Ultrafine and Fine Particles and Hospital Admissions in Central Europe
Results from the UFIREG Study

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Abstract

Rationale: Evidence of short-term effects of ultrafine particles (UFP) on health is still inconsistent and few multicenter 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 (particulate matter with an aerodynamic diameter less than 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 focusing on cardiovascular and respiratory diseases were obtained for Augsburg and Dresden (Germany), 2011–2012; Chernivtsi (Ukraine), 2013 to March 2014; and Ljubljana (Slovenia) and Prague (Czech Republic), 2012–2013. Air pollution and meteorologic 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 metaanalysis methods.

Measurements and Main Results: A 2,750 particles/cm^3 increase (average interquartile range 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 to 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-d average exposure, 7.5% [4.9–10.2%]) admissions per 12.4 μg/m^3 increase (average interquartile range) 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 multicenter studies are needed using harmonized UFP measurements to draw definite conclusions on health effects of UFP.

Keywords: ultrafine particles; particulate matter; hospital admissions; respiratory; cardiovascular

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*A complete list of UFIREG study group members may be found before the beginning of the REFERENCES.

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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 multicity studies in this field and includes cities from Eastern Europe. Furthermore, exposure assessment and statistical analyses were conducted based on *a priori* fixed and harmonized protocols. Our findings indicated delayed and prolonged effects of ultrafine particles exposure on respiratory hospital admissions. Moreover, we found delayed and prolonged effects of $PM_{2.5}$ exposure on hospital admissions because of cardiovascular and respiratory diseases.

Many epidemiologic studies have investigated the association between particulate matter (PM) with an aerodynamic diameter less than 10 μm (PM_{10}) or less than 2.5 μm ($PM_{2.5}$) and (emergency) hospital admissions especially caused by cardiovascular and respiratory diseases (1–4). For example, Atkinson and colleagues (5) found increases in hospital admissions caused by cardiovascular (0.9% [0.3–1.5%]) and respiratory diseases (1.0% [−0.6 to 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 regions.

Only a few studies investigated the association between ultrafine particles (UFP) and hospital admissions worldwide. 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 biologic mechanisms than larger particles, such as PM_{10} and $PM_{2.5}$. The deposition and clearance in the respiratory tract differ between UFP and larger particles. Although 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 bloodstream to other organs (7, 8). Because of 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 with 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 and colleagues (12) reported strongest associations for accumulation mode particles in the size range 205 to 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 (PNC) and emergency hospital admissions for cardiovascular and respiratory causes in London. A study performed 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 to 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 NO_2 on cause-specific hospital admissions in these five cities. This study is one of the very few multicity 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 1 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 caused by cardiovascular (ICD-10: I00-I99) and respiratory diseases (ICD-10: J00-J99). Moreover, we investigated hospital admissions caused by diabetes (ICD-10: E10-E14) as an outcome of secondary interest. No informed consent by the patients was needed because data were anonymous and collected as daily counts. In Chernivtsi, Ljubljana, and Prague data were 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. Because of 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 because the number of hospitalizations in these categories were very high, and only acute hospitalizations were considered.

Hourly data of air pollutants and meteorologic 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 was located in a suburban background region. PNC in the range from 10 to 800 nm (for Prague, from 10 to 500 nm) was 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 meteorologic parameters were only calculated if 75% of the hourly values were available. Because of measurement uncertainties in the size range 10 to 20 nm, we investigated UFP in the size range 20 to 100 nm and PNC in the size range 20 to 800 nm (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, because of the start of the measurements and the availability of epidemiologic 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 Analyses

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, 1 d before the event] to represent effects of high temperatures and average of lags 2–13 [lag 2, 2 d before the event; lag 13, 13 d before 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 nonlinear 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 meteorologic variables were fixed to three degrees of freedom. We investigated single-lags from same day of the event (lag 0) up to 5 days before the event (lag 5). Moreover, we estimated cumulative effect models to represent immediate (2-d average, lag 0–1), delayed (average of lag 2–5), and prolonged effects (6-d average, lag 0–5).

