of the asthmatics took inhaled corticosteroids (n=44) combined with theophylline and/or inhaled short-acting β_2-agonists (n=42). Five subjects took only inhaled corticosteroids or theophylline or inhaled short-acting β_2-agonists, respectively; three took a combination of theophylline and inhaled short-acting β_2-agonists. In total, 42 subjects reported use of inhaled short-acting β_2-agonists (tables 1 and 2). Figure 1 presents the time series of the prevalence of inhaled medication use during the study period.

On average, 20% of the adult participants reported wheezing on any given day (table 2). The daily prevalence of wheezing ranged between 10–34% (fig. 1). Table 2 shows the distribution of prevalence of other symptoms.

Table 1. – Characteristics of the study population

Patient characteristics	
Number of patients	53
Age mean yrs	59.0
Sex M:F	20:33
Atopic status[#]	25
Respiratory health	
Asthma[¶]	37
Asthmatic Symptoms only[+]	16
Total	53
Medication	
Inhaled short-acting β_2-agonists	42
Inhaled corticosteroids	44
Theophylline	37
Oral corticosteroids	8
Any asthma medication[§]	53
Smoking	
Nonsmoker	53
Living with smoker	3
Occupation	
Employed	12
Unemployed	9
Pensioner	27
Others	5

M: male; F: female. [#]: Hay fever, allergic skin reactions, allergic reactions on insects or medicine; [¶]: asthma diagnosis, or "asthma" and symptoms given in questionnaire; [+]: wheezing, shortness of breath at rest or waking up with breathing problems or coughing without cold in the last 12 months; [§]: inhaled β_2-agonists agonists, inhaled corticosteroids, cromolyn sodium, theophylline, oral corticosteroids or n–acetylcysteine.

Subjects participated on average 147 days in the study (minimum 45, maximum 188). After excluding days spent outside the study area, mean contribution to the study was 122 days (minimum 25, maximum 187), corresponding to 41 diaries, completed within the study area on average each day.

Air pollutants

Mass concentrations of all particle fractions as well as SO_2 were elevated between December 1996–January 1997 (fig. 2). On 2 days, the US standard for PM_{10} (150 $\mu g \cdot m^{-3}$) was exceeded. PM_{10} average concentration was 45.4 $\mu g \cdot m^{-3}$ (table 2). Maximum observed fine particles mass concentration ($MC_{0.01-2.5}$) was 133.8 $\mu g \cdot m^{-3}$, mean was 30.3 $\mu g \cdot m^{-3}$ (table 2). Accumulation mode particles $MC_{0.1-0.5}$ had an average mass concentration of 24.8 $\mu g \cdot m^{-3}$, which represents 82% of all fine particles (table 2). Number concentrations of ultrafine particles had an average of 17,300 particles·cm^{-3}, and ranged from 3,272–46,195 particles·cm^{-3} during the study period. Temperature frequently was $<0°C$ in December and January (fig. 2). At the end of December, there was a very cold period with temperatures $<-10°C$.

Particle mass concentrations and particle number concentrations >0.1 μm where highly correlated (table 3). Fine particle mass and accumulation mode particle mass showed a nearly identical time course (r=0.997). The correlation between ultrafine particle number concentration and fine particle mass concentration was moderate (r=0.45), as well as its correlation with PM_{10} and SO_2 (table 3). The correlation of ultrafine particles with CO and NO_2 was stronger (r=0.66). Temperature was correlated negatively with all pollutants, relative humidity in contrast was positively correlated.

Association between air pollutants and health outcomes

A delayed response to ambient pollution was investigated and evidence was found in unconstrained lag models. These models suggested considering an accumulation of effects over a period of ∼5 days for inhaled short-acting β_2-agonist use and over $\geqslant 10$ days for inhaled corticosteroid use (fig. 3). To account for this, 5- 10- and 14-day running means were used in the final models. The results for 10-day running means are not shown, as they were very similar to the 14-day mean results.

An example of the effect estimates of the confounders in the multivariate models is as follows: Corticosteroid use increased with falling temperatures (odds ratio (OR) for a decrease of 5°C, when >-10°C: 1.06 (95% confidence interval (CI): 1.00–1.12)) when including the 14-day moving average of ultrafine particles. No effect of temperature was observed when $<-10°C$ (OR 0.83; 95% CI 0.68–1.02, for e.g. -12–-17°C). Weekends showed a similar medication prevalence as weekdays (OR 1.01; 95% CI 0.93–1.10), as well as Christmas holidays (OR 1.05; 95% CI 0.89–1.25).

