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Ultrafine and fine particles and hospital admissions in Central Europe, results from the UFIREG study

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At a Glance Commentary

Scientific Knowledge on the Subject: The association between particulate matter (PM_{10} and $PM_{2.5}$) and cardiorespiratory hospital admissions is well established. However, few short-term studies have investigated the association between ultrafine particles and morbidity, and results are inconsistent.

What This Study Adds to the Field: This study investigated short-term effects of ultrafine and fine particles on cause-specific hospital admissions in five Central and Eastern European cities. It is one of the very few multi-city studies in this field and includes cities from Eastern Europe. Further, exposure assessment and statistical analyses were conducted based on a priori fixed and harmonized protocols. Our findings indicated delayed and prolonged effects of UFP exposure on respiratory hospital admissions. Moreover, we found delayed and prolonged effects of $PM_{2.5}$ exposure on hospital admissions due to cardiovascular and respiratory diseases.

Abstract

Rationale: Evidence on short-term effects of ultrafine particles (UFP) on health is still inconsistent and few multi-center studies have been conducted so far especially in Europe.

Objectives: Within the UFIREG project, we investigated the short-term effects of UFP and fine particulate matter <2.5 µm ($PM_{2.5}$) on daily cause-specific hospital admissions in five Central and Eastern European cities using harmonized protocols for measurements and analyses.

Methods: Daily counts of cause-specific hospital admissions were obtained for Augsburg and Dresden (Germany) 2011-2012, Chernivtsi (Ukraine) 2013-March 2014, Ljubljana (Slovenia) and Prague (Czech Republic) 2012-2013 focusing on cardiovascular and respiratory diseases. Air pollution and meteorological data were measured at fixed monitoring sites in all cities. We analyzed city-specific associations using confounder-adjusted Poisson regression models and pooled the city-specific effect estimates using meta-analyses methods.

Main Results: A 2,750 particles/cm^3 increase (average interquartile range (IQR) across all cities) in the 6-day average of UFP indicated a delayed and prolonged increase in the pooled relative risk of respiratory hospital admissions (3.4% [95%-confidence interval:-1.7%;8.8%]). We also found increases in the pooled relative risk of cardiovascular (exposure average of lag 2-5: 1.8% [0.1%;3.4%]) and respiratory (6-day average exposure: 7.5% [4.9%;10.2%]) admissions per 12.4 µg/m^3 increase (average IQR) in $PM_{2.5}$.

Conclusions: Our findings indicated delayed and prolonged effects of UFP exposure on respiratory hospital admissions in Central and Eastern Europe. Cardiovascular and respiratory hospital admissions increased in association with an increase in $PM_{2.5}$. Further multi-center

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studies are needed using harmonized UFP measurements to draw definite conclusions on health effects of UFP.

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Introduction

Many epidemiological studies investigated the association between particulate matter (PM) with an aerodynamic diameter <10 µm (PM_{10}) or <2.5 µm ($PM_{2.5}$) and (emergency) hospital admissions especially due to cardiovascular and respiratory diseases (1-4). For example, Atkinson et al. (5) found increases in hospital admissions due to cardiovascular (0.9% [0.3%;1.5%]) and respiratory diseases (1.0% [-0.6%;2.6%]) in association with a 10 µg/m^3 increase in $PM_{2.5}$ in a combined analysis of the American, European, South East Asian and Western Pacific Region.

Only a few studies investigated the association between ultrafine particles (UFP) and hospital admissions world-wide. Moreover, European research on the health effects of UFP was primarily conducted in Western European Countries (6, 7). UFP might contribute to the reported health effects through different biological mechanisms compared to larger particles such as PM_{10} and $PM_{2.5}$. The deposition and clearance in the respiratory tract differ between UFP and larger particles. While larger and fine particles deposit mainly in the upper and lower respiratory tract, UFP can penetrate deeply into the pulmonary alveoli and can be translocated with the blood stream to other organs (7, 8). Due to the important differences in deposition, the potential for translocation and their large active surface it is assumed that UFP might have at least partly independent health effects compared to larger particles (7, 9-11) . However, the few studies investigating short-term effects of UFP on cardiovascular and respiratory diseases showed inconsistent results (6, 7).

Branis et al. (12) reported strongest associations for accumulation mode particles in the size range 205-487 nm. A 1,000 particles/cm^3 increase in the 7-day moving average of this particle size class was associated with increases in cardiovascular (16.4% [5.2%;28.7%]) and respiratory (33.4% [12.6%;57.9%]) hospital admissions in Prague. However, Atkinson and colleagues (13) only found weak associations between total particle number concentration

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(PNC) and emergency hospital admissions for cardiovascular and respiratory causes in London. A study carried out in Copenhagen found significant associations between hospital admissions for respiratory diseases and an interquartile range (IQR) increase in the 5-day average of PNC in the size range 6-700 nm; however, associations diminished after additional adjustment for PM_{10} or $PM_{2.5}$ (14).

Within the framework of the project “Ultrafine particles – an evidence based contribution to the development of regional and European environmental and health policy” (15), we investigated the association between UFP, PM and cause-specific hospital admissions in five Central European cities (Augsburg and Dresden, Germany; Chernivtsi, Ukraine; Ljubljana, Slovenia and Prague, Czech Republic). As a secondary objective we examined the short-term effects of PNC, PM_{10}, coarse particles with an aerodynamic diameter 2.5-10 µm ($PM_{2.5-10}$), and nitrogen dioxide (NO_2) on cause-specific hospital admissions in these five cities. This study is one of the very few multi-city studies in this field and further includes cities from Eastern Europe. Moreover, exposure assessment and statistical analyses were conducted based on a priori fixed and harmonized protocols. Some of the results of the UFIREG project have been previously reported in the form of abstracts (16-18).

Methods

For Augsburg, Dresden, Ljubljana and Prague daily counts of cause-specific hospital admissions were obtained from official statistics. Hospital admission data for Chernivtsi were collected directly from the hospitals. Infants younger than one year were excluded from the analyses. Only ordinary (no day-hospital) and acute (no scheduled) hospitalizations were considered. Moreover, only the primary diagnosis was considered for the identification of the outcomes.

The primary diagnoses were defined according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10). We investigated hospital admissions due to cardiovascular (ICD-10: I00-I99) and respiratory diseases (ICD-10: J00-J99). Moreover, we investigated hospital admissions due to diabetes (ICD-10: E10-E14) as an outcome of secondary interest. No informed consent by the patients was needed as data were anonymous and collected as daily counts. In Chernivtsi, Ljubljana and Prague data was restricted to people living in the city and hospitalized within the city. However, for Augsburg and Dresden, it was difficult to exclude all scheduled hospital admissions and to restrict to people living in the city and hospitalized in the city. Due to the German data protection rules, we only could restrict to people living in Augsburg and hospitalized in Bavaria and people living in Dresden and hospitalized in Saxony, respectively. Regarding respiratory hospital admissions, the categories J33 (nasal polyp), J34 (other disorders of nose and nasal sinuses) and J35 (chronic diseases of tonsils and adenoids) were excluded by hand for Augsburg and Dresden as the number of hospitalizations in these categories were very high, and only acute hospitalizations were considered.

Hourly data of air pollutants and meteorological variables (air temperature, relative humidity and barometric pressure) were measured at local fixed measurement sites in each city. All measurement sites were located in the urban background; for Prague, the monitoring station

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was located in a suburban background region. PNC in the range from 10-800 nm (for Prague from 10-500 nm) were measured using differential or scanning mobility particle size spectrometers (19). PM_{10}, $PM_{2.5}$ and NO_2 were measured in Augsburg, Dresden, Ljubljana and Prague, but were not available in Chernivtsi. $PM_{2.5-10}$ was calculated by subtracting $PM_{2.5}$ from PM_{10}. Daily 24-hour averages of air pollutants and meteorological parameters were only calculated if 75% of the hourly values were available. Due to measurement uncertainties in the size range 10 to 20 we investigated UFP in the size range 20 to 100 nm and PNC in the size range 20 to 800 (for Prague 20 to 500 nm) in all cities.

Hospital admission statistics for Augsburg and Dresden of 2013 were not available by the end of the project. Hence, due to the start of the measurements and the availability of epidemiological data, the following study periods were chosen: Augsburg and Dresden: January 2011 to December 2012; Ljubljana and Prague: January 2012 to December 2013; Chernivtsi: January 2013 until March 2014.

