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The effect of particle size on cardiovascular disorders — The smaller the worse

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ABSTRACT

Background: Previous studies observed associations between airborne particles and cardio-vascular disease. Questions, however, remain as to which size of the inhalable particles (coarse, fine, or ultrafine) exerts the most significant impact on health.
Methods: For this retrospective study, data of the total number of 23,741 emergency service calls, registered between February 2002 and January 2003 in the City of Leipzig, were analysed, identifying 5326 as being related to cardiovascular incidences. Simultaneous particle exposure was determined for the particle sizes classes <100 nm (UFP), <2.5 µm (PM2.5) and <10 µm (PM10). We used a time resolution of 1 day for both parameters, emergency calls and exposure.
Results: Within the group of cardiovascular diseases, the diagnostic category of hypertensive crisis showed a significant association with particle exposure. The significant effect on hypertensive crisis was found for particles with a size of <100 nm in diameter and starting with a lag of 2 days after exposure. No consistent influence could be observed for PM2.5 and PM10. The Odds Ratios on hypertensive crisis were significant for the particle size <100 nm in diameter from day 2 post exposure OR = 1.06 (95%CI: 1.02–1.10, p = 0.002) up to day 7 OR = 1.05 (95%CI 1.02–1.09, p = 0.005).
Conclusion: Ultrafine particles affect cardiovascular disease adversely, particularly hypertensive crises. Their effect is significant compared with PM2.5 and PM10. It appears necessary, from a public health point of view, to consider regulating this type of particles using appropriate measurands as particle number.

1. Introduction

Evidence has accumulated that airborne particulate matter affects human health. Many epidemiological studies indicated that both morbidity and mortality are influenced by this exposure (Adar and Kaufman, 2007; Brook, 2007; Mills et al., 2009; Simkhovich et al., 2009; Sun et al., 2010; Adar and Kaufman, 2007; Brook, 2007; Brook et al., 2010; Mills et al., 2009; Simkhovich et al., 2009; Sun et al., 2010; Kappos et al., 2004) The results are expressed in many preventive measures of air pollution standards and/or regulations. So far, the concern has been on PM2.5 and PM10 mass concentrations. However, the focus of scientific attention has been shifted recently to concentrations in the range of submicrometer to ultrafine particles. The number of studies in this area is still small (Andersen et al., 2008; de Hartog et al., 2003; Ibald-Mulli et al., 2001a, b, 2002; Schulz et al., 2005; Peters et al., 2002; von Klot et al., 2002; Wichmann et al., 2000). These studies found that not only particle mass have an adverse impact on human health but also smaller particles, which are better characterised by the particle number concentration. Yet, to our knowledge, not one study has examined simultaneously the association of different particle size fractions and cardiovascular effects as a time series analysis; even though epidemiological evidence has shown that airborne particles do affect the cardiovascular system. Symptoms like arrhythmia, restricted heart rate variability, vasoconstriction, enhanced plasma viscosity and hypertension have been observed repeatedly, but only working hypotheses exist for the underlying patho-physiological mechanisms of these effects. Ongoing physiological processes induced by irritation and stress result in local and systemic reactions which seem to play an important role in the hypertension effect.

On account of the enormous economic consequences and the efficaciousness of prevention strategies, it would seem to be of highest priority to sort out what type of particles – coarse, fine or ultrafine – exert the most adverse impact on health. This kind of investigation is a prerequisite in the decision making process of preventive strategies and measures. One possible reason for the lack of such a health impact evaluation, may be that previous epidemiologic studies did neither provide information on different size fractions, especially not in the submicrometer range, nor on number concentration time series

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analysis. Furthermore, the question remains how the number concentration of ultrafine particles should be measured in order to adequately describe these health risks. Generally, number concentrations in terms of quantity can be measured directly. However, an important question is whether the number concentrations of airborne particles are suitable to be a predictor of cardiovascular health effects? Or should a volume concentration (as a surrogate for mass concentration) or surface concentration of the size fraction be used to assess the health risks?

The vast majority of epidemiological studies on health effects of airborne particles used mass concentrations (e.g. PM10, PM2.5) for assessing the adverse effects. This approach indirectly implies that the amount of chemical substances within these particle fractions is playing the most important role in pathogenesis of particulate-associated diseases. In our study, we measured number concentrations of ultrafine particles. Therefore, the question arises how successfully this parameter can serve as a predictor for health impacts of this airborne particle fraction.

