Journal of Exposure Science and Environmental Epidemiology (2007) 17, 458–467

www.nature.com/jes

Daily mortality and particulate matter in different size classes in Erfurt, Germany

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The link between elevated concentrations of ambient particulate matter (PM) and increased mortality has been investigated in numerous studies. Here we analyzed the role of different particle size fractions with respect to total and cardio-respiratory mortality in Erfurt, Germany, between 1995 and 2001. Number concentrations (NC) of PM were measured using an aerosol spectrometer consisting of a Differential Mobility Particle Sizer and a Laser Aerosol Spectrometer to characterize particles between 0.01 and 0.5 and between 0.1 and 2.5 μm, respectively. We derived daily means of particle NC for ultrafine (0.01–0.1 μm) and for fine particles (0.01–2.5 μm). Assuming spherical particles of a constant density, we estimated the mass concentrations (MC) of particles in these size ranges. Concurrently, data on daily total and cardio-respiratory death counts were obtained from local health authorities. The data were analyzed using Poisson Generalized Additive Models adjusting for trend, seasonality, influenza epidemics, day of the week, and meteorology using smooth functions or indicator variables. We found statistically significant associations between elevated ultrafine particle (UFP; diameter: 0.01–0.1 μm) NC and total as well as cardio-respiratory mortality, each with a 4 days lag. The relative mortality risk (RR) for a 9748 cm^{-3} increase in UFP NC was RR = 1.029 and its 95% confidence interval (CI) = 1.003–1.055 for total mortality. For cardio-respiratory mortality we found: RR = 1.031, 95% CI: 1.003–1.060. No association between fine particle MC and mortality was found.
This study shows that UFP, representing fresh combustion particles, may be an important component of urban air pollution associated with health effects.
Journal of Exposure Science and Environmental Epidemiology (2007) **17,** 458–467; doi:10.1038/sj.jes.7500538; published online 15 November 2006

Keywords: *mortality, particulate matter, ultrafine particles, cardiovascular mortality, cardio-respiratory mortality.*

Introduction

Elevated concentrations of particulate matter (PM) have been linked with increased acute mortality worldwide (Pope and Dockery, 1999; Samet et al., 2000; Katsouyanni et al., 2001; Health Effects Institute, 2003). Evidence suggests that increased PM concentrations mainly affect the cardiovascular and respiratory systems (Peters et al., 1997a, 1999, 2000, 2001; Gold et al., 2000; Ibald-Mulli et al., 2001; Brook et al., 2002; Devlin et al., 2003; Schulz et al., 2005) and are especially associated with increased cardiovascular hospital admissions (Schwartz, 1999; Zanobetti et al., 2000; Le Tertre et al., 2002; D'Ippoliti et al., 2003; von Klot et al., 2005; Dominici et al., 2006) or increased cardiovascular mortality (Clancy et al., 2002; Forastiere et al., 2005; Zeka et al., 2005; Ostro et al., 2006).

The physical or chemical particle properties (e.g. size, elemental composition, or organic content) leading to the observed adverse short-term health effects are unknown at present. Evidence suggests that the observed adverse health effects correlate specifically with smaller diameter particles ($PM_{2.5}$, aerodynamic particle size ≤ 2.5 μm) (Schwartz et al., 1996). Hypotheses about a possible role of ultrafine particles (UFP, particle size below 100 nm) have been established (Oberdörster et al., 1995; Seaton et al., 1995; Utell and Frampton, 2000; Donaldson et al., 2001).

Recently, adverse health effects were reported for elevated particle number concentrations (NC) in the ultrafine range (Wichmann and Peters, 2000; Ibald-Mulli et al., 2002) including a decrease in peak expiratory flow (PEF) (Pekkanen et al., 1997; Peters et al., 1997b; Penttinen et al., 2001), increases in medication use of asthmatics (von Klot et al., 2002), increases in blood markers (Rückerl et al., 2006), repolarization changes in ischemic heart disease patients (Henneberger et al., 2005), increased hospital

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Received 2 June 2006; accepted 4 October 2006; published online 15 November 2006

cardiac readmissions in myocardial infarction survivors (von Klot et al., 2005) and an increase in out-of-hospital coronary deaths (Forastiere et al., 2005). Associations of mortality with UFPs have been reported to be of approximately the same magnitude per interquartile range as with $PM_{2.5}$ but independent of the $PM_{2.5}$ associations in a 3-year study (Wichmann et al., 2000, reanalyzed by Stölzel et al., 2003).

The aim of the present analysis was to evaluate the role of several particle size fractions ranging from 0.01 to 2.5 μm with respect to total and cardio-respiratory mortality for an extended period of observation and using a somewhat different modeling strategy as in the previous study (Wichmann et al., 2000; Stölzel et al., 2003).

Methods

Study Area

The study was conducted in Erfurt, the capital of the state of Thuringia in Germany. It has a population of approximately 200,000.

Air Pollution Data

Particulate air pollution was sampled at a site around 1 km south of the city center and 40 m west from the nearest major road. Measurements from this site have been shown to be representative of the air quality within Erfurt with respect to sulfate and PM_{10} (Cyrys et al., 1998). The measurements reported here were conducted during a 6-year period, from September 1995 to August 2001.

Size-specific particle NC were measured by an Aerosol Spectrometer described elsewhere (Brand et al., 1992; Tuch et al., 1997; Wichmann et al., 2000). This aerosol spectrometer consisted of two devices: a Differential Mobility Particle Sizer (DMPS) which measured particles in the size range from 0.01 to 0.5 μm and a Laser Aerosol Spectrometer (LAS-X) which covered the size range from 0.1 to 2.5 μm. The upper DMPS channels measuring particles between 0.1 and 0.5 μm were used for the mobility calibration of the LAS-X (Wichmann et al., 2000).