In a second stage, city-specific effect estimates were combined using random-effects models (20). For each metaanalytical estimate, a chi-square test for heterogeneity was performed and the corresponding P value and I^2-statistic was reported. Cities were weighted according to the precision (SE) 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 yr vs. ⩾75 yr) 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 to assess interdependencies of UFP and $PM_{2.5}$ effects and 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 supplement).

Results

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 meteorologic parameters by city is presented in Table E1 in the online supplement. Mean PM_{10} values ranged from 20.0 $\mu g/m^3$ in Augsburg to 26.2 $\mu g/m^3$ in Prague. Ljubljana showed highest $PM_{2.5}$ values with a mean of 20.7 $\mu g/m^3$, 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 rank correlation coefficient, $0.3 \leq r_s \leq 0.5$) in all cities (*see* Table E2). The correlation between PNC and PM_{10}, $PM_{2.5}$, and $PM_{2.5–10}$ was slightly higher with r_s between 0.5 and 0.6. Meteorologic 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 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 $\mu g/m^3$ 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 with $PM_{2.5}$.

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 to 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 nonsignificant 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 $PM_{2.5–10}$. 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

Table 1. Sociodemographic 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.

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 (*see* 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 greater than or equal to 75 years compared with the younger age group (*see* 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 admissions was similar during

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

Definition of abbreviations: CI = confidence interval; IQR = interquartile range; $PM_{2.5}$ = particulate matter with an aerodynamic diameter less than 2.5 μm; $PM_{2.5–10}$ = particulate matter with an aerodynamic diameter between 2.5 and 10 μm; PM_{10} = particulate matter with an aerodynamic diameter less than 10 μm; PNC = particle number concentration; UFP = ultrafine particles.
*Average interquartile range across all cities.
†Heterogeneity $P < 0.1$ and $I^2 > 50\%$.

