Respiratory Effects Are Associated with the Number of Ultrafine Particles

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The association between fine and ultrafine particles and respiratory health was studied in adults with a history of asthma in Erfurt, Eastern Germany. Twenty-seven nonsmoking asthmatics recorded their peak expiratory flow (PEF) and respiratory symptoms daily. The size distribution of ambient particles in the range of 0.01 to 2.5 μm was determined with an aerosol spectrometer during the winter season 1991–1992. Most of the particles (73%) were in the ultrafine fraction (smaller than 0.1 μm in diameter), whereas most of the mass (82%) was attributable to particles in the size range of 0.1 to 0.5 μm. Because these two fractions did not have similar time courses (correlation coefficient r = 0.51), a comparison of their health effects was possible. Both fractions were associated with a decrease of PEF and an increase in cough and feeling ill during the day. Health effects of the 5-d mean of the number of ultrafine particles were larger than those of the mass of the fine particles. In addition, the effects of the number of the ultrafine particles on PEF were stronger than those of particulate matter smaller than 10 μm (PM_{10}). Therefore, the present study suggests that the size distribution of ambient particles helps to elucidate the properties of ambient aerosols responsible for health effects. Peters A, Wichmann HE, Tuch T, Heinrich J, Heyder J. Respiratory effects are associated with the number of ultrafine particles. AM J RESPIR CRIT CARE MED 1997;155:1376–1383.

Acute exposure to inhalable particles has been found to be associated with adverse health effects (1–5). Particles with a diameter less than 10 μm can enter the lungs and cause injury upon deposition. Larger particles are deposited solely in the extrathoracic airways (6). The mass of particles smaller than 10 μm in aerodynamic diameter (PM_{10}) was associated with increased morbidity in patients with preexisting respiratory symptoms or lung disease, including decreased lung function (7–12), increased reporting of symptoms (7, 8, 10, 12), and increased use of medication (7, 12).

In these studies the particulate matter originated from different sources, but, nonetheless, it showed respiratory effects of similar sizes (1). Particulate matter was emitted by local steel mills in Utah Valley (10, 12) and in The Netherlands (7, 11), or was produced by local combustion of brown coal in Eastern Europe (8) or transported to Steubenville, Ohio, originating from Pittsburgh and the Ohio River Valley (9). PM_{10}, which has been most frequently examined, might serve as a surrogate for the properties of the particles responsible for the observed health effects. The acidity of the particles has been proposed to be an important factor (13). An effect of particle-strong acidity on peak expiratory flow (PEF) has been reported by Neas and colleagues (9) for Steubenville, where acidity of the particles was high. However, in the Utah Valley or in Europe, where acidity was low, adverse health effects in association with particulate air pollution have been observed as well.

In order to find a uniform explanation for the associations observed between respiratory health and particulate air pollution in various locations, the number of ultrafine particles has been recently proposed as a major factor contributing to the adverse health effects of particulate air pollution (14). Evidence for the involvement of chemically inert, very small particles in eliciting health effects comes from animal experiments. Exposure of rats to TiO_2 particles with a diameter of 0.02 μm showed strong inflammatory responses in the alveolar space (15, 16). The hypothesis that ultrafine particles are more closely associated with the observed health effects than is the mass of fine particles was tested in the present study. The effects of fine (0.01 to 2.5 μm) and ultrafine (0.01 to 0.1 μm) particles in an epidemiologic study of adults is reported.

METHODS

Data on the number concentrations of fine (0.01 to 2.5 μm) and ultrafine (0.01 to 0.1 μm) particles in ambient air were collected in Erfurt, Eastern Germany, between October 1, 1991 and March 31, 1992. Use of brown coal in private households and for central power generation was the major source of air pollution at the beginning of the 1990s. The city of Erfurt is located in a valley surrounded by the Thüringer Wald. During winter frequent inversions trap air in the valley.

Panel Study

Along with the measurements of particles, a panel study assessed the short-term effects of ambient air on the respiratory morbidity of adults with lung disease (8). Thirty-six nonsmoking adults were recruited in September 1990 from an outpatient clinic specializing in lung diseases where they had been identified as having a history of

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asthma. Five of them were excluded from the main study because of nonparticipation and unreliable data. During the winter of 1991–1992 data were available for 27 adults who were 44 to 80 yr of age in 1992, with a mean age of 60.1 yr; and 63% were women. A single lung function measurement at the beginning of the main study showed FEV_1/FVC ratios ranging from 80 to 23%, indicating a wide range of lung function impairment. Asthma medications (bronchodilators, theophylline, and/or cortisone) were used by 23 participants; 87% used these medications 95 or more of 100 person-days. Thirteen of the subjects reported allergies to house dust, pollen, animal hair, or fungal spores on a self-administered questionnaire.

The subjects kept symptom diaries and performed PEF measurements three times a day before and after medication use. The best of the three measurements was recorded each time. A detailed description on the quality control and patient surveillance is given elsewhere (8). The subjects recorded how they felt during the day and during the night on a scale of 1 to 5. Feeling bad to very bad during the daytime or at night was used to set the binary variables feeling ill during the daytime or at night equal to 1. Each of the symptoms cough, dyspnea, and phlegm was recorded as none, slight, severe, or very severe. If these symptoms were recorded as severe or very severe, then the subject was classified as having these symptoms on that day. The occurrence of asthma attacks was noted separately. The most prevalent symptom was dyspnea, which was recorded by an average of nine subjects each day. Feeling ill during the day, feeling ill during the night, cough, phlegm, and asthma attacks were recorded on average by one to two persons.

Exposure Assessment

The size distribution of ambient particles was determined with an aerosol size spectrometer consisting of two sensors covering different size ranges. In the range 0.01 to 0.3 μm, ambient particles were classified with an electrical mobility analyzer (Model 3071; TSI, St. Paul, MN) according to their volume-equivalent diameter and counted with a condensation particle counter (Model 3760; TSI). In the size range 0.1 to 2.5 μm, particles were classified by an optical particle counter (Model LAS-X; PMS, Boulder, CO): particles smaller than the wavelength of the applied laser light according to their volume-equivalent diameter; larger particles according to their cross-section illuminated by the laser beam. However, although the electrical classification is independent of the chemical properties, the optical classification is not. Therefore, the response function of the optical counter requires adjustment to the refraction index of the particles to be classified (17). For this adjustment, monodispersed particles selected from the ambient aerosol by the electrical mobility analyzer were frequently used in this study.