Statistical analysis

In a first step, we used quasi-Poisson regression models allowing for overdispersion to investigate the association between air pollutants and cause-specific hospital admissions for each city separately. The dispersion parameter was allowed to vary, but no important differences were observed between the cities. The same confounder model was used for all cities and confounders were chosen based on a review of the current literature. The confounder model included date order (representing time-trend), dummy variables for day of the week, a dummy variable for holidays, a dummy variable for the decrease of the populations present in the city during vacation periods (Christmas, Easter, summer vacation), a dummy variable for influenza epidemics (in Augsburg, Dresden, Ljubljana and Prague), air temperature (average of lags 0-1 [lag 0: same-day; lag 1: one day before the event] to represent effects of high temperatures and average of lags 2-13 [lag 2: two days prior to the event; lag 13: 13 days prior to the event] to represent effects of low temperatures), and relative humidity (average of lags 0-1 and average of lags 2-13). Penalized regression splines with natural cubic regression splines as smoothing basis were used to allow for non-linear confounder adjustment. The spline for date order was fixed to have four degrees of freedom per year to sufficiently represent long-term trend and seasonality. Splines for meteorological variables were fixed to three degrees of freedom. We investigated single-lags from same day of the event (lag 0) up to five days prior to the event (lag 5). Moreover, we estimated cumulative effect models to represent immediate (2-day average: lag 0-1), delayed (average of lag 2-5) and prolonged effects (6-day average: lag 0-5).

In a second stage, city-specific effect estimates were combined using random-effects models (20). For each meta-analytical estimate, a χ^2-test for heterogeneity was performed and the corresponding p-value and I^2-statistic was reported. Cities were weighted according to the precision (standard error) of the city-specific effect estimates (20, 21). For pooling the city-specific estimates the maximum likelihood effects estimator after van Houwelingen was used (22).

We investigated effect modification by age (<75 years vs. ≥75 years) and sex (females vs. males) in stratified analyses. Effect modification by season (October-March vs. April-September) was analyzed by including an interaction term in the model. Two-pollutant models were calculated in order to assess interdependencies of UFP and $PM_{2.5}$ effects as well as interdependencies of UFP and NO_2 effects. We conducted several sensitivity analyses on the confounder model to test the robustness of our results (see online data supplement).

Results

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Daily means of cause-specific hospital admissions per 100,000 inhabitants differed between the cities as presented in Table 1. A description of air pollution and meteorological parameters by city is presented in Table E1 in the online data supplement. Mean PM_{10} values ranged from 20.0 µg/m^3 in Augsburg to 26.2 µg/m^3 in Prague. Ljubljana showed highest $PM_{2.5}$ values with a mean of 20.7 µg/m^3, whereas highest UFP concentrations were observed in Augsburg with a mean of 5,880 particles/cm^3. UFP were moderately correlated with PM_{10}, $PM_{2.5}$ and $PM_{2.5-10}$ (Spearman's rank correlation coefficient $0.3 \leq r_s \leq 0.5$) in all cities (Table E2). The correlation between PNC and PM_{10}, $PM_{2.5}$ as well as $PM_{2.5-10}$ was slightly higher with r_s between 0.5 and 0.6. Meteorological parameters were low to moderately correlated to air pollution parameters ($r_s<0.6$) in all cities and high correlations were observed between PM_{10} and $PM_{2.5}$ with $r_s=0.9$ in Augsburg, Dresden, Ljubljana and Prague.

Strongest associations between air pollutants and cardiovascular and respiratory hospital admissions were found for the cumulative lag periods. Table 2 shows percent changes in relative risk (RR) of cause-specific hospital admissions together with 95%-confidence intervals (CIs) for the 2-day average, the average of lag 2-5 and the 6-day average. The associations for single time lags are presented in Table E3. We observed no association between UFP, PNC and NO_2 and cardiovascular hospital admissions in pooled (Table 2) and city-specific analyses (Figure 1A). However, we observed a delayed and prolonged association between an IQR increase in $PM_{2.5}$ and cardiovascular hospital admissions (Table 2, Figure 1B). Strongest effect estimates were observed for Augsburg showing a 4.6% [0.6%;8.7%] increase in cardiovascular admissions with a 12.4 µg/m^3 increase in the $PM_{2.5}$-average of lag 2-5. Associations between PM_{10} and $PM_{2.5-10}$ and cardiovascular hospital admissions were similar but weaker compared to $PM_{2.5}$.

For respiratory hospital admissions strongest associations were found for the 6-day averages of air pollutants. A 2,750 particles/cm^3 increase in the 6-day average of UFP was associated with a 3.4% [-1.7%;8.8%] increase in the pooled RR of respiratory hospital admissions (Table 2). A 2,750 particles/cm^3 increase in UFP was associated with significant increases in the city-specific RRs of respiratory hospital admissions in Augsburg (7.3% [1.4%;13.6%]) and Dresden (8.8% [1.8%;16.3%]) (Figure 2A). Chernivtsi showed a weak positive association and non-significant decreases in respiratory hospital admissions were found for Ljubljana and Prague. Results of PNC were similar. We observed increases in the pooled (Table 2) and city-specific (Figure 2B) RR of respiratory hospital admissions with increases in $PM_{2.5}$, PM_{10} and $PM_{2.5\text{-}10}$. Strongest effect estimates were observed for the $PM_{2.5}$-6-day average and respiratory hospital admissions showing a 7.5% [4.9%;10.2%] increased pooled RR. Moreover, we observed a significant increase in respiratory admissions in association with a 15.4 µg/m^3 increase in the NO_2-average of lag 2-5. Our results indicated that exposure to UFP, PNC, $PM_{2.5}$ and PM_{10} increase the pooled RR of diabetes hospital admissions (Table E3).

Associations between UFP and $PM_{2.5}$ and cardiovascular hospital admissions remained stable in single- and two-pollutant models (Figure 3A). In Augsburg, Dresden and Prague effect estimates of $PM_{2.5}$ and respiratory hospital admissions were also similar in single- and two-pollutant models (Figure 3B). In Ljubljana, the association between $PM_{2.5}$ and respiratory hospital admissions strengthened when adjusting for UFP. Adjusting for $PM_{2.5}$ weakened the association between UFP and respiratory hospital admissions in Augsburg and to a lesser extent in Dresden. Moreover, UFP and respiratory hospital admission showed a negative association when adjusting for $PM_{2.5}$ in Ljubljana. Two-pollutant models of UFP and NO_2 showed no association with respiratory hospital admissions in Augsburg.

Effects of UFP on respiratory hospital admissions were stronger in people ≥75 years compared to the younger age group (Table E4). The older age group also showed a slightly stronger increased pooled RR of cardiovascular hospital admissions with $PM_{2.5}$. We observed no effect modification by sex. The association between UFP and respiratory hospital

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admissions was similar during October-March and April-September. However, we found an increase in cardiovascular hospital admissions with a 12.4 $\mu g/m^3$ increase in $PM_{2.5}$ during the cold period; whereas, no association during the warm period. Effects of $PM_{2.5}$ on respiratory hospital admissions were slightly stronger during the cold period compare to the warm period. Sensitivity analyses were only conducted for cumulative lags periods showing the strongest associations. Table E5 shows the results of sensitivity analyses for respiratory hospital admissions and the 6-day average of UFP, for cardiovascular and respiratory hospital admissions and $PM_{2.5}$, average of lag 2-5 and 6-day average, respectively.

1) Increasing the degrees of freedom per year for the smooth function of trend decreased the pooled effect estimates for UFP and $PM_{2.5}$ on cause-specific hospital admissions compared to the original model. Whereas, using fewer degrees of freedom per year for the trend did not influence the pooled effect estimates.

Increasing the degrees of freedom for smooth functions of air temperature and relative humidity weakened the association between UFP and $PM_{2.5}$ and cause-specific hospital admissions.

2) Replacing air temperature and relative humidity by apparent temperature slightly increased the pooled effect estimate of UFP on respiratory hospital admissions. Effects of $PM_{2.5}$ on cardiovascular hospital admissions remained nearly unchanged and the association between $PM_{2.5}$ and respiratory hospital admissions decreased a bit when apparent temperature was used.

3) Adjusting for air temperature by using temperature above the median for heat effects and below the median for cold effects strengthened the association between UFP and respiratory hospital admissions. Effects of $PM_{2.5}$ on cardiovascular hospital admissions remained similar to the original model and effects of $PM_{2.5}$ on respiratory hospital admissions weakened slightly.

4) Adjusting for air temperature and relative humidity including the average of lag 0-1 and the

average of lag 2-5 strengthened the effect estimates of UFP as well as $PM_{2.5}$ and cause-specific hospital admissions.

5) Additionally adjusting for barometric pressure decreased the effect estimates of UFP and $PM_{2.5}$ on respiratory hospital admissions; whereas, the association between $PM_{2.5}$ and hospital admissions due to cardiovascular diseases remained nearly unchanged.

6) Effect estimates for Augsburg and Prague did not change significantly when the data set with imputed missing data was used (data not shown).

7) Results of second degree polynomial distributed lag models support delayed and prolonged effects of $PM_{2.5}$ exposure on hospital admissions due cardiovascular and especially respiratory diseases (Figure E1). The association between UFP and respiratory hospital admissions was positive but not significant for all time lags.

8) Using city-specific confounder models (Table E6) showed positive but weaker effect estimates of UFP and respiratory hospital admissions compared to the a priori defined confounder model. Using city-specific confounder models also weakened the association between $PM_{2.5}$ and cause-specific hospital admissions. However, effect estimates of $PM_{2.5}$ and respiratory hospital admissions remained significant. Overall, the directions of the city-specific effect estimates were similar to the a priori defined confounder model (data not shown).