2. Objective

Differences in the influence of the various sizes of particle fractions (ultrafine, fine and coarse) on cardiovascular diseases will be investigated in a time series analysis. In addition, within the complexity of cardiovascular diseases, special attention will be paid on hypertensive crisis in light of the fact that hypertension is a symptom in most cardiovascular processes linked to inhalable particles (Brook et al., 2009; Brook et al., 2010). In addition, hypertension is an objective, measurable parameter.

3. Methods

3.1. Study design and population characteristics

This investigation involves the analysis of the total number of daily calls to the emergency ambulance service of the City of Leipzig in relation to cardiovascular incidences and the unique data pool of the time series of concentrations of PM2.5, PM10 and different size fractions of submicrometer particles.

It should be mentioned that in the city one headquarters coordinates all emergency interventions. Therefore, a complete overview about the emergency calls in the city has been got and selection bias has been avoided.

In total, 23,741 emergency calls, collected over one year from February 2002 to January 2003, were analysed. Table 1 lists the study design and parameters. The cardiovascular diseases considered were angina pectoris, hypertensive crisis, cardiac arrhythmias, myocardial infarction, orthostatic syndrome and cardiac insufficiency (Table 2).

Table 2
Data sources.

Health data	City of Leipzig, Emergency Call Centre ("Zentrale Rettungsstelle")
Particle concentrations 3–800 nm	Leibniz Institute for Tropospheric Research
PM10, PM2.5	Saxon State Office for the Environment and Geology

Particle number size distributions were measured in the submicrometer size range using twin differential mobility particle sizer (TDMPS) (3–800 nm) consisting of (ultrafine) differential mobility analysers (UDMA and DMA) and (ultrafine) condensation particle counters (UCPC and CPC) (Bell et al., 2006; Tuch et al., 2003; Wehner and Wiedensohler, 2003). In addition, PM2.5 and PM10 values were determined by gravimetry.

3.1.1. Statistical methods

The applied methods follow 3 steps: In the first step, a time series is analysed to evaluate whether the variables follow a time course. This step is necessary to avoid a time-dependent correlation, which means if the diseases and the variables of influence follow the same or an inverse time course than it may derived a pseudo-correlation. This kind of correlation would be determined by the time course and not by a potential existing association. Using this analysis, also singularities will be excluded within at least the time series of the target variable (disease). It may be possible that during weekends or holidays the emergency unit may be more taken up than at workdays. This procedure is similar to that one published by Herbarth, 1995.

The second step was to control the influence of the meteorological variables. For that reason, the time course and the influence of these variables on the target variable was investigated using logistic regression models.

In the third step, a logistic regression was used to determine the link between the 3 different particle fractions and the disease.

The STATISTICA software (StatSoft, Inc. (2005)) was used for our statistical analysis (descriptive statistics and logistic regression). The target variable here was the disease. The number of ultrafine particles (UFP) was used as variable of influence Mean temperature, humidity, day of the week, month and public holidays were considered as confounders.

4. Results

The main characteristics of the study population are shown in Table 3.

Out of the 23,741 emergency calls, 5326 were found to be related to cardiovascular incidences. This was the largest group of cases, followed by emergencies associated with air way diseases (2956

Table 1
Study design and parameter.

Type of study	Retrospective epidemiological study time series analysis
Study time	February 2002–January 2003
Study area	City of Leipzig, Germany Approx: 500,000 inhabitants
Health parameters	Total number of ICD10 coded emergency calls in the City of Leipzig (daily resolution)
Measured particles	Number concentration of UFP Mass concentrations PM2.5 and PM10
Particle measurements	Number concentration, surface concentration*, volume concentration* (96 measurements per, size-resolved), urban background measuring station; PM2.5, PM10: mass concentration, mean value of all measuring stations within the city (* — calculated from size distribution)
Time resolution of the study	Daily

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Table 3
Description of the study population (2002) (Statistisches Jahrbuch, 2010/Yearbook 2010).

City area [km^2]			297.6
		Population density (inhabitants per km^2)	1663
Inhabitants			494,795
	Female		255,641
	Male		239,154
	Mean age [a]		43.5
		Female	45.6
		Male	41.2

cases). Angina pectoris ($n = 1574$) and hypertensive crisis (hypertensive emergency; $n = 1513$) were the two most frequent diagnostic categories within the cardiovascular disease classification in accordance to ICD 10 (see Fig. 1).