The measurements were taken 1 km south of the city center in Erfurt at the Institute of Hygiene. The site was located more than 40 m away from a major road. A sample flow was drawn into a mobile laboratory through a chimney with a diameter of 22 cm from a height of 4 m above the ground at an air flow of 1 m/s. Each instrument of the size spectrometer took its appropriate isokinetic sample flow from this main sample stream using specially designed inlets for each instrument. Control of the measurements, data acquisition, and evaluation were performed by a personal computer.

The aerosol spectrometer measured the particle number distribution of the ambient aerosol every 10 min; these values were aggregated into 24-h means. Assuming that all particles have a spherical shape, the number distribution can be converted into a particle–volume distribution. This was used to calculate the particle mass distribution assuming an average density of the aerosol particles. When daily total particle volume concentrations and occasional $PM_{2.5}$ measurements were compared, an apparent particle density of 1,500 kg m^{-3} could be determined for Erfurt. The derived particle mass distributions were used to calculate integral mass concentrations of particles between selected cutoff diameters; 24-h averages were obtained on 145 d (Figure 1). Missing data were due to vacation times and calibration procedures. Three discrete size ranges were chosen prior to the regression analyses in order to obtain a contrast between fractions of maximum particle number concentration and fractions of maximum particle mass concentration: 0.01 μm $\leq$ d $<$ 0.1 μm, 0.1 μm $\leq$ d $<$ 0.5 μm, 0.5 μm $\leq$ d $<$ 2.5 μm. The number concentration of particles in

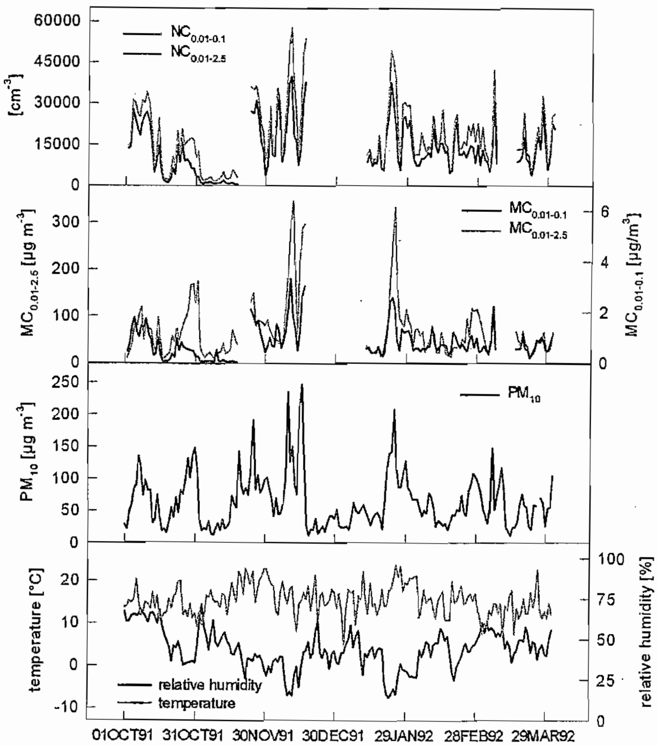

Figure 1. Time course of number and mass concentrations of particles, PM_{10} concentrations, and meteorology during the Winter 1991–1992 in Erfurt. Analyses were restricted to the time periods for which fine and ultrafine particles were measured.

these size ranges were termed: $NC_{0.01–2.5}$, $NC_{0.01–0.1}$, $NC_{0.1–0.5}$, and $NC_{0.5–2.5}$; the corresponding mass concentrations were teamed: $MC_{0.01–2.5}$, $MC_{0.01–0.1}$, $MC_{0.1–0.5}$, and $MC_{0.5–2.5}$.

In addition, the exposure to inhalable particles was characterized in the traditional way by the measurement of PM_{10} collected with a Harvard impactor (MS&T Air Sampler; Air Diagnostics & Engineering, Harrison, ME) as part of the main study at the same location. Twenty-four-hour samples were collected from 8:00 A.M. to 8:00 A.M. on the next day. Details on sampling procedures and quality control have been reported previously (18, 19).

Data Analyses

Regression models were used to estimate the association between averaged time-series of the health outcomes (Figure 2) and particulate air pollution and to simultaneously control for possible confounding by time-varying influences. Linear regression analyses were conducted for PEF measurements in the morning and in the evening before medication use. Each subject's mean PEF over the entire study period was subtracted from his or her PEF at each reporting period to obtain a deviation in PEF. The mean deviation in PEF was then calculated for all measurements contributed by the participating subjects separately for the morning and evening values. Logistic regression analyses, as proposed by Schwartz and colleagues (20) were used to analyze the prevalence of the symptoms. Each symptom (feeling ill during the daytime, feeling ill at night, cough, dyspnea, phlegm, and asthma attacks) was analyzed separately. In the initial analyses the prevalence of beta-agonist, theophylline, and cortisone use was analyzed using logistic regression models. Asthma medication was used on a regular basis by most of the subjects, and no evidence for an association between air pollution and medication use was observed.

Linear and logistic regression analyses were weighted by the number of observations of the outcome variables each day in order to adjust for fluctuation in the number of participants by day. This measure reduced the impact of a few either nonresponding or strong responding subjects and assured a more stable estimate for the whole panel.

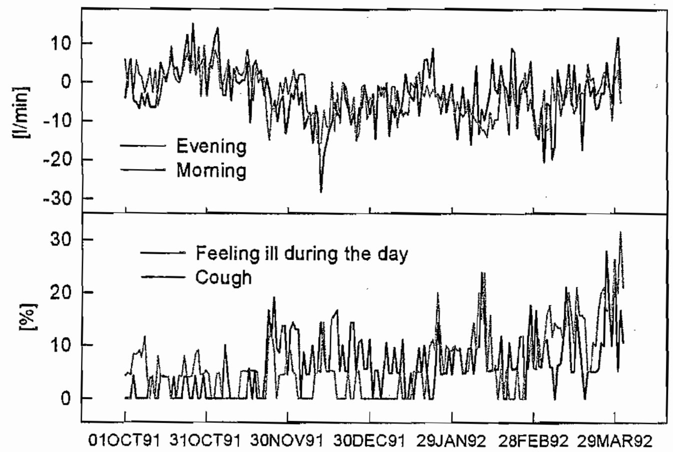

Figure 2. Deviation in PEF and prevalence of symptoms for adults with a history of asthma during the Winter 1991–1992 in Erfurt. Analyses were restricted to the time periods for which fine and ultrafine particles were measured.