Discussion

Within the UFIREG project, we investigated the association between daily air pollution concentrations and cause-specific hospital admissions in Augsburg, Chernivtsi, Dresden,

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Ljubljana and Prague. Our findings indicated delayed and prolonged effects of UFP and PNC exposure on respiratory hospital admissions (6-day average of UFP: 3.4% [-1.7%;8.8%] and PNC: 4.3% [-0.9%;9.8%]). Moreover, we found delayed and prolonged effects of $PM_{2.5}$ exposure on cause-specific hospital admissions. A 12,4 $\mu g/m^3$ increase in the $PM_{2.5}$-average of lag 2-5 was associated with a 1.8% [0.1%;3.4%] increase in the pooled RR of cardiovascular hospital admissions. Increases in the 6-day average of $PM_{2.5}$ were associated with increases in respiratory hospital admissions by 7.5% [4.9%;10.2%]. We observed an association between NO_2 and respiratory hospital admissions. Moreover, hospital admissions due to diabetes increased in association with exposure to UFP, PNC and PM. Effects of PM_{10} and $PM_{2.5-10}$ were similar but weaker compared to $PM_{2.5}$.

$PM_{2.5}$ has been shown to be associated with increases in hospital admissions especially due to cardiovascular and respiratory diseases (5, 11). For example, Stafoggia et al. (4) reported immediate (2-day average: 0.5% [0.1%;0.9%]) and prolonged (6-day average: 0.5% [0.0%;1.0%]) increases in cardiovascular hospital admissions and prolonged increases in respiratory hospital admissions (6-day average: 1.4% [0.2%; 2.5%]) in eight Southern European Regions. We also observed a delayed increase in cardiovascular hospital admissions (average of lag 2-5: 1.5% [0.1%;2.7%] per 10 $\mu g/m^3$ increment in $PM_{2.5}$). Our effect estimates of $PM_{2.5}$ and respiratory hospital admissions (6-day average: 6.0% [4.0%;8.2%]) were stronger compared to results from other European regions and the U.S. (3, 4, 23). In contrast to our study, Stafoggia et al. (4) and Zanobetti et al. (3) analyzed emergency hospital admissions. However, our association between $PM_{2.5}$ and respiratory hospital admissions was also stronger compared to a U.S. study conducted by Bell et al. (23) focusing not only on emergency hospital admissions. Our effect estimates for $PM_{2.5}$ and respiratory hospital admissions are comparable to results of $PM_{2.5}$ and hospital admissions due to chronic obstructive pulmonary disease in the U.S. Southeast Region involving 35 counties which were examined in a large study on altogether 204 U.S. urban counties (24). In our study increases in respiratory hospital admissions were also associated with exposure to NO_2, showing strongest effects for the average of lag 2-5. There is a growing literature on the health effects of NO_2 (25). For example, a review by Mills and colleagues (25) reported increases in respiratory hospital admissions by 0.6% [0.3%; 0.8%] based on estimates of the WHO American, European, South East Asian and Western Pacific Region. In contrast to our study the authors also reported an association between NO_2 and cardiovascular hospital admissions (25).

Findings of our study pointed to a five-days delayed increase of 3.6% [1.0%;6.3%] in hospital admissions due to diabetes per 10 $\mu g/m^3$ $PM_{2.5}$ increment. Increases of the same magnitude in diabetes hospital admissions (2.7% [1.3%;4.2%] and 1.1% [0.6%;1.7%] per 10 $\mu g/m^3$ increase, respectively) were also reported in two studies conducted in the U.S., however, for the 2-day average of $PM_{2.5}$ (3, 26).

We found an increase in cardiovascular hospital admissions with an average IQR increase in $PM_{2.5}$ during the cold period from October-March; whereas, no association was observed during the warm period from April-September. Bell et al. (23) also observed higher effect estimates for $PM_{2.5}$ and cardiovascular hospital admissions during winter in 202 U.S. counties. However, a multi-city study in Southern European regions found stronger effects from April-September compared to the colder period (4). Different climate conditions and also different lifestyle patterns could be possible explanations. Moreover, differences in $PM_{2.5}$ compositions between regions should be considered.

A small number of studies also reported associations between cardiovascular or respiratory hospital admissions and PNC of different size ranges (1, 12, 14). Atkinson and colleagues (13) found only weak associations between total PNC and emergency hospital admissions for cardiovascular and respiratory causes in London. Nevertheless, the results indicated a four-

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days delayed increase in respiratory hospital admissions in association with a 10,166 particles/cm^3 increase in PNC especially in people older than 65 years (13). A German study found significant two to seven days delayed associations between UFP and cardiovascular hospital admissions, especially for hypertensive crisis, in Leipzig (2). Our pooled effect estimates on cardiovascular hospital admissions did not show any association. However, our results pointed to delayed (average of lag 2-5: 2.2% [-0.9%;5.3%]) and prolonged increases (6-day average: 3.4% [-1.7%;8.8%]) in respiratory hospital admissions per 2,750 particles/cm^3 increment in UFP.

The change in effect estimates for single- and two-pollutant models on respiratory hospital admissions in Ljubljana might be an indication for a remaining collinearity between $PM_{2.5}$ and UFP in Ljubljana. Although, the Spearman correlation coefficient was moderate with r_s=0.3. In Augsburg the association between UFP and respiratory hospital admission vanished after adjusting for NO_2. There might be also a remaining collinearity between UFP and NO_2 in Augsburg since the correlation between UFP and NO_2 was higher in Augsburg and Ljubljana (r_s=0.5) compared to the other cities ($r_s \leq 0.3$). The association between UFP and respiratory hospital admissions weakened in Augsburg and Dresden after adjusting for $PM_{2.5}$. However, it has been demonstrated statistically that when there are two risk factors in a regression model and one has a higher level of precision, the one with more precision will dominate the prediction (27).

Plausible biological mechanisms

Oxidative stress in the lungs and lung inflammation caused by air pollutants, especially by fine and UFP, are one of the potential biological mechanisms leading to respiratory diseases (11, 28, 29). Three biological pathways that are assumed to not acting independently are discussed to be associated with effects beyond the lung. 1) Inhalation of particles may lead to a release of pro-inflammatory mediators or vasculoactive molecules from lung cells causing systemic oxidative stress and inflammation. This may further cause endothelial dysfunction, adverse cardiac outcomes, and a pro-coagulation state with thrombus formation and ischemic response as well as promotion of atherosclerotic lesions (30). 2) Particles deposited in the pulmonary tree may be associated with imbalance of the autonomic nervous system or heart rhythm either caused by stimulating pulmonary neural reflexes (31) or by provoking oxidative stress and inflammation in the lung. 3) UFP and PM constituents can be translocated into the blood causing endothelial dysfunction and vasoconstriction, increased blood pressure and platelet aggregation, and might also directly affect the heart and other organs (11, 28).

Moreover, systemic oxidative stress and inflammation, imbalance of the autonomic nervous system and endothelial dysfunction can lead to insulin resistance and therefore can promote the progression of type-2 diabetes (32, 33).

Because of their small size UFP are not well recognized and cleared by the immune system and can escape natural defence mechanisms. UFP have a higher biological reactivity and surface area than larger particles and can be transported to other organs (6, 7, 9, 11). Therefore, it is suggested that UFP might also be linked to different biological mechanism than larger particles.

Strengths and Limitations

One of the strengths of the UFIREG project was that the associations between ultrafine and fine particles and cause-specific hospital admissions were studied in multiple cities in Central and Eastern Europe. So far many studies were conducted including Western European countries. In all the five cities UFP was measured using harmonized measurement devices. Epidemiological analyses were conducted according to a common analysis plan in order to produce comparable results. Therefore, comparable city-specific effect estimates could be

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examined leading to adequate pooled effect estimates for the involved Central and Eastern European Countries.

Our study is limited by a short study period of two and in case of Chernivtsi only one full year. It is recommended to use longer time periods for future studies to get powerful results. However, despite the short periods we found significant effect estimates for $PM_{2.5}$, PM_{10} and $PM_{2.5\text{-}10}$ on hospital admission outcomes. Moreover, our results indicated delayed and prolonged effects of UFP exposure on respiratory diseases. For respiratory hospital admissions we observed the strongest associations with increases in the 6-day average of UFP and $PM_{2.5}$. The chance of uncontrolled confounding increases with longer time lags. However, previous studies also reported delayed associations between air pollutants and respiratory hospital admissions (4, 34). For example, Stafoggia and colleagues (4) reported strongest effects estimates for the 6-day average increase in air pollutants and respiratory hospital admission in Southern Europe.

Difficulties in the exclusion of scheduled hospital admissions and in the restriction to people living in the city and hospitalized in the city might have caused differences between the cities concerning daily counts of hospital admissions. Moreover, differences in coding the primary diagnosis and different health care systems need to be considered. Only the primary diagnosis of hospital admissions was considered therefore, the number of cases might be underestimated. For example, the number of hospital admissions due to diabetes might be higher when including also the secondary diagnosis.