Table 2. – Distributions of 24-h mean air pollutants, temperature, prevalence of medication use and symptoms between October 25, 1996–March 30, 1997

	N days[#]	Mean	Minimum	25%	Median	75%	Maximum
Number concentrations cm^{-3}							
$NC_{0.01-0.1}$	145	17300	3272	9286	16940	24484	46195
$NC_{0.1-0.5}$	147	2005	291	958	1610	2767	6700
$NC_{0.5-2.5}$	141	21.4	0.9	5.6	13.0	31.6	127.6
Mass concentrations µg·m^{-3}							
$MC_{0.1-0.5}$	147	24.8	2.4	11.4	19.6	33.1	108.3
$MC_{0.01-2.5}$	142	30.3	3.6	13.5	24.6	41.3	133.8
$PM_{2.5-10}$	140	10.3	-8.7	2.9	6.9	14.6	64.3
PM_{10}	148	45.4	4.7	19.6	35.0	59.7	172.4
Gases							
NO_2 µg·m^{-3}	157	46	8	34	45	56	119
CO mg·m^{-3}	156	0.9	0.3	0.5	0.8	1.2	3.0
SO_2 µg·m^{-3}	152	24.0	0.1	8.4	15.9	29.3	114.7
Temperature °C	152	2.6	-17.3	-1.2	3.0	7.9	18.7
Inhaled short-acting β$_2$-agonists[¶]	151	79	69	76	79	81	90
Inhaled corticosteroids[+]	153	88	80	85	88	91	96
Wheezing %[§]	146	20	10	16	20	23	34
Attack of shortness of breath and wheezing	146	13	3	10	13	17	27
Waking up with breathing problems	146	23	9	18	22	26	45
Shortness of breath	146	28	15	23	27	32	47
Phlegm	146	27	14	24	27	30	44
Cough	146	27	11	22	26	31	47

Data are presented as % unless otherwise stated. NC: number concentration of particles (numbers represent diameter of particles in µm); MC: mass concentration of particles (numbers represent diameter of particles in µm); $PM_{2.5-10}$: particulate matter with a 2.5–10 µm aerodynamic diameter; PM_{10}: particulate matter <10 µm in aerodynamic diameter; NO_2: nitrogen dioxide; CO: carbon monoxide; SO_2: sulphur dioxide. [#]: maximum number of days was 157. Lower numbers in the prevalence time series are caused by the rule of excluding days with <50% of data; [¶]: prevalence calculated in the 42 participants who ever reported use of β$_2$-agonists; [+]: prevalence calculated in the 44 participants who ever reported use of corticosteroids; [§]: prevalence calculated in all 53 participants for symptoms.

Table 4 summarises the results of the prevalence of short-acting β$_2$-agonists. There was no association of same day values of all pollutants with the prevalence of short-acting β$_2$-agonists. An association was present with the 5-day running means of almost all subfractions of particles. Only CO and the coarse particle fraction ($PM_{2.5-10}$) did not achieve statistical significance. Fourteen-day means of the pollutants mostly had lower, and often not statistically significant effect estimates.

In the two-pollutant models, the 5-day mean ultrafine particle number concentration and fine particle mass concentration appeared to have independent effects on the use of inhaled short-acting β$_2$-agonists (table 5). NO_2 seemed to be the best predictor.

Regression results of inhaled corticosteroid use are shown in table 6. Positive statistically significant associations were observed between inhaled corticosteroids and same day exposure to ultrafine particle number concentrations, fine particle number concentrations and the gases NO_2 and CO. Significant effects were found for 5-day running means of the particle fractions as well as of the gases. Noticeably higher effects were observed in association with the 14-day mean particulate air pollutants. SO_2 showed a similar, but not equally strong tendency to longer accumulated effects. CO and NO_2 demonstrated higher effects for the 5-day mean than for the 14-day mean. The magnitude of the associations of inhaled corticosteroid use with fine or ultrafine particles was similar.

In the two-pollutant models, 14-day mean $NC_{0.01-0.1}$ showed a weaker effect than $MC_{0.01-2.5}$ (table 5). $MC_{0.01-2.5}$ showed a stronger association with inhaled corticosteroid use than CO and NO_2.

Regression results of wheezing are shown in table 7. Little evidence was seen for an association between same-day pollutant measures and the prevalence of wheezing. Statistically significant associations between the 5-day mean number concentration of ultrafine particles, CO and NO_2 and the prevalence of wheezing were observed. Positive, but weaker associations were seen with mass concentrations. The observed effects of ultrafine particle and accumulation mode number concentrations increased when considering the 14-day means, but were little changed for particle mass, CO and NO_2.

Two-pollutant models, that considered the 5-day means of the pollutants, supported a strong ultrafine particle effect on the prevalence of wheezing (table 5). Ultrafine particles competed for the effect with the gases CO and NO_2, whereas the evidence of a fine particle mass effect remained poor. In the two-pollutant model with the 14-day means, there was even stronger evidence of an association of the ultrafine particles with the prevalence of wheezing.