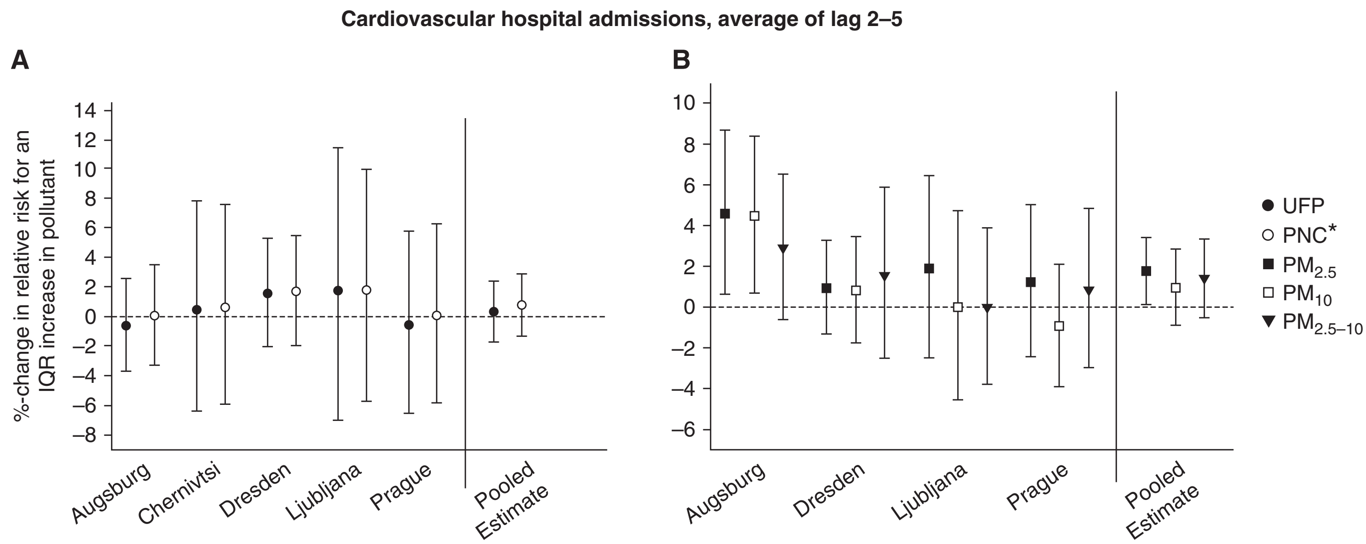

Figure 1. Percent change in the city-specific and pooled relative risk of cardiovascular hospital admissions with each interquartile range (IQR) increase in (*A*) ultrafine particles (UFP) and particle number concentration (PNC), average of lag 2–5, and (*B*) particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), less than 10 μm (PM_{10}), and between 2.5 and 10 μm ($PM_{2.5–10}$), average of lag 2–5. *Prague: PNC 20–500 nm.

October–March and April–September. However, we found an increase in cardiovascular hospital admissions with a 12.4 μg/m^3 increase in $PM_{2.5}$ during the cold period, but no association during the warm period. Effects of $PM_{2.5}$ on respiratory hospital admissions were slightly stronger during the cold period compared with the warm period. Sensitivity analyses were only conducted for cumulative lag 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 with 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

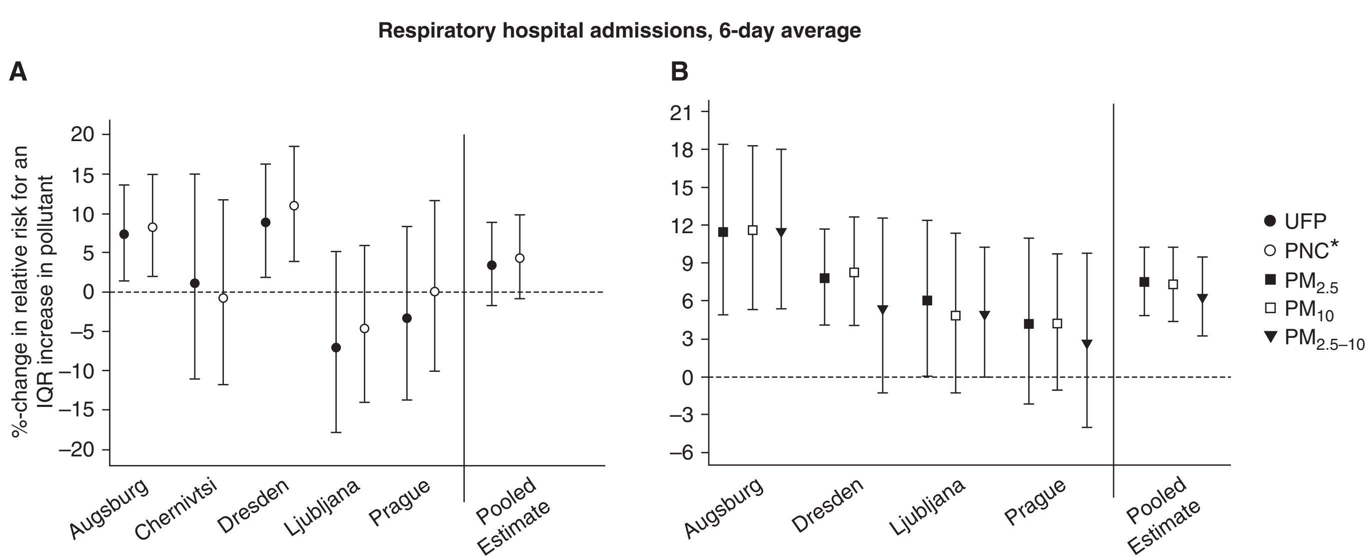

Figure 2. Percent change in the city-specific and pooled relative risk of respiratory hospital admissions with each interquartile range (IQR) increase in (*A*) ultrafine particles (UFP) and particle number concentration (PNC), 6-day average, and (*B*) particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), less than 10 μm (PM_{10}), and between 2.5 and 10 μm ($PM_{2.5–10}$), 6-day average. *Prague: PNC 20–500 nm.