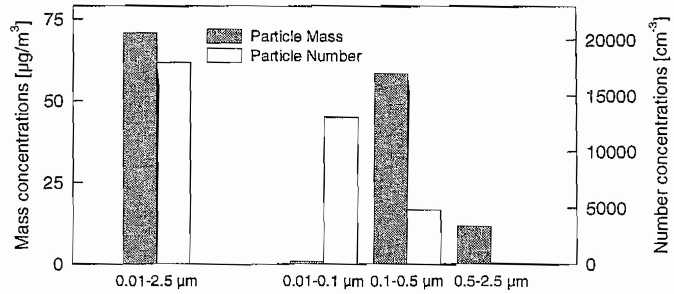

Figure 3. Mean values for particulate pollution during the Winter 1991–1992 in Erfurt.

Nonparticipation was not associated with increased levels of particulate air pollution and therefore was not likely to create a bias. Because repeated measurements were taken on each subject, an autocorrelated variance-covariance structure was considered. A first-order autocorrelation structure was detected, which reduced the observed associations between particles and PEF compared with the crude associations. Regression analyses were conducted in SAS using proc MODEL (21). Quadratic trend, quadratic temperature, relative humidity, quadratic relative humidity, and wind speed and direction were not significantly associated with PEF or symptoms and therefore were excluded. All results presented here were estimated controlling for possible confounding by 24-mean temperature, and adjusted for a linear trend and an indicator for the weekend. Low temperatures were associated with higher concentrations of air pollution in Erfurt (*see* Figure 1) and might also be related to airway responses. No evidence was found for associations of temperature on previous days (*see below*). Although the estimates for temperature did not achieve statistical significance, same-day values were included in all analyses because of their potential for confounding. A linear trend was included to control for general increases or decreases of the outcome variables. An indicator variable for the weekend was introduced to control for different habits that might affect the health outcomes. None of the covariates influenced the effect estimates of the particulate air pollution profoundly. In addition, the assumption that the associations between the health outcomes and the trend, temperature, and particulate air pollution were linear was assessed by estimating generalized additive models in Splus (22). Some evidence for a nonlinear trend was found, but no change in the effect estimates for particulate air pollution was observed. Linear modeling appeared to be reasonable both for temperature and for particulate air pollution. Another potential confounder of the association between air pollution and health outcomes is the prevalence of viral infections coinciding with air pollution episodes. The prevalence of elevated serum levels for influenza virus b were increased between January 17 and March 15 in Thüringen (Robert-Koch Institut, Berlin, personal communication). However, analyses restricted to the time period between October and December 1991 did show effect estimates similar to those reported for the whole period.

The influence of exposure to air pollution and temperature on previous days was assessed systematically with "polynomial distributed lag structures" (8, 12, 23). The data indicated that in some instances high concentrations of particulate matter on previous days were contributing to the decreases in PEF or increases in symptoms. Two and 4-d prior had then the maximal effect, but no evidence for influences of 5 d or more prior were detected. Therefore, a 5-d mean was used to summarize the cumulative impact of particulate air pollution, as has been proposed by Pope and Dockery (10). It was calculated by averaging the exposure on the current day and 4 d prior. At least three measurements had to be present in order to calculate the 5-d mean.

Three discrete fractions of the ambient aerosol (*see above*) derived from the mean number and mean mass distributions prior to regression analyses were used to estimate the impact of particulate air pollution in addition to PM_{10}. Choosing discrete fractions rather than cut-points had the advantage of avoiding a comparison between overlapping size ranges. The PM_{10} data were restricted to days on which measurements of the size distributions of the ambient particles were available. All regression coefficients were expressed as effects associated with a change in exposure for one interquartile range. The interquartile range was chosen to compare changes in the health outcomes at exposures that repeatedly occurred during the study period. Two pollutant models included jointly two of the following exposure variables: $NC_{0.01–0.1}$ as a measure of the number of particles and $MC_{0.1–0.5}$ and PM_{10} as measures of the particle mass. The two pollutant models were restricted to these exposures in order to avoid multicomparisons. Statistical significance was defined as $p < 0.05$ (two-sided); borderline significance was defined as $p < 0.10$ (two-sided).

RESULTS

Exposure to Particulate Air Pollution

The number and the mass of fine (0.01 to 2.5 µm) and ultrafine (0.01 to 0.1 µm) particles varied over time in Erfurt (Figure 1 and Table 1): 73% of the particles counted were ultrafine. However, these particles contributed 1% to the mass concentration of fine particles. 82% of the overall mass was attributable to particles in the diameter range between 0.1 and 0.5 µm. Nevertheless, these particles contributed only 27% to the number concentration of fine particles. Particles with a diameter between 0.5 µm and 2.5 µm constituted less than 0.01% of the number concentration of fine particles, but 17% of the mass of fine particles (Figure 3 and Table 1). When the mass and the number concentrations were correlated over time (Table 2), all correlation coefficients were statistically significantly different from zero ($p < 0.0001$). The number concentration of fine particles ($NC_{0.01–2.5}$) was highly correlated with the number concentration of ultrafine particles ($NC_{0.01–0.1}$). $MC_{0.1–0.5}$ showed a nearly identical time course as $MC_{0.01–2.5}$. However, $NC_{0.01–0.1}$ and $MC_{0.1–0.5}$ did not have an identical time course, which was reflected in a low correlation coefficient of 0.51. This variation of exposure over time made it possible to distinguish between the health effects associated with the particle number concentration and those health effects associated with particle mass concentration.