Partial and total NC were calculated from each spectrum. Daily means of NC were computed for several size ranges x to y μm (designated as $NC_{x\text{-}y}$, e.g. $NC_{0.01–0.03}$ stands for the UFP NC in the size range from 0.01 to 0.03 μm). An apparent mean density of 1.53 g/cm^3 of ambient aerosol was estimated based on 700 simultaneous measurements of total particle number and $PM_{2.5}$ particle mass (Tuch et al., 2000). Daily mass concentrations (MC) were calculated for each size range x to y μm (designated as $MC_{x\text{-}y}$) assuming spherical particles of the observed mean density (Wichmann et al., 2000). $MC_{0.01–2.5}$ is therefore a close approximate of $PM_{2.5}$. Note that the geometric diameter of 2.5 μm measured with the LAS-X corresponds to an aerodynamic diameter of 3.1 μm of the Erfurt ambient aerosol; therefore the $MC_{0.01–2.5}$ range exceeds slightly beyond $PM_{2.5}$.

In addition, PM_{10} and $PM_{2.5}$ were collected on Harvard Impactors. Samples were collected for 24 h from 23:00 to 11:00 before 6 October 1999 and from midnight to midnight thereafter.

Missing values in the $NC_{0.01–0.1}$, $MC_{0.01–2.5}$ and the PM_{10} Harvard Impactor time series were imputed using concurrent measurements of the UFP NC by a Scanning Mobility Particle Sizer (SMPS) at the same site, concurrent Harvard impactor $PM_{2.5}$ measurements at the same site, or concurrent Total Suspended Particles or PM_{10} measurements obtained from a state-run surveillance station located 2 km away from our measurement station, respectively. The imputations were carried out using linear regression in Generalized Additive Models (GAM, Hastie and Tibshirani, 1990) including a smooth function of time to account for temporal variations in the relationship between the different measurement devices. At the end of the time series the imputations were carried out using simple linear regressions, as the smooth functions tended to fray there. The coefficients of determination (r^2) of the GAMs or the linear regressions used for the imputations were 0.94 for $NC_{0.01–0.1}$ (GAM), 0.75 for $MC_{0.01–2.5}$ between 09/01/1995 and 10/06/1999 (GAM), 0.88 for $MC_{0.01–2.5}$ between 10/07/1999 and 08/14/2001 (GAM), 0.90 for $MC_{0.01–2.5}$ from 08/15/2001 onwards (linear regression), 0.72 for PM_{10} until 09/14/95 (linear regression), 0.76 for PM_{10} between 09/15/1995 and 12/31/2000, and 0.92 for PM_{10} from 01/01/2001 onwards (GAM). Altogether, 42 $NC_{0.01–0.1}$, 203 $MC_{0.01–2.5}$, and 214 PM_{10} values were imputed, that is, at most 10% of the scheduled measurements. The gap in the $NC_{0.01–0.1}$ time series between April and June 2000 was due to malfunction of the aerosol spectrometer and could not be imputed because the SMPS measurements started only in 2001.

Daily means of NO, NO_2, and CO concentrations were obtained from a state-run network monitoring station located 2 km away from the GSF monitoring station. Nitrogen oxide concentrations (NO and NO_2) were measured by means of a NO/NO_X monitor AC31 M (Environment SA) based on the principle of chemiluminescence. CO concentrations were measured according to the principle of infrared light absorption.

Meteorological Data

Daily means of air temperature (T) and relative humidity (RH) were obtained from a site of the German Meteorological Service located at the airport 5 km west of the measurement station.

Mortality Data

Copies of death certificates without the name and address of the deceased were obtained from the local health authorities to comply with the rules of the German data privacy law. Infant (below 1 year) and non-natural deaths (ICD-9 (International Classification of Disease, 9th revision) codes

≥800 and ICD-10 (International Classification of Disease, 10th revision) codes ≥S00, respectively) were excluded. Data collection methods and quality control mechanisms have been described previously (Wichmann et al., 2000). ICD-9 codes 390-459, 460-519, 785 and 786 and ICD-10 codes I00-I99, J00-J99, R00-R06 and R09 were considered as cardio-respiratory causes of death. If one of these ICD codes was specified at least once on the death certificate as immediate, primary, or contributing cause of death, then the death was classified as cardio-respiratory. We defined a death as owing to a cardiovascular cause when a cardiovascular cause of death (ICD-9: 390–459, 785; ICD-10: I00-I99, R00-R03, R09) was given as primary, underlying or contributing cause of death. It was classified as purely cardiovascular if in addition no respiratory cause of death (ICD-9: 460–519, 786; ICD-10: J00-J99, R04-R06, R09) was mentioned on the death certificate. We chose this approach as it was detected that the order of the causes of death on the death certificates had often been mis-specified (Wichmann et al., 2000).

Influenza Data

Data on influenza epidemics were obtained from the "Arbeitsgemeinschaft Influenza" (German Influenza Working Group, AGI, 2003). They consist of a weekly doctor's practice index (PI) for each winter season (October to April) indicating the relative deviation of the number of doctor visits owing to acute respiratory symptoms in comparison to a background level averaged for whole Germany.