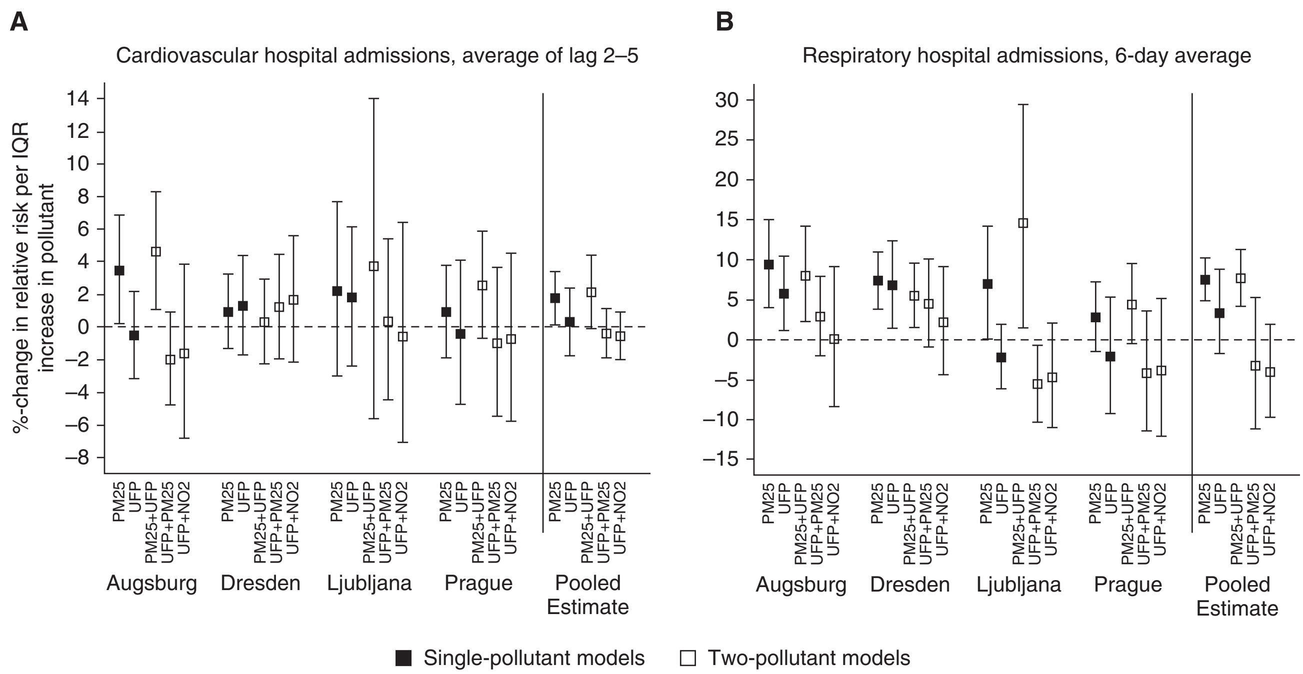

Figure 3. Percent change in the city-specific and pooled relative risk of (*A*) cardiovascular hospital admissions per interquartile range (IQR) increase in pollutant (average of lag 2–5) and (*B*) respiratory hospital admissions per IQR increase in pollutant (6-day average) using single- and two-pollutant models. $PM_{2.5}$ = main effects of particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$); $PM_{2.5}$ + UFP = effects of $PM_{2.5}$ adjusted for ultrafine particles (UFP); UFP = main effects of UFP; UFP + $PM_{2.5}$ = effects of UFP adjusted for $PM_{2.5}$; UFP + NO_2 = effects of UFP adjusted for NO_2.