Measurement error might be an explanation for the weaker effect estimates of UFP and respiratory hospital admissions compared to $PM_{2.5}$ and respiratory hospital admissions (27). However, an extensive quality assurance program was an essential part of the project in order to provide reliable and comparable data between the measurement stations (35). UFP have been shown to have a higher spatial variability than fine particles. Therefore, exposure misclassification might be a bigger issue than with $PM_{2.5}$ or PM_{10}. A study conducted in Augsburg reported high temporal correlations in PNC across different sites in the city area of Augsburg despite differing magnitudes in space (36). Moreover, another German study showed low spatial variability in PNC among urban background stations in Dresden (37). It was suggested that short-term UFP exposure of the average population might be adequately represented by a fixed urban background station if the location is chosen carefully (36).

Conclusions

Our findings indicated delayed and prolonged effects of UFP exposure on respiratory hospital admissions in Central and Eastern Europe. Cardiovascular and respiratory hospital admissions increased in association with an increase in $PM_{2.5}$, PM_{10} and $PM_{2.5\text{-}10}$ showed similar results. Effects of $PM_{2.5}$ on respiratory hospital admissions were stronger compared to results from other European regions and the U.S. (3, 4, 23). Moreover, respiratory hospital admissions increased in association with exposure to NO_2 and we observed an increase in hospital admissions due to diabetes in association with increases in air pollutants.

Based on our experience with the UFIREG study, we suggest integrating UFP into routine measurement networks to provide data for further short- and long-term studies on health effects of UFP. So far, hardly any long-term studies on UFP have been conducted (38). Further studies are needed investigating the association between UFP and morbidity at multiple locations using harmonized UFP measurements.

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Figure Legends

Figure 1. Percent change in the city-specific and pooled relative risk of cardiovascular hospital admissions with each IQR increase in A) UFP and PNC, average of lag 2-5; B) $PM_{2.5}$, PM_{10} and $PM_{2.5-10}$, average of lag 2-5.

*Prague: PNC 20-500 nm

Figure 2. Percent change in the city-specific and pooled relative risk of respiratory hospital admissions with each IQR increase in A) UFP and PNC, 6-day average; B) $PM_{2.5}$, PM_{10} and $PM_{2.5-10}$, 6-day average.

*Prague: PNC 20-500 nm

Figure 3. Percent change in the city-specific and pooled relative risk of A) cardiovascular hospital admissions per IQR increase in pollutant and B) respiratory hospital admissions per IQR increase in pollutant using single- and two-pollutant models.

$PM_{2.5}$: main effects of $PM_{2.5}$, UFP: main effects of UFP, $PM_{2.5}$+UFP: effects of $PM_{2.5}$ adjusted for UFP, UFP+$PM_{2.5}$: effects of UFP adjusted for $PM_{2.5}$, UFP+NO_2: effects of UFP adjusted for NO_2.

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Tables

Table 1. Socio-demographical information and cause-specific hospital admissions per 100,000 inhabitants by city.

City	Year	Population	City area (km^2)	Daily mean (SD)/100,000 inhabitants of hospital admissions		
				Cardiovascular	Respiratory	Diabetes
Augsburg*	2011	266,647	147	7.3 (3.2)	3.1 (1.5)	0.8 (0.7)
	2012	272,699	147	7.2 (3.2)	3.2 (1.6)	0.8 (0.6)
Chernivtsi	2013	258,371	153	4.7 (2.2)	2.0 (1.3)	0.3 (0.4)
Dresden*	2011	517,765	328	6.5 (2.5)	2.2 (0.9)	0.6 (0.4)
	2012	525,105	328	6.5 (2.5)	2.2 (0.9)	0.6 (0.4)
Ljubljana	2012	280,607	275	4.1 (2.0)	3.0 (1.7)	0.2 (0.3)
	2013	282,994	275	3.6 (1.7)	2.6 (1.3)	0.2 (0.3)
Prague	2012	1,246,780	496	1.8 (0.7)	0.6 (0.3)	0.1 (0.1)
	2013	1,243,201	496	2.0 (0.7)	0.8 (0.4)	0.1 (0.1)

*Reference: Research Data Centers of the Federal Statistical Office and the Statistical Offices of the Länder, Hospital Admission Statistics, 2011-2012, own calculations

Table 2. Percent changes in the pooled relative risk (95%-CI) of cause-specific hospital admissions with each average IQR increase in air pollutants.

Association under investigation	IQR†	2-day average	average of lag 2-5	6-day average
Cardiovascular hospital admissions				
UFP (n/cm^3)	2,750	-0.6 (-2.4; 1.1)	0.3 (-1.7; 2.4)	-0.1 (-2.6; 2.4)
PNC (n/cm^3)	3,675	-0.6 (-2.3; 1.3)	0.8 (-1.3; 2.9)	0.4 (-2.1; 3.0)
$PM_{2.5}$ (µg/m³)	12.4	0.5 (-1.2; 2.3)	1.8 (0.1; 3.4)	1.7 (-0.1; 3.6)
PM_{10} (µg/m³)	16.0	-0.2 (-2.5; 2.1)*	1.0 (-0.9; 2.9)	0.8 (-1.9; 3.5)*
$PM_{2.5-10}$ (µg/m³)	4.7	-0.3 (-2.2; 1.6)	1.4 (-0.5; 3.4)	1.0 (-1.1; 3.2)
NO_2 (µg/m³)	15.4	-0.8 (-2.8; 1.2)	0.0 (-2.3; 2.3)	-0.8 (-3.5; 2.0)
Respiratory hospital admissions				
UFP (n/cm^3)	2,750	1.5 (-3.4; 6.7)*	2.2 (-0.9; 5.3)	3.4 (-1.7; 8.8)
PNC (n/cm^3)	3,675	1.9 (-3.2; 7.3)*	3.1 (-0.1; 6.5)	4.3 (-0.9; 9.8)
$PM_{2.5}$ (µg/m³)	12.4	3.5 (0.3; 6.7)*	6.4 (4.1; 8.8)	7.5 (4.9; 10.2)
PM_{10} (µg/m³)	16.0	4.1 (1.1; 7.1)	6.0 (3.3; 8.6)	7.3 (4.4; 10.3)
$PM_{2.5-10}$ (µg/m³)	4.7	3.4 (0.9; 5.8)	4.9 (2.2; 7.6)	6.3 (3.2; 9.5)
NO_2 (µg/m³)	15.4	2.7 (-2.1; 7.8)*	5.1 (0.7; 9.7)	6.8 (-0.2; 14.2)*
Diabetes hospital admissions				
UFP (n/cm^3)	2,750	0.4 (-4.7, 5.7)	2.8 (-3.2; 9.1)	2.9 (-4.5; 10.9)
PNC (n/cm^3)	3,675	0.6 (-4.7; 6.3)	3.8 (-2.4; 10.5)	3.9 (-3.7; 12.1)
$PM_{2.5}$ (µg/m³)	12.4	1.2 (-3.3; 5.9)	4.5 (-0.6; 9.8)	4.1 (-1.5; 9.9)
PM_{10} (µg/m³)	16.0	0.5 (-4.0; 5.2)	4.7 (-0.4; 10.1)	3.9 (-1.7; 9.8)
$PM_{2.5-10}$ (µg/m³)	4.7	-1.2 (-6.2; 4.1)	2.0 (-3.9; 8.3)	0.7 (-5.9; 7.6)
NO_2 (µg/m³)	15.4	0.3 (-5.8; 6.7)	-1.9 (-8.9; 5.7)	-0.8 (-9.1; 8.2)

†average interquartile range across all cities
*heterogeneity p-value<0.1 and I^2>50%