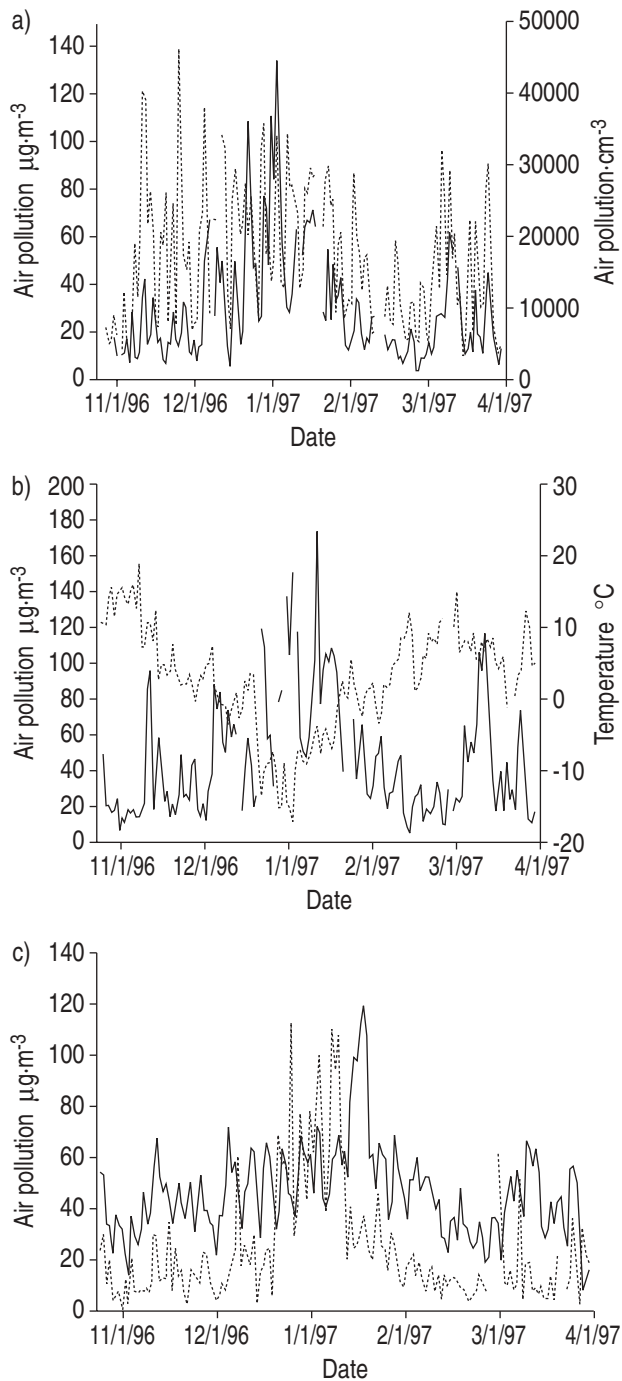Table 8 shows the main results of the other

Fig. 2. – Air pollution and temperature in Erfurt, Germany during the winter of 1996–1997. a) Number concentrations of ultrafine particles, 0.01–0.1 μm in diameter (NC0.01–0.1): ··········; mass concentrations of fine particles 0.01–2.5 μm in diameter (MC0.01–2.5): ——. b) Particulate matter <10 μm in aerodynamic diameter: ——; Temperature: ········ c) Nitrogen dioxide (NO₂): ········ Sulphur dioxide (SO₂): ——.

symptoms. Shortness of breath and its combination with wheezing both showed a similar pattern as wheezing, whereas for "waking up with breathing problems" in addition a 5-day mean $PM_{2.5}$ effect and an immediate NO_2 effect were found. Cough and phlegm showed consistent and significant associations

with ultrafine and fine particles, as well as with NO_2. The effect of 5- and 14-day running means were comparable.

Discussion

Summary of results

In the present study, increased inhaled asthma medication use and symptoms of asthma, such as wheezing, were associated with particulate air pollution.

Short-acting β_2-agonist use was associated with 5-day means of pollutants. Nearly all pollutants showed a significant association of a similar magnitude. In two-pollutant models, effect estimates of ultrafine particle number concentration and fine particle mass concentration were comparable (fig. 4). Inhaled corticosteroid use in contrast was strongly associated with the 14-day running means of fine and ultrafine particles. In two-pollutant models, the mass concentration of fine particles showed stronger effects than the ultrafine particle number concentration.

The 5- and 14-day average concentrations of ultrafine particles were associated with the prevalence of wheezing. No evidence for an immediate effect was observed. No significant association was seen for mass or number concentrations of fine particles. The gases CO and NO_2 showed a positive association with the prevalence of wheezing. Two-pollutant models underlined the effect of ultrafine particles. Other asthma symptoms showed consistent effects.

Medication use

The observed association between particulate mass concentrations and inhaled short-acting β_2-agonist use is consistent with other studies, that were conducted in children or adults with respiratory symptoms or asthma [7, 8, 27–31]. Evidence of a cumulative effect of air pollution on medication use has been found [7, 8, 28–31]. However, studies are reported that observed no association between β_2-agonist use and PM10 [32, 33]. Inhaled corticosteroid use was previously analysed within a category of "maintenance medication" [7, 27, 28] or "asthma medication" (including inhaled β_2-agonists and corticosteroids) [5], only two of these showed an association with PM10 [5, 27]. In a study on adult asthmatics, little evidence of an association of inhaled corticosteroids (as separate category) with PM10 and black smoke was observed [29]. An explanation for this might be that this study was conducted in summer, had a shorter follow-up period and lower pollution concentration than the present study.