PM_{10} data measured with a Harvard impactor were available on 144 of the 145 d for which aerosol data had been collected. On 54 d the calculated fine mass $MC_{0.01–2.5}$ (Table 1) exceeded PM_{10}. PM_{10} did not show an identical time course

TABLE 1

CHARACTERISTICS OF AMBIENT AEROSOL BETWEEN OCTOBER 1991 AND MARCH 1992 ON 145 DAYS IN ERFURT

	Same Day (n = 145)						Five-Day Mean (n = 143)					
Particle Sizes	0%	5%	50%	95%	100%	IQR	0%	5%	50%	95%	100%	IQR
Number concentration, cm^{-3}												
$NC_{0.01-2.5}$	1,530	2,520	15,040	39,460	57,570	15,120	2,300	3,110	17,130	34,680	42,380	10,580
$NC_{0.01-0.1}$	420	920	11,230	30,780	39,650	12,000	680	1,080	12,920	25,000	28,120	9,200
$NC_{0.1-0.5}$	230	1,000	3,690	12,430	18,640	4,410	1,140	1,400	4,140	11,980	15,080	3,000
$NC_{0.5-2.5}$	5	8	34	190	279	50	8	12	37	159	197	44
Mass concentration, $\mu g\ m^{-3}$												
$MC_{0.01-2.5}$	9.1	13.3	50.8	200.3	346.9	57	15.5	21.3	53.1	203.3	267.1	50
$MC_{0.01-0.1}$	0.0	0.1	0.6	2.2	3.3	0.6	0.0	0.1	0.7	1.8	2.3	0.5
$MC_{0.1-0.5}$	7.4	11.5	44.1	166.8	289.4	47.5	13.4	18.0	44.5	169.3	224.6	39.7
$MC_{0.5-2.5}$	0.9	1.8	7.0	39.3	60.4	10.5	1.9	2.6	7.7	32.5	40.3	9.9
PM_{10}, $\mu g\ m^{-3}$	12	21	59	148	247	51	20	26	60	135	155	50

Definition of abbreviation: IQR = interquartile range.

with the counted particles, but it was strongly correlated with the mass concentrations (Table 2).

Associations Between Particles and Peak Expiratory Flow

Elevated levels of fine and ultrafine particle pollution were associated with small, but consistent, decreases in PEF (Table 3). Analyses were adjusted for a linear trend, mean daily temperature, and weekend. None of the covariates achieved borderline significance. Decreases in PEF in association with particulate air pollution on the same day were observed for the ultrafine and fine particles, but only the estimates for $MC_{0.01-0.1}$ and $MC_{0.01-2.5}$ achieved statistical significance. Concurrent values of PM_{10} were not associated with decreases in lung function. Evidence for a cumulative effect of the exposure to ultrafine particles and PM_{10} on PEF in the evening was found in polynomial distributed lag structures. For $NC_{0.01-0.1}$ and PM_{10}, a quadratic polynomial fitted the data best, with a maximum of 2 to 3 d prior to the decreases in PEF. Five-day means of the exposure quantified the association between health outcomes and cumulative exposure, including the last 4 d. Twofold to threefold larger effect estimates for the 5-d mean than for the same-day values of $NC_{0.01-0.1}$, $MC_{0.01-0.1}$, and $NC_{0.01-2.5}$ were calculated and therefore supported the temporal association determined by polynomial distributed lag structures. In addition, statistically significant effect estimates were observed for the 5-d means of $MC_{0.01-2.5}$, $MC_{0.1-0.5}$, $MC_{0.5-2.5}$, $NC_{0.1-0.5}$, and PM_{10}.

Estimates for the association between measures of particles on the same day and the lung function measurement on the next morning were slightly smaller than in the evening before (Table 3). The air pollution concentrations on the previous day were used in regression analyses of the PEF in the morning to assure that the exposure preceded the measurement of the health outcome. A negative trend over time and lower values on the weekends were predicted for the PEF in the morning. Statistically significant associations between particulate air pollution on the previous day and PEF in the morning were observed for the ultrafine particles ($NC_{0.01-0.1}$, $MC_{0.01-0.1}$, and $NC_{0.01-2.5}$), the fine particles ($MC_{0.1-0.5}$, $MC_{0.1-0.5}$, and $MC_{0.01-2.5}$), and PM_{10}. Only particles larger than 0.5 μm ($MC_{0.5-2.5}$ and $NC_{0.5-2.5}$) were not strongly associated with decreases in lung function. Some evidence for a cumulative impact of air pollution on the PEF in the morning was observed for ultrafine particles; nearly twofold larger estimates for 5-d means of $NC_{0.01-0.1}$, $MC_{0.01-0.1}$, and $NC_{0.01-2.5}$ were calculated compared with the estimates for the same day.

The number of ultrafine particles ($NC_{0.01-0.1}$) and the mass of fine particles ($MC_{0.1-0.5}$) were chosen as representatives to compare the effects of the number and the mass of the particles in two pollutant models (Table 5). In addition, two pollutant models were calculated to compare the effect sizes between $NC_{0.01-0.1}$ and PM_{10}, whereas a comparison of $MC_{0.1-0.5}$ with PM_{10} would have suffered from the impact of collinearity between the two measures of particulate mass given the correlation coefficient of 0.83 (Table 2). Strong evidence was found for an association between the 5-d mean of $NC_{0.01-0.1}$ and PEF in the evening and also in the morning. This association

TABLE 2

PEARSON'S CORRELATION COEFFICIENTS FOR THE DIFFERENT FRACTIONS OF PARTICLES

	$NC_{0.01-2.5}$	$NC_{0.01-0.1}$	$NC_{0.1-0.5}$	$NC_{0.5-2.5}$	$MC_{0.01-2.5}$	$MC_{0.01-0.1}$	$MC_{0.1-0.5}$	$MC_{0.5-2.5}$	PM_{10}
$NC_{0.01-2.5}$	1.00	0.96*	0.76	0.57	0.70	0.96	0.71	0.60	0.73
$NC_{0.01-0.1}$		1.00	0.56	0.38	0.51	0.93	0.51	0.42	0.60
$NC_{0.1-0.5}$			1.00	0.84	0.95	0.73	0.95	0.84	0.81
$NC_{0.5-2.5}$				1.00	0.93	0.57	0.90	0.99	0.82
$MC_{0.01-2.5}$					1.00	0.72	1.00	0.94	0.84
$MC_{0.01-0.1}$						1.00	0.72	0.61	0.71
$MC_{0.1-0.5}$							1.00	0.91	0.83
$MC_{0.5-2.5}$								1.00	0.84
PM_{10}									1.00

* The underlined coefficients give the correlation between the number of the ultrafine particles $NC_{0.01-0.1}$ and all other fractions (*see* Figure 3).