Statistical Analysis

The daily total and cardio-respiratory mortality counts were regressed on the mean daily particulate concentration in Poisson regression models. Model building was carried out in a similar way as in the APHEA II study (Touloumi et al., 2004). We fitted trend, season, major influenza epidemics, air temperature, and RH by smooth functions in a GAM. These terms were included step-by-step into the model. Models were compared based on Akaike's Information Criterion (AIC). Model building was carried out without air pollution variables in the model. Only terms with plausible dose–response relationships were selected, for example, we assumed *a priori* a positive association of the doctor's PI indicating the severity of an influenza epidemic and mortality. For air temperature and RH, the lag with the best AIC was selected out of lags 0 to 2. In the last step of model building, negative autocorrelation of the residuals was minimized by decreasing the number of degrees of freedom for the smooth function of time.

We controlled for long-term trend and season using a penalized spline where the number of degrees of freedom were chosen to minimize the autocorrelation of the residuals (altogether 8 degrees of freedom for total mortality and 7 for cardio-respiratory mortality).

The doctor's PI indicating the severity of the influenza epidemics for a particular winter season was only included if it improved the model fit in terms of a smaller AIC. As the influenza epidemics may reach their peaks in Erfurt at another time than in whole Germany, shifts of up to plus or minus 3 weeks were tested. The epidemics in the winters 1995/96, 1998/99, 1999/00, and 2000/01 turned out to improve the model fit for total mortality, the epidemics in winters 1995/96, 1997/98, 1998/99, and 1999/2000 for cardio-respiratory mortality. They were controlled for by penalized splines with approximately 3 degrees of freedom or they were included as linear predictors depending on the AIC.

We also controlled for temperature at lags 0 and 1 and humidity effects lagged 2 days using penalized splines. The lags and the smoothing parameters were chosen to minimize the AIC. Indicators for Sundays were included in the model to account for calendar effects. Indicators for public holidays did not improve the model fit.

The associations between daily mortality counts and pollutant concentrations were computed for lags of up to 5 days. Cumulative effects were investigated by polynomial distributed lag models (Pope and Schwartz, 1996; Schwartz, 2000). First, we fitted a polynomial of third degree for lags 0 to 5. If a negative weight for lag 0 or lag 5 was determined we also fitted a polynomial omitting this lag.

A number of sensitivity analyses were performed to test the robustness of the final model with respect to changes in the modelling of the confounders.

All computations were carried out using the statistical software package R version 1.8.1 (R Development Core Team, 2003).

Results

Air Pollution Levels and Mortality Data

Table 1 summarizes particle NC and particle MC in several size ranges as well as meteorological parameters and mortality counts. About 90% of the scheduled aerosol spectrometer data were available. The 0.01–0.03 μm size range ($NC_{0.01–0.03}$) accounted for about two-thirds of the total UFP NC ($NC_{0.01–0.1}$), the 0.1–0.5 μm size range ($MC_{0.1–0.5}$) for more than 75% of the total MC below 2.5 μm ($MC_{0.01–2.5}$). The calculated fine particle MC ($MC_{0.01–2.5}$) and the $PM_{2.5}$ concentration measured by a Harvard Impactor were in good agreement (Spearman correlation coefficient: 0.78). The air pollution situation in Erfurt during the study period was characterized by moderate levels of PM.

The peak concentrations of fine particle MC and UFP NC occurred in winter (Figure 1). The magnitude of the winter peaks of particle MCs declined during the study period. This behavior was less pronounced for UFP NCs.

Table 1. Descriptive statistics for particle number and particle mass concentrations, meteorological parameters, and mortality counts in Erfurt, Germany, from 1 September 1995 to 31 August 2001.

	N	Available (%)	*N* miss	Mean	SD	5%	25%	50%	75%	95%
$NC_{0.01–0.03}$ (cm^{-3})	1958	89.3	234	9016	5926	2532	4706	7415	11574	21327
$NC_{0.03–0.05}$ (cm^{-3})	1958	89.3	234	2801	2105	852	1414	2092	3502	6870
$NC_{0.05–0.1}$ (cm^{-3})	1958	89.3	234	1731	1344	510	882	1329	2147	4202
$NC_{0.01–0.1}$ (cm^{-3})	1958	89.3	234	13549	8853	4198	7238	11015	17104	31681
$NC_{0.01–0.1}$ (cm^{-3})[a]	2000	91.2	192	13491	8789	4212	7282	10977	17030	31253
$MC_{0.1–0.5}$ ($\mu g/m^3$)	1958	89.3	234	17.6	14.8	4.5	8.4	13.3	21.5	47.3
$MC_{0.01–2.5}$ ($\mu g/m^3$)	1958	89.3	234	22.7	19.7	5.8	10.5	16.4	27.7	62.7
$MC_{0.01–2.5}$ ($\mu g/m^3$)[a]	2161	98.6	31	22.3	19.2	5.9	10.5	16.3	27.3	62.2
$PM_{2.5}$ HI[b] ($\mu g/m^3$)	1994	91.0	198	21.7	17.6	5.7	10.5	16.4	26.8	56.8
PM_{10} HI[b] ($\mu g/m^3$)	1976	90.1	216	32.3	23.3	9.2	16.7	26.6	40.5	81.1
PM_{10} HI[b] ($\mu g/m^3$)[a]	2190	99.9	2	31.9	23.2	9.4	16.5	26.0	39.5	79.9
NO ($\mu g/m^3$)	2131	97.2	61	20.5	26.1	4.1	7.0	11.6	21.7	71.6
NO_2 ($\mu g/m^3$)	2154	98.3	38	32.4	13.2	12.9	23.3	31.0	40.5	55.8
CO (mg/m^3)	2187	99.8	5	0.47	0.39	0.12	0.23	0.35	0.57	1.23
Temperature (°C)	2190	99.9	2	8.4	7.6	4.7	2.8	9.0	14.6	19.8
Relative humidity (%)	2190	99.9	2	80	11	60	74	82	89	96
Daily total mortality	2192	100	0	4.9	2.3	2	3	5	6	9
Daily cardio-respiratory mortality	2192	100	0	3.9	2.0	1	2	4	5	7

[a]Imputed time series.
[b]Harvard Impactor.