Inhaled corticosteroids are not an on-demand medication like inhaled short-acting β_2-agonists, they should be used on a regular basis. Hence, with perfect compliance an association between air pollution and inhaled corticosteroids would not be expected. It had been hypothesised that particulate air pollution may particularly affect the use of on-demand medication. In contrast, considerable variation in the use
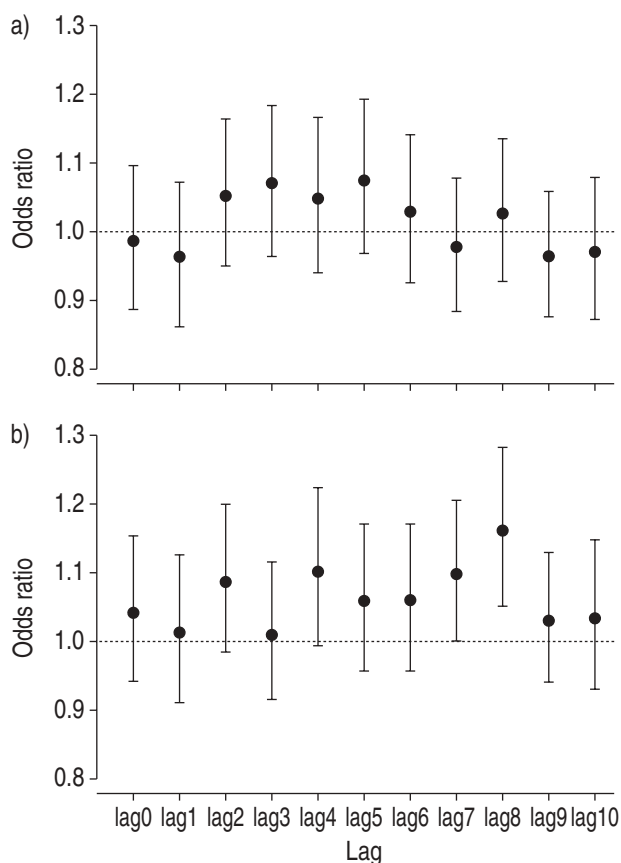
Fig. 3. – Unconstrained lag models of the association between reported medication use and number concentrations of ultrafine particles, 0.01–0.1 μm in diameter ($NC_{0.01–0.1}$), lags 0–10, adjusting for cubic trend, temperature, weekend, Christmas holidays and first-order autocorrelation (odds ratios calculated for increase in one interquartile range). a) Short-acting β_2-agonist use, and b) corticosteroid use.

and accumulated over a more extended period. The unsatisfactory compliance that was observed might be responsible for this phenomenon; patients might stop the usage of their medication when they don't feel ill and restart to inhale when they feel bad due to external stressors, for example after a prolonged period of high air pollution levels.

Unconstrained lag models showed a contribution of the exposure over >10 preceding days on the prevalence of corticosteroid use and a shorter cumulated effect on short-acting β_2-agonist use (fig. 3). It is important to note that the individual estimates in these models cannot be readily interpreted due to the high correlation between the individual lags. The present authors considered moving averages that assign equal weights to each lag in the final models in order to overcome this limitation [26]. The largest effect estimates for wheezing and for corticosteroid use were seen with the 14-day running means. This might be explained by a provocation of an inflammatory reaction in association with exposure to accumulated ultrafine particle number concentration. This is in line with NEUKIRCH et al. [34], who found effects of air pollution on symptoms that continued for several days after the exposure, and who suggested that the inflammatory process in the airways was the reason for this.

A key difference between this study and most previous investigations is that the present study examined effects of air pollution with lags ⩽14 days, rather than just a few days. Had the study used exposure on the same or the previous few days only, the effects seen would have been much weaker. The results were confirmed, when considering non-parametric lag functions of trend. Hence, a key finding of this study is the need to examine longer lags.

Wheezing

Several studies have analysed the effect of particles and other air pollutants on wheezing within

of corticosteroids was observed; effects of ambient particulate air pollution were higher for the use of corticosteroids than for the use of inhaled β_2-agonists,

Table 3. – Pearson's correlation coefficients for the pollutants (same day values) and temperature between October 25, 1996–March 30, 1997 in Erfurt, Germany

	$NC_{0.1–0.5}$	$NC_{0.5–2.5}$	$MC_{0.1–0.5}$	$MC_{0.01–2.5}$	$PM_{2.5–10}$	PM_{10}	NO_2	CO	SO_2	Temperature
Number concentrations										
$NC_{0.01–0.1}$	0.55	0.34	0.45	0.45	0.41	0.51	0.66	0.66	0.36	-0.40
$NC_{0.1–0.5}$		0.76	0.95	0.93	0.50	0.85	0.75	0.79	0.51	-0.62
$NC_{0.5–2.5}$			0.92	0.94	0.48	0.88	0.54	0.46	0.66	-0.68
Mass concentrations										
$MC_{0.1–0.5}$				1.00	0.51	0.91	0.69	0.66	0.60	-0.71
$MC_{0.01–2.5}$[#]					0.52	0.94	0.68	0.65	0.62	-0.71
$PM_{2.5–10}$						0.67	0.45	0.42	0.28	-0.27
PM_{10}							0.74	0.69	0.55	-0.62
Gases										
NO_2								0.82	0.36	-0.50
CO									0.32	-0.46
SO_2										-0.67

Data are presented as Pearson's correlation coefficients. NC: number concentration of particles (numbers represent diameter of particles in μm); MC: mass concentration of particles (numbers represent diameter of particles in μm); $PM_{2.5–10}$: particulate matter with a 2.5–10 μm aerodynamic diameter; PM_{10}: particulate matter <10 μm in aerodynamic diameter; NO_2: nitrogen dioxide; CO: carbon monoxide; SO_2: sulphur dioxide. [#]: Correlation of $MC_{0.01–2.5}$ and $PM_{2.5}$ r=0.97.