TABLE 3

ASSOCIATIONS BETWEEN PARTICULATE AIR POLLUTION AND PEAK EXPIRATORY FLOW*

	Evening Peak Expiratory Flow (*L/min*)				Morning Peak Expiratory Flow (*L/min*)			
	Same-day		Five-day Mean		Previous day		Five-day Mean	
Particle Size	Beta	CI	Beta	CI	Beta	CI	Beta	CI
$NC_{0.01–2.5}$	−1.49	−3.32 to 0.33	−3.58	−5.28 to −1.89	−1.42	−2.61 to −0.23	−2.38	−3.61 to −1.14
$NC_{0.01–0.1}$	−1.37	−3.13 to 0.39	−4.04	−6.06 to −2.01	−1.20	−2.39 to −0.01	−2.55	−3.95 to −1.14
$NC_{0.1–0.5}$	−1.49	−3.11 to 0.13	−2.24	−3.93 to −0.55	−1.14	−2.23 to −0.05	−1.57	−2.76 to −0.38
$NC_{0.5–2.5}$	−1.03	−2.42 to 0.35	−1.35	−3.10 to 0.41	−0.65	−1.56 to 0.25	−0.73	−1.97 to 0.51
$MC_{0.01–2.5}$	−1.38	−2.78 to 0.01	−2.18	−3.80 to −0.57	−1.01	−1.92 to −0.11	−1.42	−2.57 to −0.28
$MC_{0.01–0.1}$	−1.42	−2.73 to −0.11	−3.90	−5.60 to −2.21	−1.21	−2.13 to −0.30	−2.29	−3.45 to −1.12
$MC_{0.1–0.5}$	−1.40	−2.80 to 0.00	−2.13	−3.67 to −0.59	−1.05	−1.96 to −0.14	−1.44	−2.53 to −0.36
$MC_{0.5–2.5}$	−1.17	−2.57 to 0.24	−2.02	−3.89 to −0.14	−0.78	−1.69 to 0.13	−1.02	−2.36 to 0.32
PM_{10}	−0.37	−1.83 to 1.08	−2.31	−4.54 to −0.08	−1.30	−2.36 to −0.24	−1.51	−3.20 to 0.19

* The mean effect (beta) and 95% confidence intervals (CI) refer to increase in particle concentrations by one interquartile range (*see* Table 1).

proved to be stronger than the associations observed for 5-d means of $MC_{0.1–0.5}$ and PM_{10}.

Associations Between Particles and Respiratory Symptoms

Associations between exposure to particles and symptoms were observed for feeling ill during the day and cough. In contrast, no associations were found between exposure to particulate air pollution on the previous days and feeling ill during the night. In addition, the prevalence of the respiratory symptoms phlegm and dyspnea and asthma attacks were not predicted by increased levels of particulates on the same day. No evidence for an association with particulate air pollution on prior days were found for feeling ill during the night, phlegm, dyspnea, and asthma attacks. Therefore, the results presented here have been restricted to the estimates for the symptoms feeling ill during the day and cough.

A linear increase in the prevalence of feeling ill during the day was detected during the winter of 1991–1992. The prevalence of feeling ill during the day increased in association with all measures of particulate air pollution on the same day, and the odds ratios had similar sizes (Table 4). Odds ratios for feeling ill during the day were larger for the 5-d means of $NC_{0.01–0.1}$ and PM_{10} than the odds ratios for $NC_{0.01–0.1}$ and PM_{10} on the same day. The cumulative association for PM_{10} was supported by a second order polynomial with a maximum of 2 d prior, which fitted best for PM_{10}. However, none of the lag structures for $NC_{0.01–0.1}$ achieved statistical significance. Two pollutant models were not able to distinguish between the contribution of prolonged exposure to PM_{10} and $NC_{0.01–0.1}$ (Table 5) and attributed the increases in prevalence of feeling ill during the day to both measures of particulate matter.

A linear increase in the prevalence of cough was detected during the winter of 1991–1992. Weak associations between particulate air pollution on the same day and the prevalence of cough were observed for the number of ultrafine particles ($NC_{0.01–0.1}$, $NC_{0.01–2.5}$), but the estimate for $MC_{0.01–0.1}$ achieved statistical significance. Fine particles ($MC_{0.1–0.5}$, and $MC_{0.01–2.5}$) were associated with increases in cough, of which $MC_{0.01–2.5}$ was the best predictor. The symptom cough showed the strongest associations with particles larger than 0.5 μm ($MC_{0.5–2.5}$ and $NC_{0.5–2.5}$) and PM_{10}. The increases of the prevalence of cough were best predicted by concurrent exposure to PM_{10}. However, an association between a 5-d mean of $NC_{0.01–0.1}$ and cough was confirmed by two pollutant models being stronger than the associations between cough and 5-d means of PM_{10} or $MC_{0.1–0.5}$.