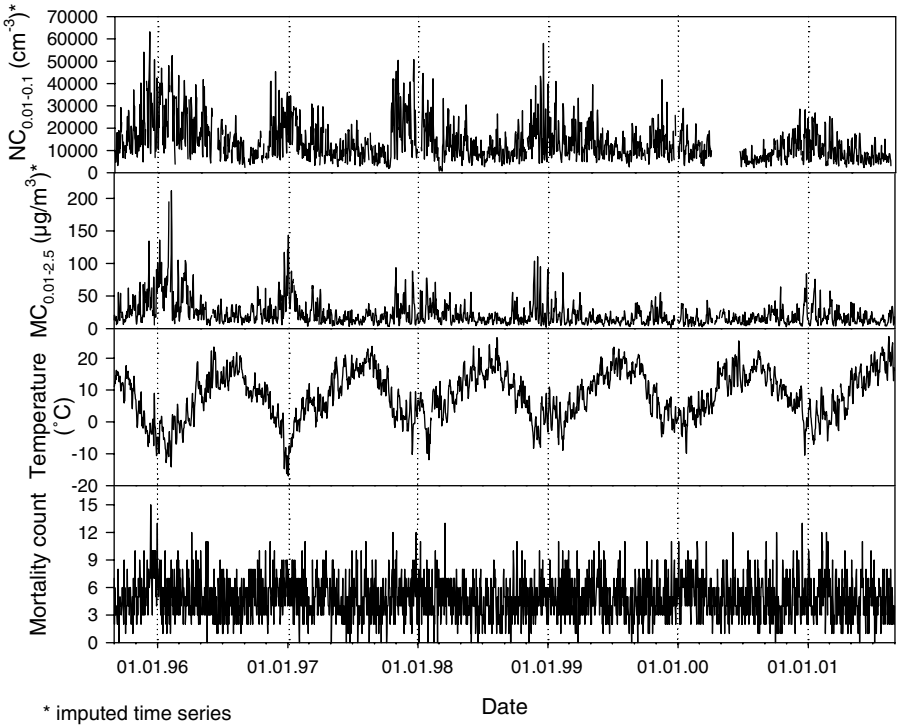

Figure 1. Time series of UFP NC, fine particle MC, temperature, and mortality counts in Erfurt, Germany, from 1 September 1995 to 31 August 2001.

NO, NO_2, and CO exhibit a similar yearly pattern as the particulate pollutants with peaks in winter. Similar as for UFP NC, the magnitude of the winter peaks declined during the study period (data not shown).

The negative correlations between temperature and the pollutants show that the pollutant concentrations in winter were in general higher than in summer (Table 2). The particle NC between the different ultrafine size ranges were highly

Table 2. Spearman correlation coefficients between particle number and particle mass concentrations and meteorological parameters in Erfurt, Germany, from 1 September 1995 to 31 August 2001.

	$NC_{0.03–0.05}$	$NC_{0.05–0.1}$	$NC_{0.01.01}$[a]	$MC_{0.1–0.5}$	$MC_{0.01–2.5}$[a]	PM_{10}[a]	NO	NO_2	CO	Temperature	Relative humidity	
$NC_{0.01–0.03}$	*0.86*	*0.71*	*0.98*	0.44	0.42	0.48	0.63	0.61	0.50	−0.41	0.12	$NC_{0.01–0.03}$
$NC_{0.03–0.05}$		*0.93*	*0.94*	0.62	0.60	0.66	0.67	0.66	0.62	−0.35	0.06	$NC_{0.03–0.05}$
$NC_{0.05–0.1}$			*0.83*	*0.75*	*0.73*	*0.74*	0.61	0.64	0.60	−0.26	0.04	$NC_{0.05–0.1}$
$NC_{0.01–0.01}$[a]				0.54	0.51	0.56	0.66	0.65	0.57	−0.40	0.11	$NC_{0.01–0.01}$[a]
$MC_{0.1–0.5}$					*0.99*	*0.85*	0.52	0.60	0.58	−0.30	0.21	$MC_{0.1–0.5}$
$MC_{0.01–2.5}$[a]						*0.84*	0.51	0.58	0.57	−0.28	0.23	$MC_{0.01–2.5}$[a]
PM_{10}[a]							0.54	0.62	0.50	−0.15	0.10	PM_{10}[a]
NO								*0.84*	*0.70*	−0.35	0.32	NO
NO_2									*0.71*	−0.31	0.21	NO_2
CO										−0.57	0.36	CO
Temperature											−0.54	Temperature

[a]Imputed time series.
Italic: Spearman correlation >0.7.

correlated. The fine particle MC ($MC_{0.01–2.5}$) had a variation nearly identical with the MC in the size range from 0.1 to 0.5 μm ($MC_{0.1–0.5}$). Both parameters were also highly correlated with $PM_{2.5}$ and PM_{10} measured by Harvard Impactors. Ultrafine NC and fine MC were moderately correlated (Table 2). The gaseous pollutants were highly correlated with each other. They were moderately correlated with UFP NC in different size ranges with CO exhibiting the smallest correlation coefficients. The gaseous pollutants were also moderately correlated with $MC_{0.01–2.5}$ and PM_{10}.