Table 4. – Effect estimates[#] for the association between the prevalence of inhaled short-acting β_2-agonists agonist use and particulate and gaseous pollution (odds ratios (OR) and 95% confidence intervals (CI) are given for an increase of one interquartile range (IQR))

	Same day			5-day mean			14-day mean		
	IQR	OR	CI	IQR	OR	CI	IQR	OR	CI
Number concentrations									
$NC_{0.01-0.1}$	15000	0.97	0.90–1.04	10000	1.11	1.01–1.21	7700	1.08	0.96–1.21
$NC_{0.1-0.5}$	1800	0.99	0.92–1.05	1500	1.10	1.03–1.19	1450	0.95	0.86–1.05
$NC_{0.5-2.5}$	26	0.99	0.93–1.05	22	1.09	1.01–1.17	17	1.08	1.02–1.15
Mass concentrations									
$MC_{0.1-0.5}$	21	0.98	0.92–1.04	21	1.11	1.02–1.20	17	1.01	0.93–1.10
$MC_{0.01-2.5}$	28	0.96	0.90–1.04	26	1.10	1.01–1.20	20	1.03	0.95–1.12
$PM_{2.5-10}$	12	1.01	0.95–1.06	11	1.01	0.94–1.09	6.7	0.92	0.86–1.00
Gases									
NO_2	22	1.00	0.94–1.06	16	1.08	1.02–1.14	12	1.03	0.97–1.08
CO	0.6	0.98	0.93–1.03	0.6	1.04	0.97–1.12	0.54	0.93	0.86–1.01
SO_2	21	1.03	0.98–1.08	17	1.06	1.00–1.12	13	1.07	1.02–1.12

NC: number concentration of particles (numbers represent diameter of particles in μm); MC: mass concentration of particles (numbers represent diameter of particles in μm); $PM_{2.5-10}$: particulate matter with a 2.5–10 μm aerodynamic diameter; NO_2: nitrogen dioxide; CO: carbon monoxide; SO_2: sulphur dioxide. [#]: Adjusted for cubic trend, temperature, weekend, Christmas holidays, first order autocorrelation. Analysis period October 29, 1996–March 30, 1997 (153 days).

the "lower respiratory symptoms" category. An association with elevated PM_{10} concentrations was observed in symptomatic children [4, 5, 28, 31]. In other recent studies, however, PM_{10} showed no effect on lower respiratory symptoms in adults [32] and children [9, 33, 35] (PEACE study). In the PEACE study, the short follow-up period made it difficult to control for seasonal or other time trends. This study, with a longer follow-up had less difficulty in this regard.

Significant effects of PM_{10}, SO_2 and NO_2 on the prevalence of wheezing as a separate outcome were observed in asthmatic adults [34]. Associations of PM_{10}, SO_2 and black smoke with wheezing were found in children [7]. Other studies did not observe significant associations between wheezing and particulate matter (PM_{10}, $PM_{2.5}$) [27, 30], or gases (NO_2, SO_2) [30].

Only one study, in which wheezing was aggregated together with breathlessness in an asthma symptom category, considered ultrafine particle number concentrations as well as $PM_{2.5}$ and PM_{10} as exposures [15]. This study, which had been conducted in Finland, showed effects of ultrafine particles on peak expiratory flow (PEF), but in contrast to the present study, no effects on the symptoms (including wheezing).

Table 5. – Effect estimates[#] of the association between two pollutants, jointly in one model, and the health outcomes (odds ratios (OR) and 95% confidence intervals (CI) are given for an increase of one interquartile range (IQR) as specified in table 4)

Prevalence of	Pollutant		$MC_{0.01-2.5}$		Pollutant		$NC_{0.01-0.1}$	
	OR	CI	OR	CI	OR	CI	OR	CI
Inhaled short-acting β_2-agonist use[¶]								
$NC_{0.01-0.1}$	1.07	0.97–1.18	1.07	0.98–1.18				
NO_2	1.10	1.02–1.19	1.00	0.89–1.12	1.09	1.02–1.18	1.01	0.90–1.13
CO	1.00	0.91–1.11	1.10	0.98–1.22	1.01	0.91–1.11	1.10	0.98–1.25
SO_2	1.05	0.99–1.11	1.07	0.98–1.17	1.06	1.00–1.12	1.08	0.99–1.19
Inhaled corticosteroid use[+]								
$NC_{0.01-0.1}$	1.01	0.87–1.18	1.53	1.39–1.69				
NO_2	1.02	0.95–1.10	1.51	1.35–1.68	1.19	1.07–1.32	1.06	0.85–1.32
CO	0.89	0.81–0.98	1.63	1.49–1.78	0.81	0.72–0.91	1.82	1.54–2.15
SO_2		Correlation coefficient larger than 0.8			1.24	1.19–1.29	1.28	1.15–1.44
Wheezing[¶]								
$NC_{0.01-0.1}$	1.12	1.01–1.24	1.02	0.92–1.12				
NO_2	1.05	0.97–1.14	1.01	0.89–1.15	1.01	0.94–1.09	1.12	0.99–1.26
CO	1.15	1.04–1.27	0.96	0.86–1.08	1.09	0.98–1.22	1.05	0.92–1.19
SO_2	0.97	0.91–1.04	1.09	0.99–1.20	0.97	0.92–1.03	1.14	1.04–1.26