The gender ratio (female to male) was 1.3:1 for the total number of cardiovascular incidences and 2.5:1 for hypertensive crises. Significant differences in the number of emergency calls between workdays (Monday to Friday) and/or weekends were not found. Mainly elder people suffered from cardiovascular events (Table 4).

Table 5 lists the particle number and mass concentrations measured during the study period. PM10 yearly mean concentrations were moderate in comparison to the tolerated limit value of 40 mg/m^3 in Europe. Similar to other countries, in Germany PM2.5 contributes to high percentages of PM10 (Kappos et al., 2004), which results in highly significant Spearman correlation coefficients of $R = 0.85$. The correlations of these mass concentrations with UFP concentrations are much smaller ($R(\text{PM2.5 vs UFP}) = -0.06$; $R(\text{PM10 vs UFP}) = 0.00$), indicating that other particle sources and sinks play a role. This also allows separating the effects of UFP exposures from the effects of particle mass exposures effectively.

Only for hypertensive crisis, an association could be seen. Fig. 2 shows this association between the number of calls for emergency hypertensive crises, the particle size, and the timing of the exposure. The cardiovascular associations are presented dependent upon particle exposure and differences in lag time, starting with lag 0 (immediate influence) and up to 9 days. Exposure particle concentrations were broken down into the size ranges <100 nm, $<2.5\ \mu\text{m}$ (PM 2.5) and $<10\ \mu\text{m}$ (PM 10). The Odds Ratios (OR) were calculated per 1000 particles/cm^3 (particles<100 nm) and per 1 $\mu\text{g/m}^3$ (PM 2.5, PM 10), respectively.

The results of the logistic regression are shown in Fig. 1. After controlling for mean temperature, humidity, day of the week, month and public holidays, all 3 particles fractions (UFP–PM2.5–PM10) used as variables of influence were tested including all together in combined model for every time lag. To keep the clarity of Fig. 1, the p-values for the models and the single variables for the different time lags are shown in Table 6. Again, every model is characterised by one column for every considered lag in Table 6.

The investigation using the total number of cardiovascular emergency calls shows no clear tendency in any direction and neither for particles <100 nm nor for PM2.5 or PM10. Summarised following results have been received for the Odds Ratios (OR) for the range between lag 0 and lag 10 using the mentioned particle fraction as variable of influence and the total number of cardiovascular emergencies as target variable:

Particles<100 nm:	1.03 … 1.08, with $p = 0.06 \ldots 0.94$
PM2.5:	0.99 … 1.02, with $p = 0.16 \ldots 0.99$
PM10:	0.99 … 1.01, with $p = 0.30 \ldots 0.94$

Surface and volume concentrations of the ultrafine particles were tested instead of the number of particles in order to determine those parameters, which are most correlated with the cardiovascular health effects. The odds ratios for the surface concentration of the UFP are between 0.99 and 1.01 (p between 0.07 and 0.94) and for the volume concentration OR between 0.56 and 2.56 (p between 0.03 and 0.99). The only parameter that resulted in systematic significant adverse effects remained the total number of particles (number concentration). Systematic means that the effect was visible over a connected period of at least 3 days. The calculated risk for the surface and volume concentrations was smaller and statistically insignificant. As a rule, the same was observed for temperature, humidity and the variables of time (week day, public holidays and month).

5. Discussion and conclusions

The results demonstrated very clearly the significant association number concentration of ultrafine particles (<100 nm diameter) on hypertensive crisis. These particle effects were more significantly impairing than that of the PM 2.5 or PM 10 particle mass concentration. The strongest impact was observed for ultrafine particles on hypertensive crises starting to be observed shortly after exposure on (lag day 2) (Fig. 1).

As far as the differences in measurements of the particle number concentrations are concerned, surface and volume concentrations were not found to be correlated significantly with any adverse

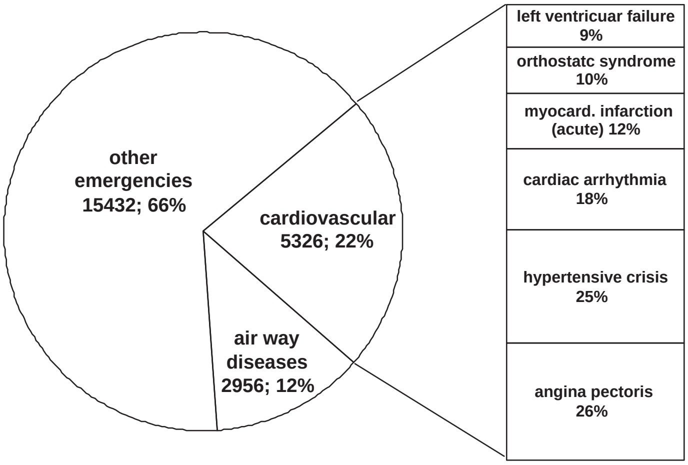

Fig. 1. Distribution of the frequency of emergency units from 02/2002 until 01/2003.