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Figures

Cardiovascular hospital admissions, average of lag 2-5

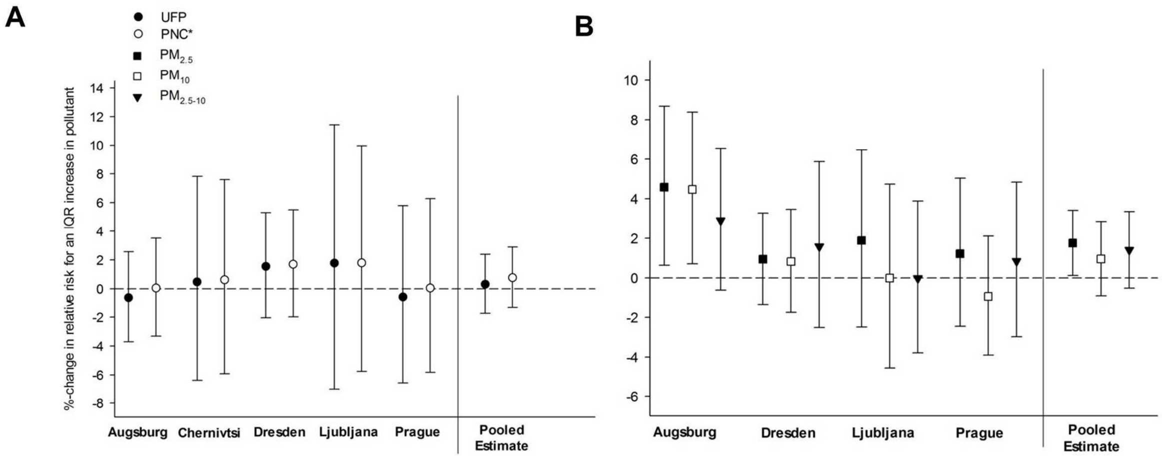

Figure 1

Respiratory hospital admissions, 6- day average

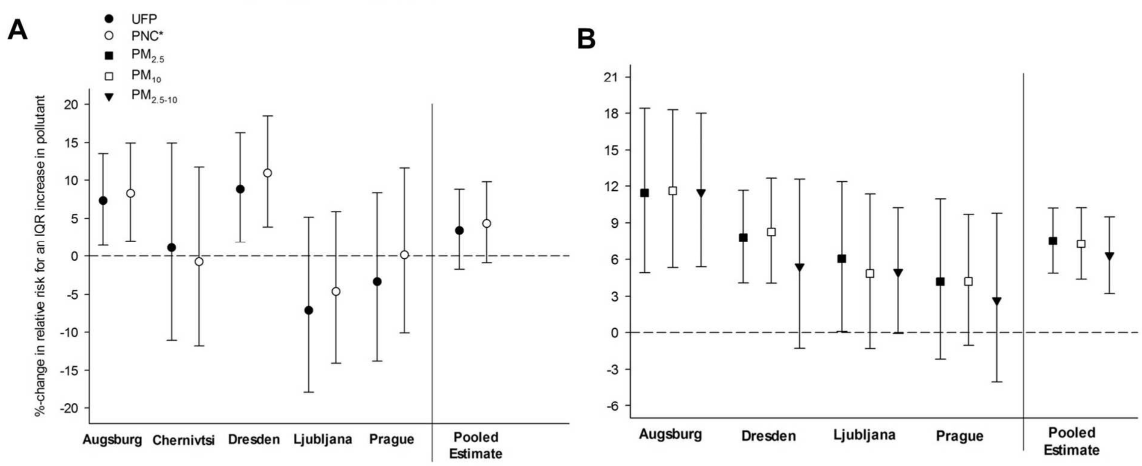

Figure 2

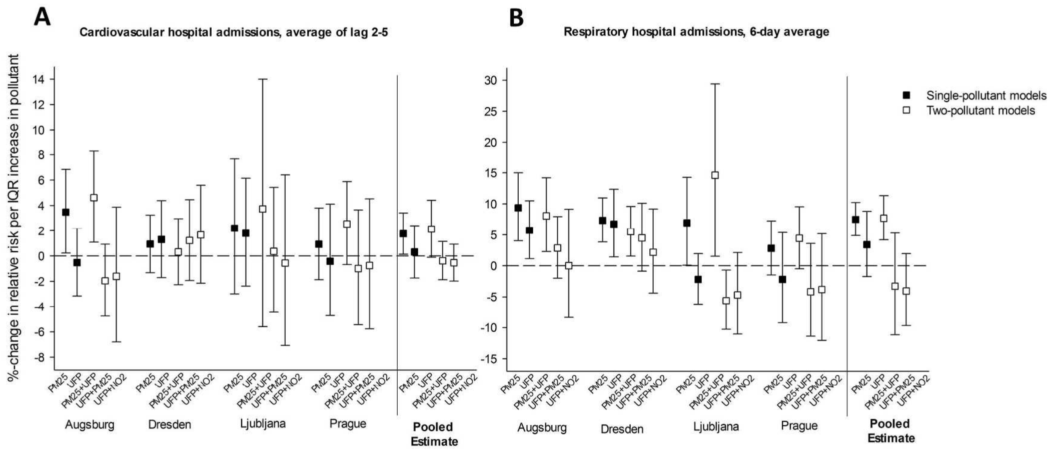
A
Cardiovascular hospital admissions, average of lag 2-5
%-change in relative risk per IQR increase in pollutant
PM25
UFP
PM25+UFP
UFP+PM25
UFP+NO2
Augsburg
Dresden
Ljubljana
Prague
Pooled Estimate
B
Respiratory hospital admissions, 6-day average
Single-pollutant models
Two-pollutant models

Figure 3

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Ultrafine and Fine particles and hospital admissions in Central Europe, Results from the UFIREG study

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Online Data Supplement

Methods

Data collection

Hospital admission statistics for Augsburg and Dresden were obtained from the Research Data Centres of the Federal Statistical Office and the Statistical Offices of the Free States of Bavaria and Saxony, respectively. For Ljubljana, hospital admission data were obtained from the National Institute of Public Health in Slovenia. The Institute of Health Information and Statistics of the Czech Republic provided hospital admissions statistics for Prague.

Information on influenza epidemics in Augsburg and Dresden were provided by the German Influenza Working Group of the Robert Koch Institute (https://influenza.rki.de/Default.aspx). Data on influenza epidemics in Prague were obtained from the National Institute of Public Health in Prague and the Hygiene Station of the City of Prague. In Ljubljana, these data were provided by the National Institute of Public Health in Slovenia. No information on influenza epidemics was available in Chernivtsi. Sociodemographic information for Augsburg derived from the Statistical Yearbook of Augsburg. For Dresden, data were obtained from the census in 2011 and the Statistical Office of the Free State of Saxony. The Statistical Office of the Republic of Slovenia provided socio-demographic data for Ljubljana. Data for Prague were obtained from the Institute of Health Information and Statistics of the Czech Republic and the Czech statistical office. For Chernivtsi data derived from the Main Statistic Department in Chernivtsi Region.

PNC measurements were performed using differential or scanning mobility particle size spectrometers (DMPS/SMPS). They enable highly size-resolved PNC measurements in the range from 10 to 800 nm (except in Prague: 10 to 500 nm) with particle number concentrations between 100 to 100,000 particles per cm^3. Data processing (so-called inversion) of the electrical mobility distribution (measured by the spectrometer) into the true

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particle number size distribution included the multiple charge correction according to Pfeifer et al. (1), coincidence correction of the condensation particle counter (CPC) and the correction of the counting efficiency of the CPC. Particle losses due to diffusion in the inlet system and the spectrometer were also quantified using theoretical functions in the data evaluation software (2). PM_{10} and $PM_{2.5}$ mass concentrations were either determined with a tapered element oscillating microbalance/filter dynamics measurement system (TEOM/FDMS in Dresden and Ljubljana), high volume samplers (HVS in Dresden and Ljubljana) or via ß-absorption (in Augsburg and Prague). All TEOM/FDMS measurements were validated by HVS which is a filter based method. More information on the measurement instruments can be found elsewhere (3). Imputation of missing particulate matter data was possible for Augsburg and Prague where an additional urban background measurement station was available. We imputed missing data according to a modified APHEA (Air Pollution and Health: A European approach) procedure (4). Missing hours of one monitor were imputed by a weighted average of the other monitor. If the respective hourly mean value was not available at both monitors, the average of the preceding and the following hourly means was used.

Sensitivity analyses

To test the robustness of our results we conducted the following sensitivity analyses:

1) We tested different values of smoothness (less and more degrees of freedom (df) for time-trend and meteorological variables.

2) Apparent temperature was included in the model replacing air temperature and relative humidity. Apparent temperature was calculated based on the following formula (5, 6): $at = -2.653 + (0.994 \times temp) + (0.0153 \times dp \times dp)$

with at= apparent temperature, temp=air temperature and dp=dew point temperature.

Dew point temperature (dp) was calculated as follows:

$$dp = \frac{1}{\frac{1}{temp + 241.413} - \frac{\log_{10}(\frac{rh}{100})}{1838.675}} - 241.413$$

with temp= air temperature and rh=relative humidity.

3) We adjusted for air temperature by using temperature above the median for heat effects and below the median for cold effects as shown by Stafoggia et al. (7).

4) We adjusted for air temperature and relative humidity including the average of lag 0-1 and the average of lag 2-5.

5) Air pollution effects were additionally adjusted for barometric pressure.

6) Air pollution effects for Augsburg and Prague were recalculated using a dataset of imputed missing particulate matter data.

7) Distributed lag non-linear models as described by Gasparrini et al. (8) were used to analyse the association between air pollutants and cause-specific hospital admissions. We estimated up to 7 lags using a second degree polynomial and pooled the results according to Gasparrini et al. (9).

8) We reanalyzed the air pollution effects using a city-specific confounder model. We used the absolute value of the sum of the partial autocorrelation function for the selection of df for time trend. Model selection for the other variables (day of the week, holidays, vacation periods, influenza, air temperature and relative humidity) was carried out by minimizing Akaike's Information criterion (AIC). The best cumulative lag for air temperature and relative humidity was chosen and meteorological variables were included linearly or smoothly depending on the AIC value.