During the study period, 10,762 death certificates were collected which met the inclusion criteria, on average 4.9 per day. 8561 of them were classified as cardio-respiratory (3.9 per day), that is, on their death certificate at least one cardiovascular or respiratory cause of death was mentioned as primary, underlying, or contributing cause of death.

Associations with Mortality

The regression results point at an increase of daily mortality counts in association with UFP NC (Table 3a and b) for both total and cardio-respiratory mortality. The highest relative risk was observed consistently for lag 4 throughout all UFP size fractions. With the exception of $NC_{0.05–0.1}$ the observed associations were statistically significant. In polynomial distributed lag models a statistically significant cumulative association of lags 0–4 was observed for $NC_{0.01–0.1}$ and $NC_{0.01–0.03}$ and an at least borderline significant association of lags 0–5 for the other two size fractions for total mortality. Lags 0 and 4 always had the largest weights. For cardio-respiratory mortality, always lags 0 to 5 were combined and a similar pattern as for total mortality was found, again with lags 0 and 4 carrying the largest weights.

No significant association was observed for particle mass measures, neither with total mortality nor with cardio-respiratory mortality (Table 3c and d).

When regressing cardiovascular mortality on the UFP NC in different size classes (0.01–0.03 μm and 0.01–0.1 μm, respectively) with a lag of 4 days we found slightly higher relative risk estimates (Figure 2). They were slightly larger for cardiovascular only mortality.

Results suggest an immediate although nonsignificant association between UFP NC and respiratory mortality (any mention of ICD-9: 460–519, 786; ICD-10: J00-J99, R04-R06, R09 on the death certificate) occurring at lags 0 (relative risk (RR) per IQR: 1.050, 95% confidence interval (CI): −0.981; 1.123) and 1 (RR per IQR: 1.053, 95% CI: 0.986; 1.124). For $MC_{0.01–2.5}$ and PM_{10}, no pronounced pattern could be detected.

The gaseous pollutants NO, NO_2, and CO were not significantly associated with total mortality (Table 3e). The strongest associations were observed at lag 3 for NO and NO_2 and at lags 2 and 4 for CO. When we adjusted for gaseous pollutants in two-pollutant models the risk estimates for total mortality in association with $NC_{0.01–0.1}$ increased slightly (Figure 3).

We performed a number of sensitivity analyses (Table 4). The results were stable when the imputed values in the $NC_{0.01–0.1}$ time series (lag 4 days) were omitted, when a dummy variable for each day of the week was included instead of using the indicator variable for Sundays only, when the same temperature model as in the previous 3-year study (Wichmann et al., 2000) was used, or when deaths in those suburbs were excluded which were incorporated into the city of Erfurt only in 1994 and which are usually situated outside the basin where air pollution concentrations are highest. Doubling the number of degrees of freedom in the spline, which adjusted for trend and seasonality decreased the risk estimate slightly, but introduced also much negative residual autocorrelation indicating overfitting of the model. When we adjusted for temperature at lag 4 days (same lag where the strongest UFP effects were seen) we observed a

Table 3. Relative risks of mortality and 95% confidence intervals (in parentheses) for an increase of several pollutants over their interquartile ranges in Erfurt, Germany, 1 September 1995 to 31 August 2001.

(a) Number concentrations of ultrafine particles and total mortality

Lag	$NC_{0.01–0.1}$[a]	$NC_{0.01–0.03}$	$NC_{0.03–0.05}$	$NC_{0.05–0.1}$
0	1.020 (0.993; 1.049)	1.023 (0.995; 1.053)	1.015 (0.990; 1.040)	1.014 (0.990; 1.038)
1	1.001 (0.975; 1.029)	0.999 (0.972; 1.027)	1.008 (0.984; 1.032)	1.009 (0.987; 1.032)
2	0.997 (0.972; 1.023)	0.989 (0.962; 1.016)	1.005 (0.982; 1.029)	1.011 (0.989; 1.033)
3	1.012 (0.986; 1.038)	1.012 (0.985; 1.039)	1.012 (0.990; 1.035)	1.008 (0.986; 1.029)
4	1.029 (1.003; 1.055)*	1.028 (1.002; 1.056)*	1.026 (1.004; 1.049)*	1.019 (0.998; 1.041)
5	1.006 (0.981; 1.032)	1.005 (0.979; 1.032)	1.006 (0.983; 1.028)	1.002 (0.981; 1.023)
pdl[b]	1.042 (1.014; 1.070)*	1.046 (1.017; 1.075)*	1.034 (1.005; 1.064)*	1.026 (0.999; 1.055)*

(b) Number concentrations of ultrafine particles and cardio-respiratory mortality

Lag	$NC_{0.01–0.1}$[a]	$NC_{0.01–0.0.03}$	$NC_{0.03–0.05}$	$NC_{0.05–0.1}$
0	1.015 (0.985; 1.047)	1.021 (0.990; 1.053)	1.006 (0.979; 1.034)	1.007 (0.981; 1.033)
1	0.992 (0.963; 1.021)	0.988 (0.958; 1.018)	0.998 (0.972; 1.025)	1.006 (0.982; 1.032)
2	0.992 (0.964; 1.021)	0.983 (0.954; 1.012)	1.000 (0.975; 1.026)	1.011 (0.987; 1.035)
3	1.007 (0.979; 1.036)	1.006 (0.977; 1.036)	1.009 (0.984; 1.035)	1.007 (0.984; 1.031)
4	1.031 (1.003; 1.060)*	1.030 (1.001; 1.060)*	1.028 (1.003; 1.053)*	1.021 (0.998; 1.044)
5	1.009 (0.981; 1.037)	1.010 (0.981; 1.039)	1.007 (0.983; 1.033)	1.002 (0.979; 1.026)
pdl[c]	1.030 (0.999; 1.062)	1.038 (1.012; 1.064)*	1.028 (1.002; 1.054)*	1.023 (0.994; 1.053)