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 and $PM_{2.5}$ 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 caused by 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 caused by cardiovascular and especially respiratory diseases (*see* 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 (*see* Table E6) showed positive but weaker effect estimates of UFP and respiratory hospital admissions compared with 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, Ljubljana, and Prague. Our findings indicated delayed and prolonged effects of UFP and PNC exposure on respiratory hospital admissions (6-d average of UFP, 3.4% [−1.7 to 8.8%] and PNC, 4.3% [−0.9 to 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 caused by 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 with $PM_{2.5}$.

$PM_{2.5}$ has been shown to be associated with increases in hospital admissions especially caused by cardiovascular and respiratory diseases (5, 11). For example, Stafoggia and colleagues (4) reported immediate (2-d average, 0.5% [0.1–0.9%]) and prolonged (6-d average, 0.5% [0.0–1.0%]) increases in cardiovascular hospital admissions and prolonged increases in respiratory hospital admissions (6-d 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-d average, 6.0% [4.0–8.2%]) were stronger compared with results from other European regions and the United States (3, 4, 23). In contrast to our study, Stafoggia and colleagues (4) and Zanobetti and colleagues (3) analyzed emergency hospital admissions. However, our association between $PM_{2.5}$ and respiratory hospital admissions was also stronger compared with a U.S. study conducted by Bell and colleagues (23) focusing not only on emergency hospital admissions.

Our effect estimates for $PM_{2.5}$ and respiratory hospital admissions are comparable with results of $PM_{2.5}$ and hospital admissions caused by chronic obstructive pulmonary disease in the U.S. Southeast region involving 35 counties that 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 World Health Organization 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 5-day delayed increase of 3.6% (1.0–6.3%) in hospital admissions caused by 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 United States, 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 to March, whereas no association was observed during the warm period from April to September. Bell and colleagues (23) also observed higher effect estimates for $PM_{2.5}$ and cardiovascular hospital admissions during winter in 202 U.S. counties. However, a multicity study in Southern European regions found stronger effects from April to September compared with 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 4-day 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 2- to 7-day 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 to 5.3%]) and prolonged increases (6-d average, 3.4% [−1.7 to 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 because the correlation between UFP and NO_2 was higher in Augsburg and Ljubljana ($r_s = 0.5$) compared with 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 dominates the prediction (27).

Plausible Biologic Mechanisms

Oxidative stress in the lungs and lung inflammation caused by air pollutants, especially by fine particles and UFP, are one of the potential biologic mechanisms leading to respiratory diseases (11, 28, 29). Three biologic pathways that are assumed to not act independently are discussed to be associated with effects beyond the lung. (*1*) Inhalation of particles may lead to a release of proinflammatory mediators or vasculoactive molecules from lung cells causing systemic oxidative stress and inflammation. This may further cause endothelial dysfunction, adverse cardiac outcomes, and a procoagulation 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 defense mechanisms. UFP have a higher biologic 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 biologic mechanisms 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. Epidemiologic analyses were conducted according to a common analysis plan to produce comparable results. Therefore, comparable city-specific effect estimates could be 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 2 and in case of Chernivtsi only 1 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 $PM_{2.5–10}$ 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 caused by 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 with $PM_{2.5}$ and respiratory hospital admissions (27). However, an extensive quality assurance program was an essential part of the project to provide reliable and comparable data between the measurement stations (35). UFPs 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 $PM_{2.5–10}$ and showed similar results. Effects of $PM_{2.5}$ on respiratory hospital admissions were stronger compared with results from other European regions and the United States (3, 4, 23). Moreover, respiratory hospital admissions increased in association with exposure to NO_2 and we observed an increase in hospital admissions caused by 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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References