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Effects of UFP on cause-specific hospital admissions are presented as percent changes in relative risk per 2,750 particles/cm^3 increase (average interquartile range (IQR) across all five cities) in daily UFP. Effects of $PM_{2.5}$ are presented as percent changes in relative risk per 12.4 µg/m^3 increase (average IQR across Augsburg, Dresden, Ljubljana and Prague) in daily $PM_{2.5}$. PNC (20-800nm (20-500nm in Prague)), PM_{10}, $PM_{2.5\text{-}10}$, NO_2 and SO_2 were investigated as pollutants of secondary interest. Results of secondary pollutants are presented as percent changes in relative risk per 3,675 particles/cm^3, 16 µg/m^3, 4.7 µg/m^3, 15.4 µg/m^3 and 2.8 µg/m^3 increase in PNC, PM_{10}, $PM_{2.5\text{-}10}$and NO_2, respectively.

Data management was conducted using SAS statistical package (version 9.3; SAS Institute Inc, Cary, NC). Statistical analyses were performed using R project for statistical computing (version 2.15.3, http://www.r-project.org/) using the “mgcv”, “splines”, “dlnm” ,“metafor” and “mvmeta” packages. We used the gam function to estimate quasi-Poisson models and the rma function for random effects models.

Results

Effect modification

Effect modification by age, sex and season were analyzed for the association between UFP and respiratory hospital admissions, 6-day average, $PM_{2.5}$ and cardiovascular hospital admissions, average of lag 2-5 and $PM_{2.5}$ and respiratory hospital admissions, 6-day average since we observed the strongest associations for those cumulative lags.

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Table E1. Description of air pollution and meteorological parameters by city.

City (study period)	N	min	median	mean (SD)	max	IQR*
Augsburg (2011-2012)						
Air temperature (°C)	720	-13.4	9.9	10.0 (8.0)	26.8	12.4
Relative humidity (%)	720	39.6	78.3	77.1 (13.0)	100	20.3
PM_{10}† (μg/m³)	725	2.7	17.2	20.0 (12.5)	91.5	14.5
$PM_{2.5}$‡ (μg/m³)	720	1.7	12.4	14.9 (9.8)	86.3	10.8
$PM_{2.5-10}$" (μg/m³)	714	0.1	5.3	6.0 (4.2)	36.0	5.3
UFP§ (n/cm³)	712	1,161	5,172	5,880 (3,016)	28,800	3,332
PNC# (n/cm³)	712	1,369	6,409	7,239 (3,644)	29,470	4,124
NO_2& (μg/m³)	718	4.2	26.9	28.0 (11.8)	74.0	16.1
Chernivtsi (2013)						
Air temperature (°C)	291	-7.4	13.9	11.9 (8.2)	27.4	13.8
Relative humidity (%)	291	31.7	74	74.0 (15.6)	100	22.6
PM_{10}† (μg/m³)	.	.	.	.	.	.
$PM_{2.5}$‡ (μg/m³)	.	.	.	.	.	.
$PM_{2.5-10}$" (μg/m³)						
UFP§ (n/cm³)	340	1,769	5,018	5,511 (2,615)	19,160	3,324
PNC# (n/cm³)	340	2,212	6,908	7,775 (3,782)	29,030	4,325
NO_2& (μg/m³)	.	.	.	.	.	.
Dresden (2011-2012)						
Air temperature (°C)	731	-13.4	11.7	11.7 (8.2)	29.6	12.8
Relative humidity (%)	731	36	69.6	69.5 (11.1)	94.3	16.7
PM_{10}† (μg/m³)	726	2.2	16.5	20.9 (15.2)	103.5	14.3
$PM_{2.5}$‡ (μg/m³)	720	1.5	11.6	16.2 (13.8)	95.7	13.1
$PM_{2.5-10}$" (μg/m³)	717	0.0	4.3	4.7 (2.7)	21.6	3.0
UFP§ (n/cm³)	639	677	3,752	4,286 (2,339)	14,440	2,882
PNC# (n/cm³)	639	855	5,446	5,851 (2,902)	16,710	4,068
NO_2& (μg/m³)	719	3.9	20.4	22.3 (10.0)	67.3	12.9
Ljubljana (2012-2013)						
Air temperature (°C)	730	-8.8	12.2	11.7 (8.7)	29.4	14.0
Relative humidity (%)	731	37.8	74.3	73.8 (13.7)	97.5	23.6
PM_{10}† (μg/m³)	682	3.0	20.0	24.9 (16.8)	130.0	18.0
$PM_{2.5}$‡ (μg/m³)	694	3.4	16.5	20.7 (14.3)	114.8	14.4
$PM_{2.5-10}$" (μg/m³)	646	0.0	3.9	5.0 (5.1)	29.8	5.8
UFP§ (n/cm³)	435	855	4,400	4,693 (1,897)	13,920	1,935
PNC# (n/cm³)	435	1,685	6,071	6,750 (3,122)	24,360	2,689
NO_2& (μg/m³)	683	1.8	22.2	25.1 (14.8)	119.4	16.4
Prague (2012-2013)						
Air temperature (°C)	723	-13.7	9	9.2 (8.4)	27.2	13.1
Relative humidity (%)	704	40.8	78.2	77.3 (13.2)	98.9	20.4
PM_{10}† (μg/m³)	681	5.1	22.2	26.2 (15.7)	100.9	17.2
$PM_{2.5}$‡ (μg/m³)	612	1.6	13.1	16.2 (11.6)	78.8	11.4
$PM_{2.5-10}$" (μg/m³)	579	1.7	9.2	9.8 (4.0)	44.6	4.6
UFP§ (n/cm³)	464	960	3,797	4,197 (2,010)	14,960	2,278

PNC$ (n/cm^3)	464	1,217	5,417	5,799 (2,537)	16,950	3,168
NO_2& (μg/m³)	707	4.5	19.5	21.9 (11.7)	74.2	16.2

*interquartile range

†particulate matter with a size range of <10 μm in aerodynamic diameter

‡particulate matter with a size range of <2.5 μm in aerodynamic diameter

"coarse particles with a size range of 2.5-10 μm in aerodynamic diameter

§ultrafine particles with a size range of 0.02 to 0.1 μm in aerodynamic diameter (20-100 nm)

#particle number concentration with a size range of 0.02 to 0.8 μm in aerodynamic diameter (20-800 nm)

$particle number concentration with a size range of 0.02 to 0.5 μm in aerodynamic diameter (20-500 nm)

&nitrogen dioxide

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Table E2. Spearman's rank correlation coefficients for meteorological and air pollution parameters.

Augsburg (2011-2012)	Air temperature (°C)	Relative humidity (%)	PM_{10}† (µg/m³)	$PM_{2.5}$‡ (µg/m³)	$PM_{2.5\text{-}10}$ (µg/m³)	UFP§ (n/cm³)	PNC# (n/cm³)	NO_2& (µg/m³)
Air temperature (°C)	1.00	-0.57	-0.19	-0.33	0.17	0.06	0.01	-0.53
Relative humidity (%)		1.00	-0.03	0.11	-0.30	-0.37	-0.33	0.19
PM_{10}† (µg/m³)			1.00	0.93	0.78	0.43	0.54	0.70
$PM_{2.5}$‡ (µg/m³)				1.00	0.53	0.37	0.49	0.73
$PM_{2.5\text{-}10}$" (µg/m³)					1.00	0.45	0.50	0.44
UFP§ (n/cm³)						1.00	0.99	0.51
PNC# (n/cm³)							1.00	0.58
NO_2& (µg/m³)								1.00
Chernivtsi (2013)	Air temperature (°C)		PM_{10}† (µg/m³)	$PM_{2.5}$‡ (µg/m³)	$PM_{2.5\text{-}10}$ (µg/m³)	UFP§ (n/cm³)	PNC# (n/cm³)	NO_2& (µg/m³)
Air temperature (°C)	1.00	-0.55	.	.	.	0.08	0.01	.
Relative humidity (%)		1.00	.	.	.	-0.29	-0.19	.
PM_{10}† (µg/m³)			.	.	.	.	.	.
$PM_{2.5}$‡ (µg/m³)				.	.	.	.	.
$PM_{2.5\text{-}10}$" (µg/m³)					.	.	.	.
UFP§ (n/cm³)						1.00	0.97	.
PNC# (n/cm³)							1.00	.
NO_2& (µg/m³)								.
Dresden (2011-2012)	Air temperature (°C)	Relative humidity (%)	PM_{10}† (µg/m³)	$PM_{2.5}$‡ (µg/m³)	$PM_{2.5\text{-}10}$ (µg/m³)	UFP§ (n/cm³)	PNC# (n/cm³)	NO_2& (µg/m³)
Air temperature (°C)	1.00	-0.50	-0.28	-0.37	0.17	0.29	0.19	-0.42
Relative humidity (%)		1.00	0.06	0.14	-0.28	-0.42	-0.35	0.28
PM_{10}† (µg/m³)			1.00	0.97	0.58	0.37	0.56	0.68
$PM_{2.5}$‡ (µg/m³)				1.00	0.40	0.30	0.50	0.68