DISCUSSION

Decreases in PEF and increased reporting of feeling ill during the day and of cough were associated with the number concentration and the mass concentration of the fine and ultrafine

TABLE 4

ASSOCIATIONS BETWEEN PARTICULATE AIR POLLUTION AND RESPIRATORY SYMPTOMS*

	Feeling Ill during the Day				Cough			
	Same-day		Five-day Mean		Same-day		Five-day Mean	
Particle Size	OR	CI	OR	CI	OR	CI	OR	CI
$NC_{0.01–2.5}$	1.29	1.05 to 1.58	1.39	1.15 to 1.68	1.16	0.97 to 1.38	1.17	1.01 to 1.37
$NC_{0.01–0.1}$	1.21	0.98 to 1.50	1.44	1.15 to 1.81	1.12	0.95 to 1.33	1.26	1.06 to 1.50
$NC_{0.1–0.5}$	1.27	1.08 to 1.50	1.23	1.07 to 1.42	1.13	0.98 to 1.30	1.03	0.91 to 1.16
$NC_{0.5–2.5}$	1.23	1.07 to 1.14	1.20	1.04 to 1.39	1.24	1.11 to 1.38	1.06	0.93 to 1.20
$MC_{0.01–2.5}$	1.24	1.09 to 1.41	1.21	1.06 to 1.38	1.19	1.07 to 1.33	1.02	0.91 to 1.15
$MC_{0.01–0.1}$	1.22	1.05 to 1.41	1.33	1.12 to 1.58	1.13	1.00 to 1.28	1.13	0.98 to 1.30
$MC_{0.1–0.5}$	1.23	1.09 to 1.40	1.19	1.05 to 1.35	1.18	1.06 to 1.31	1.02	0.91 to 1.14
$MC_{0.5–2.5}$	1.27	1.11 to 1.46	1.25	1.06 to 1.46	1.24	1.10 to 1.39	1.05	0.92 to 1.21
PM_{10}	1.20	1.01 to 1.44	1.47	1.16 to 1.86	1.32	1.16 to 1.50	1.30	1.09 to 1.55

* The odds ratios (OR) and 95% confidence intervals (CI) refer to increase in particle concentrations by one interquartile range (*see* Table 1).

TABLE 5
TWO POLLUTANT MODELS*

Particle Size†	Evening Peak Expiratory Flow (*L/min*) Same-day Beta	CI	Five-day Mean Beta	CI	Morning Peak Expiratory Flow (*L/min*) Previous day Beta	CI	Five-day Mean Beta	CI
$NC_{0.01-0.1}$	−0.40	−1.89 to 1.09	−4.25	−7.14 to −1.36	−0.60	−1.59 to 0.39	−2.74	−4.85 to −0.63
$MC_{0.1-0.5}$	−1.27	−2.78 to 0.25	−0.91	−2.55 to 0.73	−0.81	−1.80 to 0.17	−0.65	−1.84 to 0.55
$NC_{0.01-0.1}$	−0.86	−2.87 to 1.14	−3.70	−6.12 to −1.27	−1.05	−2.24 to 0.15	−2.56	−4.34 to −0.78
PM_{10}	−0.53	−2.38 to 1.32	−0.36	−3.35 to 2.62	−0.62	−1.96 to 0.72	0.02	−2.17 to 2.21
	Feeling Ill During the Day				**Cough**			
	Same-day OR	CI	Five-day Mean OR	CI	Previous day OR	CI	Five-day Mean OR	CI
$NC_{0.01-0.1}$	1.06	0.83 to 1.35	1.29	0.97 to 1.72	1.05	0.87 to 1.27	1.36	1.10 to 1.67
$MC_{0.1-0.5}$	1.24	1.03 to 1.50	1.12	0.94 to 1.34	1.11	0.95 to 1.30	0.93	0.80 to 1.07
$NC_{0.01-0.1}$	1.17	0.91 to 1.50	1.25	0.93 to 1.68	0.98	0.80 to 1.19	1.22	0.97 to 1.52
PM_{10}	1.13	0.92 to 1.39	1.27	0.93 to 1.73	1.20	1.07 to 1.34	1.06	0.83 to 1.35

* The regression coefficients (beta) and 95% confidence intervals (CI) refer to increase in particle concentrations by one interquartile range (*see* Table 1).
† Air pollutants listed underneath each other were analyzed jointly in the regression analyses.

particles. As the number and the mass of the particles characterize different properties of the aerosol in the atmosphere, the goal of the analyses presented here was to distinguish between their contribution to the health effects. The overall number of fine particles ($NC_{0.01-2.5}$) was dominated by the number of ultrafine particles ($NC_{0.01-0.1}$), whereas most of the particle mass ($MC_{0.01-2.5}$) was found among particles between 0.1 and 0.5 μm ($MC_{0.1-0.5}$). Because $NC_{0.01-0.1}$ and $MC_{0.1-0.5}$ were not highly correlated over time, it was possible to distinguish between their contribution to the observed health effects.

The aerosol spectrometer combined two particle-counting devices with different physical principles. In the size range between 0.1 and 0.3 μm both devices counted particles. The laser spectrometer (LAS-X) was calibrated frequently with ambient particles to assure the validity of the combined spectra (17). Therefore, differences in the time course of $NC_{0.01-0.1}$ and $MC_{0.1-0.5}$ appear to be attributable to different properties of the aerosol rather than to different measurement techniques for fine and ultrafine particles. Given the high correlation between the fractions of particles and the small differences observed between the effect estimates, the following criteria were applied in order to possibly attribute the health effects observed to either $NC_{0.01-0.1}$ or $MC_{0.1-0.5}$. (*1*) Fractions that were highly correlated with $NC_{0.01-0.1}$ (such as $NC_{0.01-2.5}$ and $MC_{0.01-0.1}$) or $MC_{0.1-0.5}$ (such as $NC_{0.1-0.5}$, $MC_{0.01-2.5}$) had to show effect estimates of similar magnitude, variability, and lagstructure. (*2*) Either $NC_{0.01-0.1}$ or $MC_{0.1-0.5}$ had to be more closely associated with the effects in two pollutant models.

The largest decreases in PEF were observed for 5-d means of $NC_{0.01-0.1}$ both for the lung function measurement in the morning and in the evening. The importance of $NC_{0.01-0.1}$ is supported by considering the decreases in PEF in the evening presented in Table 3 for the 5-d means in light of the correlation coefficients between all other fractions and $NC_{0.01-0.1}$ shown in Table 2. It appears that the "observed health effects" are the stronger the closer this correlation is (Figure 4), and it suggests that all other associations observed might be spurious and only caused by the correlation with the number of ultrafine particles. Two pollutant models confirmed that the decreases in PEF were most closely associated with 5-d means of $NC_{0.01-0.1}$ (Table 5).