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Table 4
Age distribution [%] of the total and different cardiovascular diseases.

Age [a]	Cardiovascular total	Angina pectoris	Hypertensive crisis	Cardiac arrhythmica	Myocard. infarction	Orthostatic syndrome	Left ventricular failure
>70	55.3	51.5	59.3	53.5	49.3	48.5	78.5
60–70	22.2	25.1	23.0	21.6	28.6	14.2	15.4
50–60	10.6	12.1	10.5	10.6	14.0	9.8	4.3
40–50	6.4	8.3	4.7	6.3	6.4	7.3	1.6
<40	5.4	2.9	2.5	7.9	1.7	20.2	0.2

cardiovascular effects. Yet, as mentioned above, the number concentration was significantly correlated. This could be interpreted that following inhalation of ultrafine particles, the pathogenic mechanisms were more affected by the number of particles and less by their volume or surface/surface load. The maximal change was found to be 5% in the emergency call rate per 1000 particles/cm³ (ultrafine particles). This has to be seen in comparison to an annual mean of ~12,000 particles/cm³. No consistent effect was detected for PM 2.5 (annual mean 20.6 μg/m³) and PM10 (annual mean of 32.5 μg/m³).

The above mentioned discussion may be supported by the observed p-values of the models. Until 3 days after exposure (lag 3), the models can be explained mainly by the UFPs. Although the effect of UFPs keep significant until lag 7 other variables than particles may have an additional influence, which is not known and not considered in the models.

Potential limitations of this study, for instance, are the retrospective aspect of the investigation. All patients' data derived from records written up at the time of the emergency incidence by various attending physicians-on-call, i.e., patients could not be checked during the acute phase of the cardiovascular event. Furthermore, some patients had multiple diagnoses. In those cases, the study investigators assigned a final "main" diagnosis based on the complete patient file report. Another limiting factor could be that the available data of exposure did not necessarily come from the immediate vicinity of the patients. Measurement stations were selected under the criteria to cover and be representative for the entire city. This was correctly assumed as the area of the city is only around 200 km² with a population of approximately half million and no specific topographical features (flat country). The population of other cities in some East European countries and in other countries around the world as e.g. in Asian Megacities is exposed to often much higher concentrations and to different compositions of airborne pollutants (Leitte et al., 2009; Leitte et al., 2010). Therefore, our findings cannot be directly used for health effect assessment in these areas. Despite of pollutants, populations are different, too. The concentrations of air pollutants in Leipzig may rather be compared to other German, Central and Northern European cities (Boldo et al., 2006; Medina et al., 2004). We assume that health impacts in these regions may be similar to the found effects. Within the APHEIS programme, effect modifying covariates have been discussed (e.g. APHEIS Air Pollution and Health, 2005). Thus, e.g. a temperature effect could be modified by air conditioning. In a city with a high rate of air conditioned houses air temperature could not be sufficient as thermal confounder. Air condition is not common in Germany and exists in a rather small number of office buildings, only. On the other hand, the rather high mean age of patients strongly indicates that people typically are retired and are not occupationally exposed.

People in Central Europe spend the majority of their time indoors. Therefore, indoor particle sources may also play an important role for development and exacerbation of air pollution related diseases. On the other hand, outdoor particles can enter the indoor environment (Franck et al., 2006) easily by open windows and doors. But, indoor concentrations differ from outdoor one. Particle concentrations vary within a city (Tuch et al., 2006). Taking these facts into account the adverse effects may be in our study design underestimated rather than overestimated.

Table 5
Exposure parameters–size dependent particle concentration.

	Mean	Median	Minimum	Maximum	Standard deviation
UFP (cm^{-3})	12,094.50	10,893.43	1487.326	34,650.61	6329.975
Total number (cm^{-3})	14,043.02	13,111.47	2450.543	35,338.37	6628.781
PM10 (μg/m³)	32.48	28.56	6.829	109.72	16.384
PM2.5 (μg/m³)	20.61	18.18	1.375	84.06	12.890

5.1. Advantages

- Advantages of this study were the availability of these exposure measurement data of the ultrafine particle fraction with daily time resolution over the epidemiologically relevant study period. According to our knowledge, this is the first time that an assessment of this kind of study – daily cardiovascular morbidity due to UFP number and particle masses for a whole city – has been made.
- Another advantage is that the mobile emergency service has only one coordination centre for the entire city. This means that all calls had been registered centrally and, thus, all data used in this study were collected under the same standards and for the whole city population. Thus, the findings can be assumed to be representative for the city under consideration.