	Air temperature (°C)	Relative humidity (%)	PM_{10}† (µg/m³)	$PM_{2.5}$‡ (µg/m³)	$PM_{2.5-10}$ (µg/m³)	UFP§ (n/cm³)	PNC# (n/cm³)	NO_2& (µg/m³)
$PM_{2.5-10}$" (µg/m³)					1.00	0.51	0.58	0.37
UFP§ (n/cm³)						1.00	0.96	0.33
PNC# (n/cm³)							1.00	0.45
NO_2& (µg/m³)								1.00
Ljubljana (2012-2013)	Air temperature (°C)	Relative humidity (%)	PM_{10}† (µg/m³)	$PM_{2.5}$‡ (µg/m³)	$PM_{2.5-10}$ (µg/m³)	UFP§ (n/cm³)	PNC# (n/cm³)	NO_2& (µg/m³)
Air temperature (°C)	1.00	-0.45	-0.44	-0.53	-0.06	-0.17	-0.22	-0.54
Relative humidity (%)		1.00	0.06	0.16	-0.14	0.08	0.13	0.38
PM_{10}† (µg/m³)			1.00	0.95	0.67	0.36	0.59	0.57
$PM_{2.5}$‡ (µg/m³)				1.00	0.43	0.27	0.50	0.55
$PM_{2.5-10}$" (µg/m³)					1.00	0.46	0.55	0.40
UFP§ (n/cm³)						1.00	0.95	0.54
PNC# (n/cm³)							1.00	0.62
NO_2& (µg/m³)								1.00
Prague (2012-2013)	Air temperature (°C)	Relative humidity (%)	PM_{10}† (µg/m³)	$PM_{2.5}$‡ (µg/m³)	$PM_{2.5-10}$ (µg/m³)	UFP§ (n/cm³)	PNC$ (n/cm³)	NO_2& (µg/m³)
Air temperature (°C)	1.00	-0.52	-0.19	-0.25	0.14	0.31	0.15	-0.46
Relative humidity (%)		1.00	0.00	0.12	-0.16	-0.31	-0.18	0.35
PM_{10}† (µg/m³)			1.00	0.96	0.77	0.29	0.54	0.68
$PM_{2.5}$‡ (µg/m³)				1.00	0.61	0.25	0.50	0.66
$PM_{2.5-10}$" (µg/m³)					1.00	0.40	0.56	0.43
UFP§ (n/cm³)						1.00	0.94	0.26
PNC$ (n/cm³)							1.00	0.46
NO_2& (µg/m³)								1.00

†particulate matter with a size range of <10 µm in aerodynamic diameter

‡particulate matter with a size range of <2.5 µm in aerodynamic diameter

"coarse particles with a size range of 2.5-10 µm in aerodynamic diameter

§ultrafine particles with a size range of 0.02 to 0.1µm in aerodynamic diameter (20-100 nm)

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#particle number concentration with a size range of 0.02 to 0.8µm in aerodynamic diameter (20-800 nm)

$particle number concentration with a size range of 0.02 to 0.5µm in aerodynamic diameter (20-500 nm)

&nitrogen dioxide

Table E3. Percent changes in the pooled relative risk (95%-CI) of cause-specific hospital admissions with each average IQR increase in air pollutants, single lags.

Association under investigation	IQR†	lag 0	lag 1	lag 2	lag 3	lag 4	lag 5
Cardiovascular hospital admissions							
UFP (n/cm^3)	2,750	-0.9 (-2.2; 0.5)	0.1 (-1.3; 1.5)	0.3 (-1.0; 1.7)	0.1 (-1.6; 1.9)	0.5 (-0.8; 1.9)	-0.2 (-1.6; 1.1)
PNC (n/cm^3)	3,675	-0.9 (-2.4; 0.5)	0.1 (-1.4; 1.6)	0.5 (-1.0; 1.9)	0.1 (-1.7; 1.8)	0.7 (-0.7; 2.2)	0.2 (-1.2; 1.6)
$PM_{2.5}$ (µg/m³)	12.4	0.5 (-1.0; 2.0)	0.6 (-0.8; 2.0)	0.8 (-0.5; 2.0)	1.0 (-0.2; 2.3)	1.0 (-0.3; 2.3)	1.6 (0.1; 3.1)
PM_{10} (µg/m³)	16.0	-0.3 (-1.9; 1.4)	0.2 (-1.7; 2.1)	0.1 (-1.8; 2.1)*	0.5 (-0.8; 1.8)	0.6 (-0.7; 1.9)	1.2 (-0.1; 2.5)
$PM_{2.5-10}$ (µg/m³)	4.7	-0.6 (-2.0; 0.8)	0.5 (-0.9; 1.9)	0.7 (-0.9; 2.4)	0.5 (-0.8; 1.8)	0.5 (-0.9; 1.8)	1.0 (-0.3; 2.3)
NO_2 (µg/m³)	15.4	-0.2 (-1.9; 1.5)	-1.1 (-3.5; 1.4)	-1.3 (-3.0; 0.5)	-0.3 (-2.0; 1.4)	0.2 (-1.5; 1.9)	1.0 (-0.7; 2.7)
Respiratory hospital admissions							
UFP (n/cm^3)	2,750	0.5 (-3.1; 4.3)*	1.4 (-2.6; 5.6)*	0.6 (-1.5; 2.8)	1.3 (-0.6; 3.3)	0.4 (-1.6; 2.3)	1.2 (-0.8; 3.1)
PNC (n/cm^3)	3,675	0.6 (-3.3; 4.6)*	2.0 (-2.3; 6.4)*	1.0 (-1.3; 3.3)	2.1 (0.0; 4.2)	0.9 (-1.2; 3.0)	1.5 (-0.7; 3.7)
$PM_{2.5}$ (µg/m³)	12.4	1.6 (-1.8; 5.1)*	4.2 (2.2; 6.2)	3.5 (1.8; 5.4)	4.3 (2.6; 6.1)	3.5 (1.6; 5.5)	3.8 (1.9; 5.7)
PM_{10} (µg/m³)	16.0	2.2 (-0.8; 5.3)*	4.6 (2.6; 6.6)	3.7 (1.9; 5.5)	4.2 (2.3; 6.0)	3.2 (1.3; 5.1)	3.3 (1.1; 5.5)
$PM_{2.5-10}$ (µg/m³)	4.7	1.6 (-0.7; 4.0)	3.0 (1.1; 4.8)	2.2 (0.4; 4.1)	3.3 (1.4; 5.2)	2.0 (0.1; 3.9)	2.2 (0.2; 4.3)
NO_2 (µg/m³)	15.4	1.7 (-2.6; 6.2)*	2.4 (-1.1; 6.1)*	1.0 (-1.4; 3.5)	2.7 (-0.4; 5.9)	3.0 (0.5; 5.4)	3.6 (1.3; 6.1)
Diabetes hospital admissions							
UFP (n/cm^3)	2,750	0.4 (-3.5; 4.5)	0.2 (-3.8; 4.5)	-0.4 (-4.3; 3.6)	-2.8 (-6.9; 1.4)	7.4 (1.9; 13:3)	1.7 (-2.4; 5.9)
PNC (n/cm^3)	3,675	0.4 (-3.8; 4.9)	0.2 (-4.2; 4.8)	-0.5 (-4.7; 3.9)	-2.0 (-6.5; 2.7)	6.3 (2.0; 10.8)	3.1 (-2.4; 8.9)
$PM_{2.5}$ (µg/m³)	12.4	0.8 (-3.3; 5.0)	0.9 (-3.1; 5.0)	1.4 (-2.5; 5.5)	1.7 (-2.2; 5.8)	2.1 (-1.9; 6.3)	5.6 (1.6; 9.8)
PM_{10} (µg/m³)	16.0	0.1 (-4.0; 4.3)	0.5 (-3.5; 4.7)	0.3 (-4.1; 4.9)	1.6 (-2.3; 5.8)	2.6 (-1.5; 6.8)	6.6 (2.2; 11.1)
$PM_{2.5-10}$ (µg/m³)	4.7	-0.6 (-5.4; 4.4)	-1.5 (-5.8; 3.1)	-1.1 (-5.3; 3.3)	-0.6 (-4.7; 3.7)	1.7 (-2.4; 6.0)	4.0 (-0.2; 8.4)
NO_2 (µg/m³)	15.4	0.2 (-5.1; 5.8)	0.4 (-5.0; 6.0)	-2.3 (-7.5; 3.2)	-3.5 (-8.6; 1.9)	-0.5 (-5.7; 5.0)	2.9 (-2.3; 8.5)

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†average interquartile range across all cities
*heterogeneity p-value<0.1 and I^2>50%

Table E4. Effect modification by age, sex and season of the association between air pollutants and cause-specific hospital admissions.