Levels of PM_{10} and sulfate concentrations of fine particles were moderate in Erfurt at the beginning of the 1990s (only seven values exceeded 150 μg/m³) (18, 19). PM_{10} and $MC_{0.01-2.5}$ showed a similar time course, but $MC_{0.01-2.5}$ exceeded PM_{10} occasionally. However, a later comparison between $MC_{0.01-2.5}$ and $PM_{2.5}$ measurements with a Harvard impactor in Erfurt in 1995 achieved similar results (r = 0.98). Therefore, the disagreement between the PM_{10} and the $MC_{0.01-2.5}$ data might reflect a larger variability in the PM_{10} measurements than in the $PM_{2.5}$ measurements.

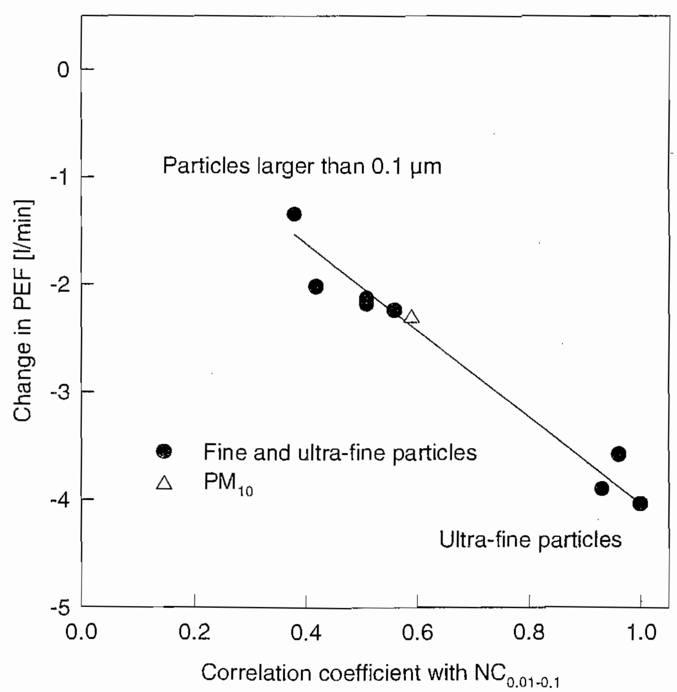

Figure 4. Changes in peak expiratory flow (PEF), as given in Table 3, by correlation between all fractions and the number of ultrafine particles ($NC_{0.01-0.1}$).

The health effects associated with the number of the ultrafine particles were compared with effect estimates derived for PM_{10} to ensure the comparability of the results to previously published health effects of particulate matter. Although $NC_{0.01-0.1}$ predicted decreases in PEF in the evening better than did PM_{10}, both showed effect estimates of similar size for feeling ill during the day. The prevalence of cough was more closely associated with same-day concentrations of PM_{10} than of $NC_{0.01-0.1}$. However, the five-day means of $NC_{0.01-0.1}$ predicted increases in cough better than PM_{10}. Therefore, the results obtained in the analyses presented here are consistent with results for PM_{10} reported in previous studies (1–5).

Because the exposure of the panelists was quantified by a single outdoor monitor only, the individual exposure might be overestimated or underestimated. In addition, the panelists spent on average only 2.3 h per day outside during the winter of 1991–1992. Little data on indoor/outdoor ratios are available for particles below 1 μm. Thatcher and Layton (24) were able to show that for submicron particles (0.3 to 1 μm) in absence of indoor sources such as smoking or gas stoves the indoor/outdoor ratio was one for a Californian house without air conditioning. The panelists spent only 2.0 h outdoors on days when the 5-d mean of PM_{10} exceeded 100 $\mu g/m^3$. Although the participants changed their behavior slightly on the more polluted days, given the high agreement between indoor and outdoor concentrations (24), it appears to be unlikely that a bias was present. However, nondifferential misclassification of the exposure is likely to bias the effect estimates towards the null.

The panel of adults with a history of asthma included patients with a wide range of disease severity. Given the small sample size, it was not possible to identify a subgroup of strongly responding subjects and attribute this characteristic to the severity of their disease. The decrease in lung function and the increase of feeling ill during the day might be caused by an inflammation as a response to the intrapulmonary deposition of ultrafine particles, as has been hypothesized recently by Seaton and colleagues (14). Exposure of rats to high doses of ultrafine TiO_2 particles with a diameter of 0.02 μm was associated with increased numbers of polymorphonuclear neutrophils and alveolar macrophages as well as to increased protein content in the lavage fluid of the lungs 24 h after exposure (15). Drastic effects of ultrafine particles have been observed when rats were exposed to ultrafine particles of 0.7 to 1.0 10^6 cm^{-3} generated from Teflon. The exposed animals died of acute hemorrhagic pulmonary inflammation after 10 to 30 min. This phenomena might be caused by an extreme load of ultrafine particles rather than by degradation products of polytetrafluoroethylen (25).

In a prospective cohort study, the Harvard Six City Study, Dockery and colleagues (26) showed that the effects of air pollution on mortality were associated to a similar extent with fine particles ($PM_{2.5}$) (odds ratio: 1.27; 95% confidence interval: 1.08 to 1.48) and PM_{10} (odds ratio: 1.26; 95% confidence interval: 1.08 to 1.47) when comparing the most to the least polluted city. However, graphic examination revealed stronger associations for $PM_{2.5}$ than for PM_{10}. The association between mortality and annual mean levels of fine particles was confirmed by an analysis of Pope and colleagues (27) in a report of prospectively collected data from 51 cities.

The chemical composition of the particles might be an additional factor to consider in order to identify the responsible agent. Results from a recent study in The Netherlands (7) indicated that the concentrations of iron in the particulate matter might be independently associated with increased respiratory symptoms and medication use. The aerosol in the atmosphere of Erfurt originated from combustion of brown coal in a local power plant as well as in domestic heating. However, data on the chemical composition of the particles were not available. Particle-strong acidity was usually below the detection limit probably because of neutralization by high concentrations of ammonia in the air (18) and thus can be ruled out as an alternative explanation (8).

The data presented here suggest that the size distribution of ambient particles helps to elucidate the properties of ambient aerosols responsible for the health effects. Furthermore, the chemical composition of particles should be analyzed in order to understand the underlying mechanisms leading to adverse health effects. Future research considering the particle size distribution and the chemical composition of particles might be crucial to develop efficient strategies to reduce the effects of air pollution exposure on the population.