NC: number concentration of particles (numbers represent diameter of particles in μm). NO_2: nitrogen dioxide; CO: carbon monoxide; SO_2: sulphur dioxide; MC: mass concentration of particles (numbers represent diameter of particles in μm); [#]: adjusted for cubic trend, temperature, weekend, Christmas holidays, first order autocorrelation; [¶]: air pollution exposures: 5-day means; [+]: air pollution exposures: 14-day means.

Table 6. – Effect estimates[#] for the association between the prevalence of inhaled corticosteroid use and particulate and gaseous pollution (odds ratios (OR) and 95% confidence intervals (CI) are expressed for an increase of one interquartile range (IQR))

	Same day			5-day mean			14-day mean		
	IQR	OR	CI	IQR	OR	CI	IQR	OR	CI
Number concentrations									
$NC_{0.01-0.1}$	15000	1.07	1.00–1.15	10000	1.22	1.12–1.33	7700	1.45	1.29–1.63
$NC_{0.1-0.5}$	1800	1.06	0.99–1.14	1500	1.23	1.14–1.32	1450	1.51	1.37–1.67
$NC_{0.5-2.5}$	26	1.13	1.06–1.21	22	1.28	1.19–1.37	17	1.44	1.36–1.53
Mass concentrations									
$MC_{0.1-0.5}$	21	1.09	1.02–1.17	21	1.28	1.18–1.39	17	1.49	1.38–1.61
$MC_{0.01-2.5}$	28	1.10	1.02–1.18	26	1.28	1.18–1.39	20	1.54	1.43–1.66
$PM_{2.5-10}$	12	1.03	0.98–1.08	11	1.12	1.04–1.20	6.7	1.27	1.18–1.37
Gases									
NO_2	22	1.15	1.09–1.23	16	1.29	1.22–1.37	12	1.21	1.15–1.28
CO	0.6	1.05	1.00–1.11	0.6	1.25	1.17–1.34	0.54	1.06	0.97–1.15
SO_2	21	1.03	0.98–1.09	17	1.21	1.14–1.28	13	1.28	1.22–1.33

NC: number concentration of particles (numbers represent diameter of particles in μm); MC: mass concentration of particles (numbers represent diameter of particles in μm); $PM_{2.5-10}$: particulate matter with a 2.5–10 μm aerodynamic diameter; NO_2: nitrogen dioxide; CO: carbon monoxide; SO_2: sulphur dioxide. [#]: adjusted for cubic trend, temperature, weekend, Christmas holidays, first order autocorrelation. Analysis period October 25, 1996–March 30, 1997 (157 days).

Here, the symptom wheezing has been specifically discussed, but remarkably consistent effects on other asthma symptoms were also detected.

Asthma symptoms and medication

Asthma medication might be a confounder or effect modifier of the association between air pollution and asthma. In an epidemiological study of patients with severe asthma, pulmonary function increased when particulate matter exposure was elevated [10]. This was interpreted as confounding by medication. In asthmatic children the association between symptoms and particulate air pollution was modified by medication use [11]. In a stratified analysis of asthmatic adults, the subgroup that regularly inhaled short-acting β_2-agonist, showed no effects, whereas variably medicated subjects showed adverse health effects of pollutants [34]. Recent studies showed that in children the adverse effects of particulate air pollution could not be prevented by medication [11, 12, 31]. In the present study, an association of ultrafine particles with asthma symptoms was observed, although there was an increased use of inhaled short-acting β_2-agonists and corticosteroids with elevated ultrafine particle number concentrations. Thus, the effect estimates for particulate air pollution on, for example, wheezing might be underestimated. An effect of fine particle mass on wheezing was not detectable, because it might have been effectively compensated by the inhaled corticosteroids.

Table 7. – Effect estimates[#] for the association between the prevalence of wheezing and particulate and gaseous pollution (odds ratios (OR) and 95% confidence intervals (CI) are expressed for an increase of one interquartile range (IQR))