1. Belleudi V, Faustini A, Stafoggia M, Cattani G, Marconi A, Perucci CA, Forastiere F. Impact of fine and ultrafine particles on emergency hospital admissions for cardiac and respiratory diseases. *Epidemiology* 2010;21:414–423.
2. Franck U, Odeh S, Wiedensohler A, Wehner B, Herbarth O. The effect of particle size on cardiovascular disorders—the smaller the worse. *Sci Total Environ* 2011;409:4217–4221.
3. Zanobetti A, Franklin M, Koutrakis P, Schwartz J. Fine particulate air pollution and its components in association with cause-specific emergency admissions. *Environ Health* 2009;8:58-069X-8-58.
4. Stafoggia M, Samoli E, Alessandrini E, Cadum E, Ostro B, Berti G, Faustini A, Jacquemin B, Linares C, Pascal M, *et al*.; MED-PARTICLES Study Group. Short-term associations between fine and coarse particulate matter and hospitalizations in Southern Europe: results from the MED-PARTICLES project. *Environ Health Perspect* 2013;121:1026–1033.
5. Atkinson RW, Kang S, Anderson HR, Mills IC, Walton HA. Epidemiological time series studies of PM2.5 and daily mortality and hospital admissions: a systematic review and meta-analysis. *Thorax* 2014;69:660–665.
6. WHO. Review of evidence on health aspects of air pollution – REVIHAAP Project. Technical Report; 2013 [accessed 2015 May 8]. Available from: http://www.euro.who.int/__data/

