ORIGINAL ARTICLE

Impact of Ambient Ultrafine Particles on Cause-Specific Mortality in Three German Cities

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Abstract

Rationale: Exposure to ambient air pollution has been associated with adverse effects on morbidity and mortality. However, the evidence for ultrafine particles (UFPs; 10–100 nm) based on epidemiological studies remains scarce and inconsistent.

Objectives: We examined associations between short-term exposures to UFPs and total particle number concentrations (PNCs; 10–800 nm) and cause-specific mortality in three German cities: Dresden, Leipzig, and Augsburg.

Methods: We obtained daily counts of natural, cardiovascular, and respiratory mortality between 2010 and 2017. UFPs and PNCs were measured at six sites, and measurements of fine particulate matter ($PM_{2.5}$; ⩽2.5 μm in aerodynamic diameter) and nitrogen dioxide were collected from routine monitoring. We applied station-specific confounder-adjusted Poisson regression models. We investigated air pollutant effects at aggregated lags (0–1, 2–4, 5–7, and 0–7 d after UFP exposure) and used a novel multilevel meta-analytical method to pool the results. Additionally, we assessed interdependencies between pollutants using two-pollutant models.

Measurements and Main Results: For respiratory mortality, we found a delayed increase in relative risk of 4.46% (95% confidence interval, 1.52 to 7.48%) per 3,223-particles/cm^3 increment 5–7 days after UFP exposure. Effects for PNCs showed smaller but comparable estimates consistent with the observation that the smallest UFP fractions showed the largest effects. No clear associations were found for cardiovascular or natural mortality. UFP effects were independent of $PM_{2.5}$ in two-pollutant models.

Conclusions: We found delayed effects for respiratory mortality within 1 week after exposure to UFPs and PNCs but no associations for natural or cardiovascular mortality. This finding adds to the evidence on the independent health effects of UFPs.

Keywords: ambient air pollution; ultrafine particles; particle number concentrations; particulate matter; respiratory mortality

Evidence of adverse health effects of ambient air pollution has been consistently growing in recent decades. By now, there are numerous studies that have found an association between short- and long-term exposure to particulate matter (PM) or nitrogen dioxide (NO_2) and morbidity (1, 2) and mortality (3, 4); however, air pollution comprises a complex mixture of many other substances, sometimes originating from similar sources (5).

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At a Glance Commentary

Scientific Knowledge on the Subject: Ambient air pollution has been associated with adverse health effects on morbidity and mortality, but the epidemiological evidence for unregulated ultrafine particles (UFPs; 10–100 nm) remains scarce and inconclusive. To date, UFPs are not routinely monitored, and therefore time-series analyses assessing the link between short-term UFP exposures and cause-specific mortality need dedicated monitoring campaigns.

What This Study Adds to the Field: This multicity epidemiological time-series study included a highly standardized exposure monitoring network with data from eight consecutive years (2010–2017). It is one of the first studies to incorporate multiple UFP monitoring stations per area region in three German cities. A novel multilevel meta-analytical approach showed a delayed increase in the risk of respiratory mortality after exposure to UFPs. These observations were independent of other air pollutants. Further analysis revealed larger associations for women and no difference by age or season. UFPs, particularly smaller size fractions (nucleation-mode particles, 10–30 nm), may contribute to the overall risk of mortality from ambient air pollution.

Ultrafine particles (UFPs) are an important part of particulate air pollution but differ from PM in many ways. UFPs are conventionally defined as particles with an aerodynamic diameter ⩽0.1 μm. As a result of their small particle size, they contribute negligibly to the total particle mass but dominate the number concentration (6). In addition, a large surface area per unit mass and high surface reactivity give UFPs the ability to transport chemical compounds; thus, UFPs are considered more hazardous than PM (7). UFPs are emitted directly or formed secondarily in the air by photochemical processes from gaseous precursors (8). Traffic exhaust, nucleation processes from several sources, or general combustion have been reported to be the main contributors to UFPs in urban air (9). To date, UFPs are not routinely monitored because the measurement techniques are more elaborate and complex, and there are no regulatory initiatives yet that would incorporate continuous measurements (8). We were the first to publish evidence of delayed impacts of UFPs on daily mortality in a high-pollution setting in Erfurt, Germany, in the 1990 s (10, 11). However, recent review articles have reported a growing number of epidemiological studies that suggested associations between the number concentrations of UFPs and several morbidity (6, 12, 13) and mortality (6, 12) outcomes. Nevertheless, evidence was summarized as insufficient and inconclusive because of heterogeneity in exposure assessment and assignment (e.g., different measurement devices or exposure metrics) and study methods (e.g., modeling strategies or copollutant adjustment) (6, 8, 12, 13).