	Same day			5-day mean			14-day mean		
	IQR	OR	CI	IQR	OR	CI	IQR	OR	CI
Number concentrations									
$NC_{0.01-0.1}$	15000	0.94	0.86–1.01	10000	1.13	1.03–1.24	7700	1.27	1.13–1.43
$NC_{0.1-0.5}$	1800	1.00	0.93–1.07	1500	1.08	1.00–1.17	1450	1.11	1.00–1.24
$NC_{0.5-2.5}$	26	1.03	0.95–1.10	22	1.05	0.97–1.13	17	1.03	0.96–1.10
Mass concentrations									
$MC_{0.1-0.5}$	21	1.01	0.94–1.08	21	1.08	0.99–1.17	17	1.05	0.96–1.15
$MC_{0.01-2.5}$	28	1.01	0.93–1.09	26	1.07	0.98–1.17	20	1.07	0.98–1.17
$PM_{2.5-10}$	12	0.97	0.91–1.02	11	1.06	0.98–1.15	6.7	1.05	0.96–1.15
Gases									
NO_2	22	1.01	0.95–1.08	16	1.06	1.01–1.12	12	1.09	1.03–1.15
CO	0.6	1.03	0.97–1.08	0.6	1.13	1.05–1.22	0.54	1.14	1.05–1.25
SO_2	21	1.00	0.95–1.06	17	0.99	0.93–1.05	13	0.99	0.95–1.04

NC: number concentration of particles (numbers represent diameter of particles in μm); MC: mass concentration of particles (numbers represent diameter of particles in μm); $PM_{2.5-10}$: particulate matter with a 2.5–10 μm aerodynamic diameter; NO_2: nitrogen dioxide; CO: carbon monoxide; SO_2: sulphur dioxide. [#]: adjusted for cubic trend, temperature, weekend, Christmas holidays, first order autocorrelation. Analysis period November 4, 1996–March 30, 1997 (147 days).

Table 8. – Effect estimates[#] for the association between the prevalence of respiratory symptoms and particulate air pollution and NO_2 (odds ratios (OR) and 95% confidence intervals (CI) are expressed for an increase of one interquartile range (IQR))

	Same day			5-day mean			14-day mean		
	IQR	OR	CI	IQR	OR	CI	IQR	OR	CI
Attack of shortness of breath and wheezing									
$NC_{0.01-0.1}$	15000	1.01	0.91–1.12	10000	1.08	0.96–1.21	7700	1.26	1.08–1.48
$MC_{0.01-2.5}$	28	0.99	0.89–1.10	26	1.02	0.91–1.14	20	1.13	1.02–1.26
NO_2	22	1.03	0.95–1.11	16	1.06	0.99–1.14	12	1.08	1.00–1.16
Waking up with breathing problems									
$NC_{0.01-0.1}$	15000	1.04[¶]	0.96–1.13	10000	1.09	0.99–1.19	7700	1.26	1.13–1.41
$MC_{0.01-2.5}$	28	1.03[¶]	0.96–1.10	26	1.16	1.06–1.25	20	1.15	1.06–1.24
NO_2	22	1.07[¶]	1.01–1.13	16	1.10	1.04–1.15	12	1.12	1.07–1.18
Shortness of breath									
$NC_{0.01-0.1}$	15000	0.98	0.90–1.06	10000	1.09	0.99–1.19	7700	1.24	1.11–1.40
$MC_{0.01-2.5}$	28	1.04	0.96–1.13	26	1.05	0.96–1.15	20	1.03	0.94–1.12
NO_2	22	1.00	0.94–1.06	16	1.05	0.99–1.11	12	1.11	1.05–1.17
Phlegm									
$NC_{0.01-0.1}$	15000	1.01	0.94–1.09	10000	1.11	1.02–1.21	7700	1.11	0.99–1.25
$MC_{0.01-2.5}$	28	1.05	0.98–1.13	26	1.10	1.01–1.19	20	1.06	0.97–1.15
NO_2	22	1.05	0.99–1.11	16	1.09	1.04–1.15	12	1.05	1.00–1.11
Cough									
$NC_{0.01-0.1}$	15000	1.07	0.98–1.16	10000	1.17	1.07–1.28	7700	1.20	1.06–1.35
$MC_{0.01-2.5}$	28	1.07	0.99–1.17	26	1.04	0.95–1.13	20	1.01	0.92–1.10
NO_2	22	1.03	0.97–1.09	16	1.06	1.00–1.12	12	1.09	1.03–1.15

NC: number concentration of particles (numbers represent diameter of particles in µm); MC: mass concentration of particles (numbers represent diameter of particles in µm); NO_2: nitrogen dioxide. [#]: adjusted for cubic trend, temperature, weekend, Christmas holidays, first order autocorrelation; [¶]: for the symptom "waking up with breathing problems" the effect of the concentration of pollutants on the previous day was estimated.

Interpretation of the results with respect to air pollutants

Particulate combustion emissions have the size of airborne fine particles, whereas the larger particles, also referred to as coarse particles, are mostly of geogenic origin and therefore probably less toxic [2, 36, 37]. Recent studies postulated that the ultrafine particles might have an independent effect [14, 38]. In adult asthmatics, larger decreases in PEF were observed in association with ultrafine particle number concentration compared to PM2.5 or PM10 [13–15]. In contrast, two studies on children with asthmatic symptoms showed no stronger effects of ultrafine particles than other particulate exposure [39, 40]. The present study found evidence of independent effects of fine and ultrafine particles.

The gases NO_2 and CO were highly correlated with ultrafine particles, and showed similar results as the ultrafine particles in the majority of the analyses. SO_2 was highly correlated with fine particle mass and the results corresponded more with fine particle mass. This is consistent with ultrafine particles, NO_2 and CO being emitted primarily by vehicle traffic, while only a small fraction of the SO_2 concentration originates from this source.