(c) Mass concentration of particles and total mortality

Lag	$MC_{0.01–2.5}$[a]	$MC_{0.1–0.5}$	PM_{10}[a]
0	1.007 (0.985; 1.030)	1.010 (0.986; 1.034)	1.004 (0.980; 1.029)
1	1.005 (0.984; 1.026)	1.006 (0.983; 1.029)	1.004 (0.981; 1.027)
2	1.003 (0.983; 1.023)	1.007 (0.985; 1.029)	0.998 (0.976; 1.021)
3	0.989 (0.970; 1.009)	0.994 (0.973; 1.016)	0.984 (0.962; 1.006)
4	1.002 (0.982; 1.022)	1.002 (0.981; 1.023)	0.993 (0.972; 1.015)
5	0.998 (0.979; 1.018)	0.997 (0.976; 1.018)	0.990 (0.969; 1.012)

(d) Mass concentration of particles and cardio-respiratory mortality

Lag	$MC_{0.01–2.5}$[a]	$MC_{0.1–0.5}$	PM_{10}[a]
0	1.001 (0.977; 1.026)	1.004 (0.977; 1.031)	1.007 (0.981; 1.034)
1	0.999 (0.976; 1.022)	1.004 (0.979; 1.029)	1.006 (0.981; 1.032)
2	0.998 (0.976; 1.021)	1.001 (0.978; 1.026)	0.996 (0.971; 1.021)
3	0.985 (0.964; 1.007)	0.991 (0.967; 1.014)	0.977 (0.953; 1.002)
4	1.001 (0.980; 1.022)	1.000 (0.977; 1.023)	0.994 (0.970; 1.018)
5	1.003 (0.981; 1.024)	1.000 (0.976; 1.023)	0.993 (0.969; 1.017)

(e) Gaseous pollutants and total mortality

Lag	NO	NO_2	CO
0	1.000 (0.988; 1.012)	0.992 (0.962; 1.024)	1.000 (0.977; 1.023)
1	0.996 (0.985; 1.008)	1.007 (0.979; 1.035)	1.002 (0.980; 1.024)
2	1.002 (0.991; 1.014)	1.002 (0.975; 1.030)	1.013 (0.991; 1.035)
3	1.006 (0.994; 1.017)	1.012 (0.985; 1.040)	1.007 (0.986; 1.029)
4	1.004 (0.992; 1.015)	1.007 (0.980; 1.035)	1.012 (0.990; 1.034)
5	0.996 (0.984; 1.008)	0.994 (0.967; 1.021)	0.995 (0.974; 1.017)

[a]Imputed time series.
[b]Polynomial distributed lag model, combines lags 0 to 4 for $NC_{0.01–0.03}$ and $NC_{0.01–0.1}$ and lags 0–5 for $NC_{0.03–0.05}$ and $NC_{0.05–0.1}$.
[c]Polynomial distributed lag model, combines lags 0 to 5 for all size ranges.
*Statistically significant: $P<0.05$.

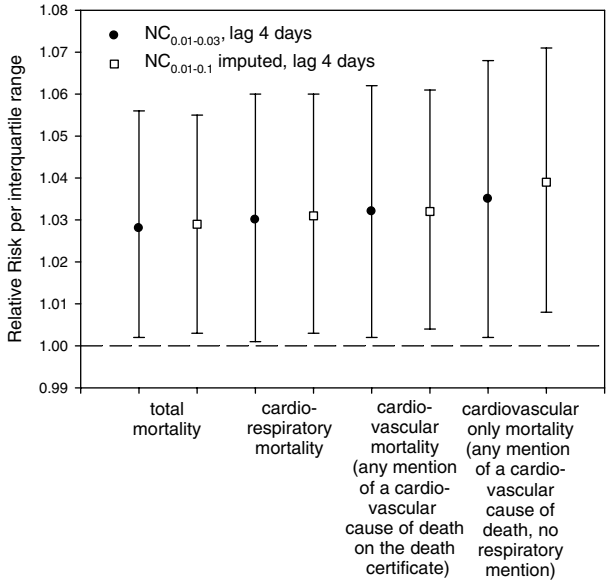

Figure 2. Relative risk estimates for different causes of death in Erfurt, Germany, September 1995 to August 2001.

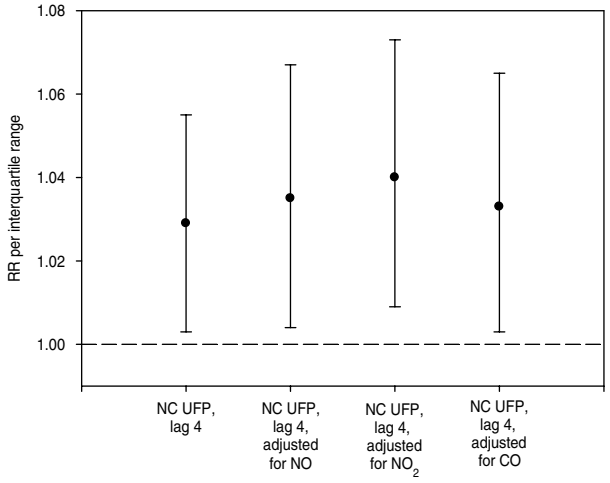

Figure 3. Relative risk estimates for UFP NC, adjusted for gaseous pollutants in two-pollutant models. Erfurt, Germany, September 1995 to August 2001.

slightly smaller, borderline significant RR of 1.025 (95% CI: 0.999; 1.052) for UFP NC.