assets/pdf_file/0004/193108/REVIHAAP-Final-technical-report-final-version.pdf
7. HEI Review Panel on Ultrafine Particles. Understanding the health effects of ambient ultrafine particles. HEI Perspectives 3. Boston, MA: Health Effects Institute; 2013.
8. Kreyling WG, Semmler-Behnke M, Möller W. Health implications of nanoparticles. *J Nanopart Res* 2006;8:543–562.
9. Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC Jr, *et al*.; Expert Panel on Population and Prevention Science of the American Heart Association. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation* 2004;109:2655–2671.
10. Peters A, Rückerl R, Cyrys J. Lessons from air pollution epidemiology for studies of engineered nanomaterials. *J Occup Environ Med* 2011; 53(Suppl 6):S8–S13.
11. Rückerl R, Schneider A, Breitner S, Cyrys J, Peters A. Health effects of particulate air pollution: a review of epidemiological evidence. *Inhal Toxicol* 2011;23:555–592.
12. Braniš M, Vyškovská J, Malý M, Hovorka J. Association of size-resolved number concentrations of particulate matter with cardiovascular and respiratory hospital admissions and mortality in Prague, Czech Republic. *Inhal Toxicol* 2010;22:21–28.
13. Atkinson RW, Fuller GW, Anderson HR, Harrison RM, Armstrong B. Urban ambient particle metrics and health: a time-series analysis. *Epidemiology* 2010;21:501–511.
14. Andersen ZJ, Wahlin P, Raaschou-Nielsen O, Ketzel M, Scheike T, Loft S. Size distribution and total number concentration of ultrafine and accumulation mode particles and hospital admissions in children and the elderly in Copenhagen, Denmark. *Occup Environ Med* 2008;65: 458–466.
15. Lanzinger S, Schneider A, Breitner S, Stafoggia M, Erzen I, Dostal M, Pastorkova A, Bastian S, Cyrys J, Zscheppang A, *et al*.; UFIREG study group. Associations between ultrafine and fine particles and mortality in five central European cities. Results from the UFIREG study. *Environ Int* 2016;88:44–52.
16. Lanzinger S. Health effects of ultrafine and fine particles in Central Europe. Results from the UFIREG Study. Presented at the ISEE conference. August 30 to September 3, 2015, Sao Paulo, Brazil.
17. Lanzinger S. Health effects of ultrafine and fine particles in Central Europe. Results from the UFIREG Study. Presented at the ISEE-Europe Young Researchers Conference. November 2–3, 2015, Utrecht, the Netherlands.
18. Lanzinger S. Health effects of ultrafine particles in Central Europe. Preliminary results from the UFIREG Project. Presented at the ISEE-Europe Young Researchers Conference. October 20–22, 2014, Barcelona, Spain.
19. UFIREG-report. Data collection and methods; 2014 [accessed 2016 April 6]. Available from: http://www.ufireg-central.eu/index.php/downloads
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–188.
21. Stafoggia M, Cesaroni G, Peters A, Andersen ZJ, Badaloni C, Beelen R, Caracciolo B, Cyrys J, de Faire U, de Hoogh K, *et al*. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the ESCAPE project. *Environ Health Perspect* 2014;122:919–925.
22. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med* 2002;21:589–624.
23. Bell ML, Ebisu K, Peng RD, Walker J, Samet JM, Zeger SL, Dominici F. Seasonal and regional short-term effects of fine particles on hospital admissions in 202 US counties, 1999-2005. *Am J Epidemiol* 2008; 168:1301–1310.
24. Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, Samet JM. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* 2006;295:1127–1134.
25. Mills IC, Atkinson RW, Kang S, Walton H, Anderson HR. Quantitative systematic review of the associations between short-term exposure to nitrogen dioxide and mortality and hospital admissions. *BMJ Open* 2015;5:e006946-2014-006946.
26. Zanobetti A, Dominici F, Wang Y, Schwartz JD. A national case-crossover analysis of the short-term effect of PM2.5 on hospitalizations and mortality in subjects with diabetes and neurological disorders. *Environ Health* 2014;13:38-069X-13-38.
27. Zidek JV, Wong H, Le ND, Burnett R. Causality, measurement error and multicollinearity in epidemiology. *Environmetrics* 1996;7:441–451.
28. Brook RD, Rajagopalan S, Pope CA III, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, *et al*.; American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation* 2010;121:2331–2378.
29. Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, Forastiere F, Franchini M, Franco OH, Graham I, *et al*.; ESC Working Group on Thrombosis, European Association for Cardiovascular Prevention and Rehabilitation; ESC Heart Failure Association. Expert position paper on air pollution and cardiovascular disease. *Eur Heart J* 2015;36:83–93b.
30. Utell MJ, Frampton MW, Zareba W, Devlin RB, Cascio WE. Cardiovascular effects associated with air pollution: potential mechanisms and methods of testing. *Inhal Toxicol* 2002;14:1231–1247.
31. Widdicombe J, Lee LY. Airway reflexes, autonomic function, and cardiovascular responses. *Environ Health Perspect* 2001;109:579–584.
32. Brook RD, Jerrett M, Brook JR, Bard RL, Finkelstein MM. The relationship between diabetes mellitus and traffic-related air pollution. *J Occup Environ Med* 2008;50:32–38.
33. Liu C, Ying Z, Harkema J, Sun Q, Rajagopalan S. Epidemiological and experimental links between air pollution and type 2 diabetes. *Toxicol Pathol* 2013;41:361–373.
34. Leitte AM, Schlink U, Herbarth O, Wiedensohler A, Pan XC, Hu M, Richter M, Wehner B, Tuch T, Wu Z, *et al*. Size-segregated particle number concentrations and respiratory emergency room visits in Beijing, China. *Environ Health Perspect* 2011;119:508–513.
35. UFIREG-report. UFP measurements: measures to assure high quality data and strategy to guarantee follow-up measurements; 2014 [accessed 2016 April 6]. Available from: http://www.ufireg-central.eu/index.php/downloads
36. Cyrys J, Pitz M, Heinrich J, Wichmann HE, Peters A. Spatial and temporal variation of particle number concentration in Augsburg, Germany. *Sci Total Environ* 2008;401:168–175.
37. Birmili W, Tomsche L, Sonntag A, Opelt C, Weinhold K, Nordmann S, Schmidt W. Variability of aerosol particles in the urban atmosphere of Dresden (Germany): effects of spatial scale and particle size. *Meteorol Z* 2013;22:195–211.
38. Ostro B, Hu J, Goldberg D, Reynolds P, Hertz A, Bernstein L, Kleeman MJ. Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: results from the California Teachers Study Cohort. *Environ Health Perspect* 2015;123:549–556.