Limitations

The sensitivity of the results was investigated with several approaches. The elimination of single covariates did not change the effects of the pollutants essentially. Modification of the composition of the sample, excluding the participants who showed no variation in the use of the respective medication (one-half), resulted in higher effect estimates. Including smokers in the regression analysis, led to slightly reduced effects. To allow for longer time patterns of temperature, 3-day running means of temperature were included in the models, instead of daily temperature terms. The effect estimates were comparable to those presented here. The regression results of the air pollution models did not change substantially, when considering trend as a nonparametric, instead of a cubic function.

The study population was not uniform with respect to the diagnosis. This is unlikely to have introduced confounding since the participants served as their own controls in the statistical analyses. Given that the panel was heterogeneous, the association with ultrafine number concentrations and fine particle mass concentrations was checked in the subgroup of participants who had doctor-diagnosed asthma (n=37). The results showed lower effects for inhaled short-acting β_2-agonists and higher effects for inhaled corticosteroids. This might be explained by the fact that this subgroup comprised the more severely affected asthmatics, who might start using their anti-inflammatory medication more readily. The healthier participants might tend to vary their inhaled short-acting β_2-agonist use in association with higher air pollution levels. The effect of air pollution on the
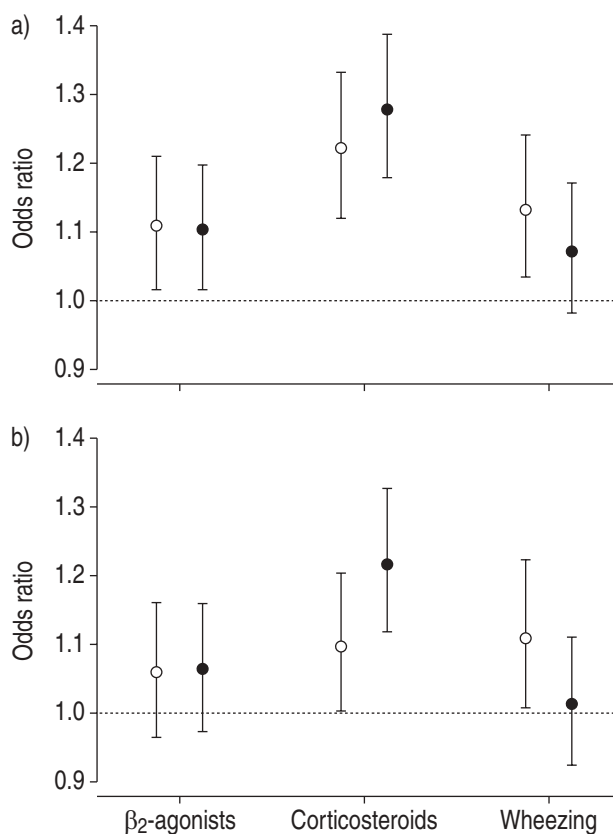
Fig. 4. – Comparison of the effect estimates of the 5-day means of fine (●) and ultrafine (○) particles in a) single and b) two-pollutant models for prevalence of inhaled short-acting β_2-agonist use, corticosteroid use and wheezing.

symptom wheezing was higher in the asthma-diagnosed participants than in the participants who had only reported asthma symptoms. The evidence on susceptibility of the asthmatics regarding air pollution is not consistent. In the PEACE study [9], children with different health conditions did not show differences in the effect of air pollution on respiratory health. On the other hand, BOEZEN et al. [41] reported higher effects of air pollution in children with elevated serum immunoglobulin E levels and bronchial hyperresponsiveness than in children without this condition. PETERS et al. [11] showed a stronger decrease in PEF in medicated than in nonmedicated children.

The incidence of short-acting β_2-agonist and corticosteroid use was analysed. Since the daily incidence rate was very low (fig. 1), no effects could be detected. The present authors conclude that the effects are a combination of prolonged and additional intake of the medication.

It was assumed that the personal exposures could be characterised using the measurements of one fixed measurement site. Since misclassification of the exposure is independent of the medication use, it is likely to be nondifferential, and therefore it may have caused an underestimation of the effect. It was assumed that at least the variation over time is comparable across the city, which has been shown for $PM_{2.5}$ and might also be true for ultrafine particles [42].

Days when persons stayed outside the city were excluded from the analyses to avoid misclassification of exposure. Sources of pollution that may have affected the individual exposure on any other day were not assessed. This could have resulted in an underestimation of the effect.

The relationship between treatment and air pollution needs to be viewed with caution, as recording of medication is not accurate. It is likely, that participants made mistakes in their regular evening recordings of medication and dosage. It appears unlikely, that this occurred in association with the pollutants, but random misclassification resulting in underestimation may have occurred.

The generalisability of the results may be restricted to Erfurt, because of the varying composition of particles caused by different sources and meteorology and due to region-dependent asthma diagnoses and treatment.

Conclusions

The results suggest that reported inhaled asthma medication use and asthma symptoms increase in association with ultrafine and fine particulate air pollution and with gaseous pollutants, such as nitrogen dioxide, in adults in Erfurt, Germany.

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