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References

1. Dockery, D. W., and C. A. Pope. 1994. Acute respiratory effects of particulate air pollution. *Annu. Rev. Public Health* 15:107–132.
2. Pope, C. A., D. V. Bates, and M. E. Raizenne. 1995. Health effects of particulate air pollution: time for reassessment? *Environ. Health Perspect.* 103:472–480.
3. Pope, C. A., D. W. Dockery, and J. Schwartz. 1995. Review of epidemiological evidence of health effects of particulate air pollution. *Inhal. Toxicol.* 7:1–18.
4. Brunekreef, B., D. W. Dockery, and M. Krzyzanowski. 1995. Epidemiologic studies on short-term effects of low levels of major ambient air pollution components. *Environ. Health Perspect.* 103:3–13.
5. Bascom, R., P. A. Bromberg, D. A. Costa, R. Devlin, D. W. Dockery, M. W. Frampton, W. Lambert, J. M. Samet, F. E. Speizer, and M. Utell. 1996. Health effects of outdoor air pollution. *Am. J. Respir. Crit. Care Med.* 153:3–50.
6. Heyder, J., J. Gebhart, G. Rudolf, C. Schiller, and W. Stahlhofen. 1986. Deposition of particles in the human respiratory tract in the size range 0.005 to 15 μm. *J. Aerosol Sci.* 17:811–825.
7. Dusseldorp, A., H. Kruize, B. Brunekreef, P. Hofschreuder, G. de Meer, and A. B. van Oudvorst. 1995. Associations of PM10 and airborne iron with respiratory health of adults living near a steel factory. *Am. J. Respir. Crit. Care Med.* 152:1932–1939.
8. Peters, A., I. F. Goldstein, U. Beyer, K. Franke, J. Heinrich, D. W. Dockery, J. D. Spengler, and H. E. Wichmann. 1996. Acute health effects of exposure to high levels of air pollutants in Eastern Europe. *Am. J. Epidemiol.* 144: 570–581.
9. Neas, L. M., D. W. Dockery, P. Koutrakis, D. J. Tollerud, and F. E. Speizer. 1995. The Association of ambient air pollution with twice daily peak expiratory flow rate measurements in children. *Am. J. Epidemiol.* 141:111–122.
10. Pope, C. A., and D. W. Dockery. 1992. Acute health effects of PM10 pollution on symptomatic and asymptomatic children. *Am. Rev. Respir. Dis.* 145:1123–1128.
11. Roemer, W., G. Hoek, and B. Brunekreef. 1993. Effect of ambient winter air pollution on respiratory health of children with chronic respiratory symptoms. *Am. Rev. Respir. Dis.* 147:118–124.
12. Pope, C. A., D. W. Dockery, J. D. Spengler, and M. E. Raizenne. 1991. Respiratory health and PM10 pollution: a daily time series analysis. *Am. Rev. Respir. Dis.* 144:668–674.
13. Report of the ATS Workshop on the Health Effects of Atmospheric Acids and Their Precursors. 1991. *Am. Rev. Respir. Dis.* 144:464–467.
14. Seaton, A., W. MacNee, K. Donaldson, and D. Godden. 1995. Particulate air pollution and acute health effects. *Lancet* 345:176–178.
15. Oberdörster, G., J. Ferin, R. Gelein, S. C. Sonderholm, and J. Finkelstein. 1992. Role of the alveolar macrophage during lung injury: studies with ultra-fine particles. *Environ. Health Perspect.* 97:193–199.
16. Oberdörster, G., J. Ferin, and B. E. Lehnert. 1994. Correlation between particle size, *in vivo* particle persistence and lung injury. *Environ. Health Perspect.* 102:173–177.
17. Brand, P., J. Gebhart, M. Below, B. Georgi, and J. Heyder. 1991. Characterisation of environmental aerosol on Helgoland and Island. *Atmos. Environ.* 25A:581–585.

18. Brauer, M., T. S. Dumyahn, J. D. Spengler, K. Gutschmidt, J. Heinrich, and H. E. Wichmmnn. 1995. Measurement of acidic aerosol species in Eastern Europe: implications for air pollution epidemiology. *Environ. Health Perspect.* 103:482–488.
19. Cyrys, J., K. Gutschmidt, M. Brauer, T. S. Dumyahn, J. Heinrich, J. D. Spengler, and H. E. Wichmann. 1995. Determination of acidic sulfate aerosols in urban atmospheres in Erfurt (FRG) and Sokolov (former CSSR). *Atmos. Environ. Pt. B-Urban* 29:3545–3557.
20. Schwartz, J., D. Wypij, D. Dockery, J. Ware, S. Zeger, J. Spengler, and B. J. Ferris. 1991. Daily diaries of respiratory symptoms and air pollution: methodological issues and results. *Environ. Health Perspect.* 90: 181–187.
21. SAS Institute. 1988. The MODEL procedure. In SAS/ETS User's Guide, 6th ed. SAS Institute Inc. Cary, NC. 315–398.
22. Chamber, J. M., and T. J. Hastie. 1993. Statistical Models in S. Chapman & Hall, New York.
23. Almon, S. 1965. The distributed lag between capital appropriations and expenditures. *Econometrica* 33:178–196.
24. Thatcher, T. L., and D. W. Layton. 1995. Deposition, resuspension and penetration of particles within a residence. *Atmos. Environ.* 29:1487–1497.
25. Oberdörster, G., R. M. Gelein, J. Ferin, and B. Weiss. 1995. Association of particulate air pollution and acute mortality: involvement of ultrafine particles? *Inhal. Toxicol.* 7:111–124.
26. Dockery, D. W., A. C. Pope, X. Xu, J. D. Spengler, J. H. Ware, M. E. Fay, B. G. Ferris, and F. E. Speizer. 1993. An association between air pollution and mortality in six U.S. cities. *N. Engl. J. Med.* 329:1753–1759.
27. Pope, A. C., M. J. Thun, M. N. Namboodiri, D. W. Dockery, J. S. Evans, F. E. Speizer, and C. W. Heath. 1995. Particulate air pollution as predictor of mortality in a prospective study of U.S. adults. *Am. J. Respir. Crit. Care Med.* 151:669–674.