5.2. Limitations

- The statements respectively the diagnosis of the physicians on the spot may be a diagnosis for the time being. The focus lays on the therapy (and measures to prolong life) and not on a polished diagnosis. Since the investigated diseases are very drastic and since the division within the cardiovascular diseases are very rough, it can be assumed that this diagnosis is correct.
- In spite of the mentioned big advantages (see above), only one year was the basis for the data. From the point of view of time series, only 365 aggregated data are available. This fact leads to a limitation in the number of variables whose can involved in the logistic regression simultaneously.

In summary, the main effects of airborne particles on cardiovascular diseases, especially hypertensive crisis, appeared due to the ultrafine particle fraction. The effect of these particles was more pronounced, showed a more immediate effect and continued longer compared to the larger particles. We hope that our results contribute to the limited reports dealing with the effect of different particle size fractions on cardiovascular health.

This data implies, with respect to the protection of public health, the need to regulate the number concentration of ultrafine particles in addition to the existing limits for the mass concentrations of particles with aerodynamic diameters <2.5 μm and <10 μm (PM2.5, PM10). At this state of knowledge, limit values are hard to define. Our approach does not allow detecting no effect levels (NOE) for airborne particles.

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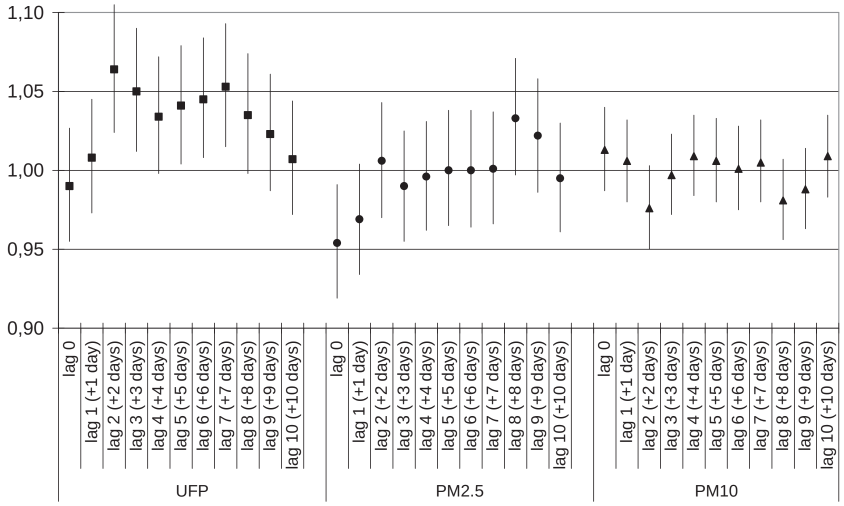

Fig. 2. OR and 95% confidence interval in emergency calls related to hypertensive crises depending on time of exposure to airborne particles and size of particles (ultrafine[UFP]–fine [PM2.5]–coarse [PM10]).

Table 6
p-values of the logistic regression models for the different time lags (significant $p<0.05$ in **bold**, trend $0.05 \leq p<0.10$ *in italics*).

Lag [days]	0	1	2	3	4	5	6	7	8	9	10
Model	**0.011**	*0.062*	**<.001**	**0.021**	0.210	0.125	0.117	**0.034**	0.104	0.433	0.829
UFP	0.600	0.649	**0.001**	**0.009**	**0.065**	**0.029**	**0.018**	**0.006**	*0.061*	0.208	0.692
PM2.5	**0.014**	*0.084*	0.760	0.557	0.821	0.980	0.987	0.967	*0.072*	0.233	0.757
PM10	0.322	0.655	*0.077*	.0814	0.482	0.654	0.950	0.681	0.149	0.370	0.504

To our knowledge, there do not exist any publications in literature, which found such a NOE for particulate matter. Therefore, limit values have to be defined pragmatically and need further research with respect to outdoor particle number concentrations and its spatial and temporal variations in the validity area of such regulations, i.e. anywhere in the member states of the European Union.

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