	UFP** and respiratory hospital admissions (6-day average)	$PM_{2.5}$† and cardiovascular hospital admissions (average of lag 2-5)	$PM_{2.5}$† and respiratory hospital admissions (6-day average)
Main effect	3.4 (-1.7; 8.8)	1.8 (0.1;3.4)	7.5 (4.9; 10.2)
Age			
<75 years	3.8 (-0.7; 8.4)	1.1 (-1.0; 3.2)	7.7 (4.0; 11.6)
≥75 years	7.0 (0.3; 14.1)	2.5 (0.3; 4.8)	7.0 (2.4;11.7)
Sex			
females	3.0 (-5.4; 12.2)*	1.7 (-0.4; 3.9)	7.2 (3.4; 11.1)
males	4.6 (-1.0; 10.5)	1.7 (-0.4; 3.9)	8.1 (3.7; 12.7)
Season			
October-March	4.6 (-2.6; 12.4)*	1.9 (0.3; 3.6)	7.5 (4.8; 10.3)
April-September	4.3 (-0.8; 9.5)	-0.1 (-3.3; 3.2)	6.6 (1.2; 12.3)

Average interquartile range for UFP: 2,750 particles/cm^3

Average interquartile range for $PM_{2.5}$: 12.4 $\mu g/m^3$

*heterogeneity p-value<0.1 and I^2>50%

**Ultrafine particles with a size range of 0.02 to 0.1µm in aerodynamic diameter (20-100 nm)

†Particulate matter with a size range of <2.5 µm in aerodynamic diameter

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Table E5. Sensitivity analyses, percent change in the pooled relative risk (95%-CI) of respiratory hospital admissions per IQR increase in UFP and percent change in the pooled relative risk of cardiovascular and respiratory hospital admissions per IQR increase in $PM_{2.5}$.

Sensitivity Analysis	UFP* and respiratory hospital admissions (6-day average)	$PM_{2.5}$† and cardiovascular hospital admissions (average of lag 2-5)	$PM_{2.5}$† and respiratory hospital admissions (6-day average)
Original Model	3.4 (-1.7; 8.8)	1.8 (0.1; 3.4)	7.5 (4.9; 10.2)
More DF‡ (DF = 6 per year) for smooth function of trend	1.4 (-2.5; 5.4)	0.9 (-0.8; 2.7)	5.7 (2.9; 8.6)
Fewer DF‡ (DF = 3 per year) for smooth function of trend	3.7 (-1.4; 9.1)	1.9 (0.1; 3.7)	7.1 (4.5; 9.7)
More DF‡ (DF = 5) for smooth functions of meteorological variables	2.4 (-3.4; 8.6)	1.4 (-0.2; 3.1)	6.5 (3.8; 9.2)
Use of apparent temperature	3.9 (0.5; 7.4)	1.8 (0.3; 3.4)	7.1 (4.6; 9.7)
Adjusting for air temperature by using temperature above the median for heat effects and below the median for cold effects	4.4 (-0.2; 9.1)	1.9 (0.3; 3.6)	7.1 (4.6; 9.6)
Adjusting for air temperature and relative humidity average of lag 0-1 and average of lag 2-5	4.3 (-1.4; 10.4)	2.5 (0.2; 4.9)	9.3 (6.7; 12.1)
Inclusion of barometric pressure	2.3 (-3.4; 8.4)	1.7 (0.0; 3.5)	6.8 (4.0; 9.7)

Using a city-specific confounder model	0.9 (-2.9; 4.8)	0.7 (-1.1; 2.5)	4.4 (1.8; 7.0)

Average interquartile range for UFP: 2,750 particles/cm^3

Average interquartile range for $PM_{2.5}$: 12.4 µg/m^3

*Ultrafine particles with a size range of 0.02 to 0.1µm in aerodynamic diameter (20-100 nm)

†Particulate matter with a size range of <2.5 µm in aerodynamic diameter

‡Degrees of freedom

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Table E6. City-specific confounder models.

	time trend	day of the week	vacation periods	holidays	influenza	air temperature	relative humidity
Cardiovascular hospital admissions							
Augsburg	df*=11	x	x	x	x	2-day average (df*=2), average of lag 2-5 (df*=3)	average of lag 2-13 (df*=2)
Dresden	df*=8	x	x	x	x	average of lag 0-5 linearly, average of lag 2-13 linearly	2-day average linearly, average of lag 2-13 (df*=4)
Ljubljana	df*=6	x	x	x	x	2-day average (df*=5), average of lag 2-13 (df*=5)	average of lag 2-5 linearly, average of lag 2-13 (df*=4)
Prague	df*=11	x	x	x		2-day average linearly, average of lag 2-13 (df*=2)	2-day average (df*=2), average of lag 2-13 linearly
Respiratory hospital admissions							
Augsburg	df*=9	x	x	x		2-day average (df*=2), average of lag 2-13 (df*=2)	average of lag 2-5 (df*=2), average of lag 2-13 (df*=2)
Chernivtsi	df*=2	x	x	x	not available	2-day average (df*=2), average of lag 2-13 linearly	average of lag 2-5 (df*=3)
Dresden	df*=8	x		x		2-day average (df*=2), average of lag 2-13 (df*=3)	
Ljubljana	df*=8	x	x	x		2-day average linearly, average of lag 2-13 (df*=7)	
Prague	df*=10	x	x			2-day average (df*=2), average of lag 2-13 (df*=2)	averalge of lag 2-5 linearly, average of lag 2-13 linearly

*degrees of freedom

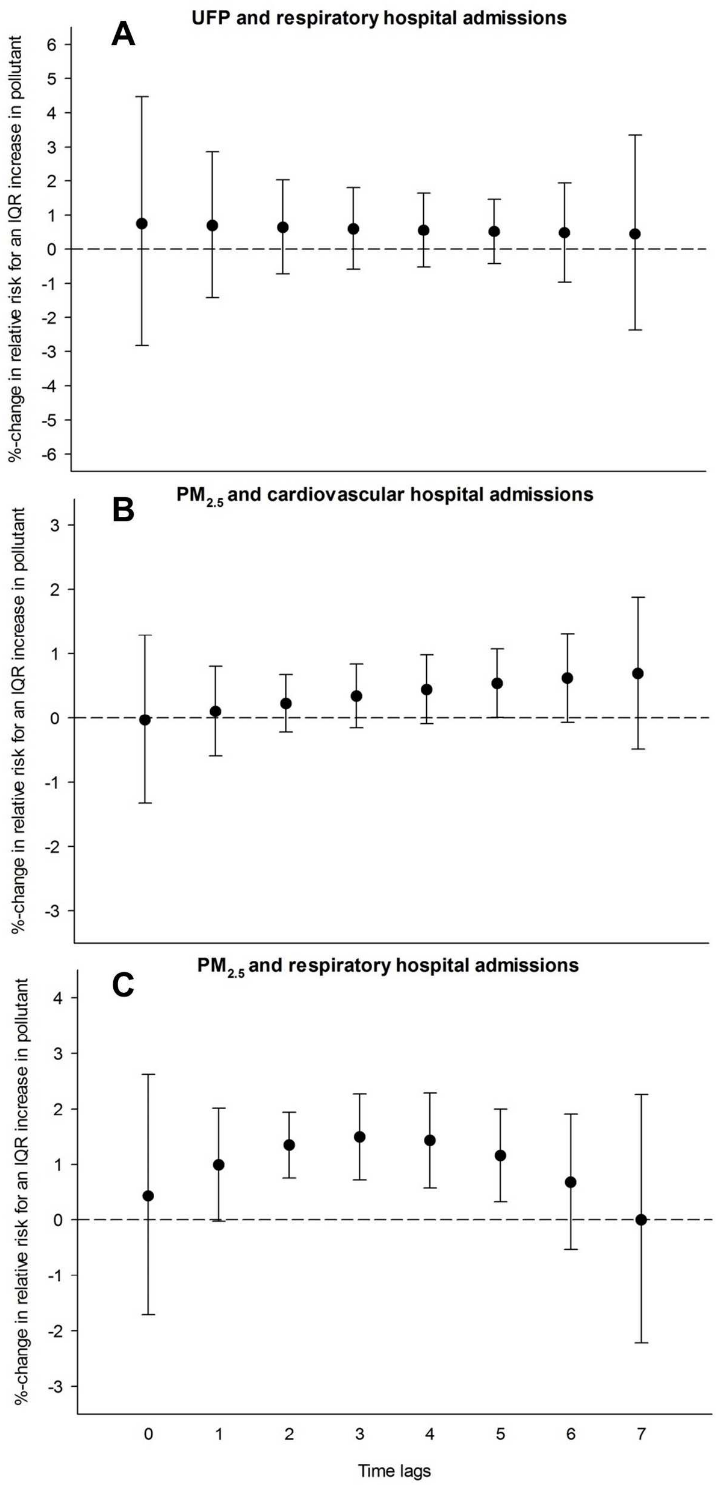

Figure E1. Results of second degree polynomial distributed lag models presented as percent changes in the pooled relative risks of A) respiratory hospital admissions per IQR increase in UFP and B) cardiovascular and C) respiratory hospital admissions per IQR increase in $PM_{2.5}$, lag 0 to 7.

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