Discussion

The association between PM and all-cause mortality has been consistently observed (Pope and Dockery, 1999; Samet et al., 2000; Katsouyanni et al., 2001; Health Effects Institute, 2003). A $10\,\mu g/m^3$ increase in the concentration of PM_{10} was associated with an increase in mortality by 0.27% in the US (Dominici et al., 2002) or by 0.6% in Europe (Katsouyanni et al., 2002), respectively. Wichmann et al. (2000) also found an association of mortality in Erfurt with several measures of PM including UFP counts for the period from 1995 to 1998. A $12{,}690\,cm^{-3}$ increase in the UFP NC was associated with an increase in mortality by 4.5% at lag 4 days, whereas a $19.9\,\mu g/m^3$ increase in the $PM_{2.5}$ concentration was associated with 3.0% more daily deaths (same day). The aim of the present study was to determine associations of particles from different size classes with mortality for an extended study period of additional 3 years using an alternative modeling approach.

Table 4. Sensitivity of the relative risk estimates for UFP number concentration, lag 4 days, with respect to model choice.

Type of model	RR per IQR (95% CI)
Original model (7 d.f. for trend)	1.029 (1.003; 1.055)
Exclude imputed values	1.029 (1.004; 1.056)
Indicator for all days of the week instead of Sunday indicator	1.032 (1.004; 1.059)
14 d.f. for trend (more than in original model)	1.023 (0.997; 1.050)
Temperature model as in Wichmann et al. (2000) with more df than the present model	1.032 (1.005; 1.059)
Include only deaths in old city limits	1.031 (1.004; 1.059)
Adjustment for temperature, lag 4 days	1.025 (0.999; 1.052)

The results are given as relative risks per interquartile range.

The highest association between ultrafine number counts and daily mortality was again observed with a lag of 4 days. The magnitude of this association (RR = 1.029 for a $9748\,cm^{-3}$ increase in UFP NC [$NC_{0.01-0.1}$]) was somewhat smaller than in the previous study with data only for the time period between 1995 and 1998 (Wichmann et al., 2000; Stölzel et al., 2003). In the present study an alternative modeling approach was used. Model building was carried out according to the principles of the APHEA study (Touloumi et al., 2004). The confounders were smoothed using penalized splines instead of loess smoothers as were applied by Wichmann et al., 2000 and Stölzel et al., 2003. This was carried out owing to recent concerns about biased estimates of the standard errors when using loess smoothers in the statistical software package S-plus in the presence of concurvity (Ramsay et al., 2003).

Additional sensitivity analyses indicated that our final model seemed to be conservative and stable with respect to the choice of the modeling parameters. Two pollutant models suggested that the observed association of UFP NC with mortality was not confounded by NO, NO_2, or CO. Other studies noted that NO_2 might serve as a surrogate of other unmeasured pollutants like UFP (Samoli et al., 2006).

In contrast to the previous study (Wichmann et al., 2000), no association of fine particle mass with mortality or cause-specific mortality was observed in the present study. There is the possibility that the properties of the particles have changed during the study period owing to measures

improving air quality. For example, the proportion of homes heated by stoves using coal decreased between 1996 and 2001 from 35% to 5%, whereas the proportion of homes heated by central heating increased from 33% to 51%. After the German unification, also the old car fleet was gradually replaced by vehicles with comparatively modern engine technology. The proportion of cars in Erfurt equipped with three-way catalysts increased during the study period from 78% to 96%.

The RR for total mortality for a $10\,\mu g/m^3$ increase in $MC_{0.01-2.5}$ (same day) in the present study was 1.004 and therefore within the 95% confidence limits of the PM_{10} risk estimate of the APHEA study which was 1.006 (95% CI: 1.004,1.008, Katsouyanni et al., 2002). The risk estimates for PM_{10} are positive only at lags 0 and 1 as also observed in a number of other studies (Dominici et al., 2002; Katsouyanni et al., 2002).

One natural limitation of this study is the relatively small size of the city of Erfurt leading to less than five natural deaths per day on average. Nevertheless, the results are internally consistent and agree qualitatively with those from a previous study over a shorter time period (Wichmann et al., 2000; Stölzel et al., 2003) with respect to UFP despite a slightly different modeling strategy. In the present study the confidence limits for the relative risk estimates are slightly smaller owing to the larger amount of data consisting of 10,762 natural cases.

There might be some uncertainty concerning the classification of the deaths as cardio-respiratory or cardiovascular. A nosologic expert opinion of a randomly selected subset of 200 death certificates revealed that the doctors who filled in the death certificates frequently tended to get the required order of immediate, primary, and contributing causes of death wrong. Much less errors were made regarding the recorded causes of death (Wichmann et al., 2000). That is why we decided to discard the placement of this information and to classify a deceased as cardio-respiratory if a cardio-respiratory ICD code was given at least once on the death certificate, that is, either as immediate, primary, or contributing cause of death. Cardiovascular mortality was defined accordingly. Therefore, we may have overestimated the share of the cardio-respiratory or cardiovascular mortality with respect to total mortality. We also included symptoms of the cardio-respiratory system (ICD-9: 785–786, ICD-10: R00-R06, R09). Most often they are mentioned together with other ICD-codes indicating cardio-respiratory causes of death. Only a marginal proportion (0.57%) of all cardio-respiratory deaths were assigned to this group based only on these codes.

In contrast, ICD-9 code 798 and the corresponding ICD-10 codes R95-R99 (sudden death) were not included. Those causes were recorded only 25 times (0.23% of all natural cases), six of which were classified as cardio-respiratory because other cardio-respiratory ICD-codes were given in addition. The remaining 19 cases were classified as ''other'' as we had no further indication of a cardio-respiratory cause of death and we considered the likelihood high that other causes might have been indeed responsible.

According to our classification criteria, around 80% of all natural deaths are due to cardio-respiratory causes. The correlation between cardio-respiratory and total mortality is 0.89. This may explain the equality of the risk estimates for total and cardio-respiratory mortality in the present study, although many studies of this type usually observe higher risk estimates for respiratory or cardiovascular mortality than for total mortality (e.g. Dominici et al., 2005). This was also observed in the previous study in Erfurt during a shorter study period, especially for respiratory diseases (Wichmann et al., 2000). However, when we restricted the analysis to cardiovascular only cases the relative risk estimate was also somewhat increased. So we conclude that the observed increase in mortality in association with UFPs seems to be due to an increase in cardiovascular mortality. In this respect we observed a similar behavior of UFPs as has been reported in many studies focusing on larger particles (Clancy et al., 2002; Zeka et al., 2005; Ostro et al., 2006).

Yet this analysis demonstrates the robustness of our models as the results of both approaches (total and cardio-respiratory mortality) are quite similar despite different confounder models. Owing to the small number of cases we were not able to look at more specific causes of death using the Poisson regression approach.

The use of a single monitoring site for the whole city of Erfurt may pose a limitation of this study. However, this site has been demonstrated to be representative for the air quality within the city of Erfurt with respect to PM_{10} and sulfate (Cyrys et al., 1998). Because UFP are mostly produced by local traffic, a greater spatial heterogeneity could be expected. However, concurrent measurements of UFP NC at different sites within one city often showed good correlations despite differing magnitudes and suggest that a background site might well represent the exposure of the average population with respect to UFP if the site is carefully chosen (Buzorius et al., 1999; Aalto et al., 2005). Furthermore, the area of the city of Erfurt is small measuring 10 km from north to south and 6 km from east to west. About 90% of the inhabitants live within a rectangular area of 5 km by 3 km. Our measurement site was also located in this area. In a sensitivity analysis we showed that the risk estimate for UFP NC did not decrease when we excluded deaths occurring in communities outside the basin in which the majority of the population of Erfurt lives. The relatively small aerial size of the city may reduce the exposure error of UFPs. As in other time series studies we use ambient PM measured at a central monitoring site as a surrogate for exposure to ''PM of ambient origin'', not as a surrogate for total PM exposure. In an analysis of exposure error in epidemiological community time series studies, Zeger et al. (2000) point out that exposures to non-ambient PM will not bias effect estimates

calculated using ambient concentrations (as a surrogate for ambient exposures) provided that ambient concentrations and the corresponding exposures to non-ambient PM are independent. As indicated by Ebelt et al. (2005), the two parameters may be considered independent as the correlation coefficient between the ambient concentrations of $PM_{2.5}$ and personal exposure to non-ambient $PM_{2.5}$ was -0.1.

There is evidence linking fine and UFPs to cardiovascular effects. High levels of ambient PM were reported to be associated with decreased heart rate variability, arterial vasoconstriction, augmented systolic blood pressure, increased plasma viscosity, and cardiac arrhythmias (Brook et al., 2002; Schulz et al., 2005). Through these possible pathways air pollution may lead to increased hospital admissions and mortality.

A number of hypotheses speculating about potential pathways how UFP can impact the human body have been postulated (Donaldson et al., 2001; Frampton, 2001; Kreyling et al., 2004): (a) UFP are biologically more reactive than larger-size particles, (b) UFP at the same MC have a much higher NC and surface area than larger particles (Oberdörster, 2001), (c) inhaled UFP have a very high deposition efficiency in the pulmonary region (International Commission on Radiological Protection, 1994), (d) UFP have a high propensity to penetrate the epithelium and reach interstitial sites. All these features may contribute to the adverse health effects of UFP observed in humans. Especially pathway (d), the translocation of UFP through the epithelium into the interstice, is expected to take some time thus providing a possible explanation for the delayed effects observed in this study. Some other epidemiological studies also showed delayed effects of UFP. In a study with persons with asthma, the cumulative effect of UFP over 5 days on decreases of the PEF was strongest (Peters et al., 1997b). Medication use in asthmatics also increased in association with the cumulative exposure to UFP over 5 or even 14 days (von Klot et al., 2002). Rückerl et al. (2006) observe the highest increases in some blood markers in patients with coronary heart disease at a lag of 48 to 71 h. However, other studies observed immediate associations of UFP on mortality or morbidity, respectively (Forastiere et al., 2005; von Klot et al., 2005).

In conclusion, this study shows that elevated levels of ambient UFP were associated with increased mortality and that UFP seem to contribute notably to the observed adverse health effects of air pollution.

Acknowledgements

The Focus-Network on Aerosols and Health coordinates and focuses all GSF research on health effects and the characterization of aerosols. It comprises research projects of the GSF Institutes of Ecological Chemistry, Epidemiology, Inhalation Biology, Radiation Protection, and Toxicology at GSF. This study was in parts supported by the Health Effects Institute (Boston, MA, USA), an organization jointly funded by the US Environmental Protection Agency (EPA) (Assistance Agreement R82811201) and automotive manufacturers. The contents of this article do not necessarily reflect the views and policies of EPA, or motor vehicle and engine manufacturers. A. Peters and H.-E. Wichmann were in parts supported by the Rochester Particle Center funded by the National Center for Environmental Research (NCER) STAR Program of the US EPA, Grant R827354.

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