In 2021, the World Health Organization (WHO) updated its air quality guidelines, recommending stricter target values for some ambient air pollutants, including PM ⩽2.5 μm in aerodynamic diameter ($PM_{2.5}$) (WHO 2021 Global Air Quality Guidelines: annual mean $PM_{2.5}$, 5 $\mu g/m^3$ [14]), based on evidence of adverse health effects even at low exposure concentrations (3). However, the assessment of epidemiological literature did not allow for the establishment of new evidence-based reference values for UFPs because the body of evidence is still inadequate (14). Nevertheless, the importance of UFPs was highlighted in a good practice statement, which particularly calls for more monitoring data and its use in epidemiological studies.

Therefore, the objective of this study was to investigate short-term associations between the number concentrations of ambient UFPs, total particle number concentrations (PNCs), and daily cause-specific mortality over a study period of 8 years in three German cities with multiple monitoring stations. Additionally, we investigated the impact of subfractions of UFPs and effect modification by age, sex, and season and assessed interdependencies between pollutants using two-pollutant models. Some of the results of this study have been previously reported in the form of an abstract (15).

Methods

Mortality Data

We obtained data on daily cause-specific death counts for the three German cities, Dresden, Leipzig, and Augsburg, between 2010 and 2017 through official statistics. Cases were considered if people lived and died in the same city. The following three cause-specific deaths were defined using the *International Classification of Diseases, 10th Revision*: natural (A00–R99), cardiovascular (I00–I99), and respiratory mortality (J00–J99). No informed consent or approval was needed because data are collected routinely and anonymously.

Environmental Data

Hourly air pollution data and hourly air temperature, relative humidity, and barometric pressure were measured at six fixed monitoring stations that were part of the former German Ultrafine Aerosol Network (GUAN). A map of all GUAN stations is shown in Figure 1. Stations were selected based on three criteria: *1*) representativeness of the exposure setting for the population, *2*) an adequate number of cases, and *3*) high standardization and good comparability of the measurement devices. More details are provided in the online supplement. Four selected stations were considered as urban background stations. In addition, two traffic-related stations were included to capture peak concentrations more adequately. Particle number size distributions were obtained in a size range of 10–800 nm using mobility particle size spectrometers. $PM_{2.5}$ mass concentrations were measured by tapered element oscillating microbalance for Augsburg and high-volume samplers at the other stations. Black carbon (BC) mass concentrations were obtained by multiangle absorption photometers for all stations except Augsburg, where an aethalometer was used. Daily mean concentrations were calculated if ⩾75% of the hourly data were available.

We considered the number concentrations of particles in the ultrafine range (10–100 nm, i.e., UFPs) and total PNCs (10–800 nm) as exposures of primary interest. In addition, we also assessed nucleation-mode particles (10–30 nm; NuMPs), Aitken-mode particles (30–100 nm; AiMPs), and accumulation-mode particles (100–800 nm; AcMPs). Air pollutants of secondary interest were NO_2, $PM_{2.5}$, and BC.

Abbreviation	Station name
ANA	Annaberg-Buchholz
AFH	Augsburg
BOS	Bösel
DDN	Dresden-Nord
DDW	Dresden-Winckelmannstraße
HPB	Hohenpeißenberg
LAN	Langen
LEI	Leipzig-Eisenbahnstraße
LMI	Leipzig-Mitte
LTR	Leipzig-TROPOS
LWE	Leipzig-West
MEL	Melpitz
MST	Mülheim-Styrum
NEU	Neuglobsow
SCH	Schauinsland
WAL	Waldhof
ZSF	Zugspitze (Schneefernerhaus)

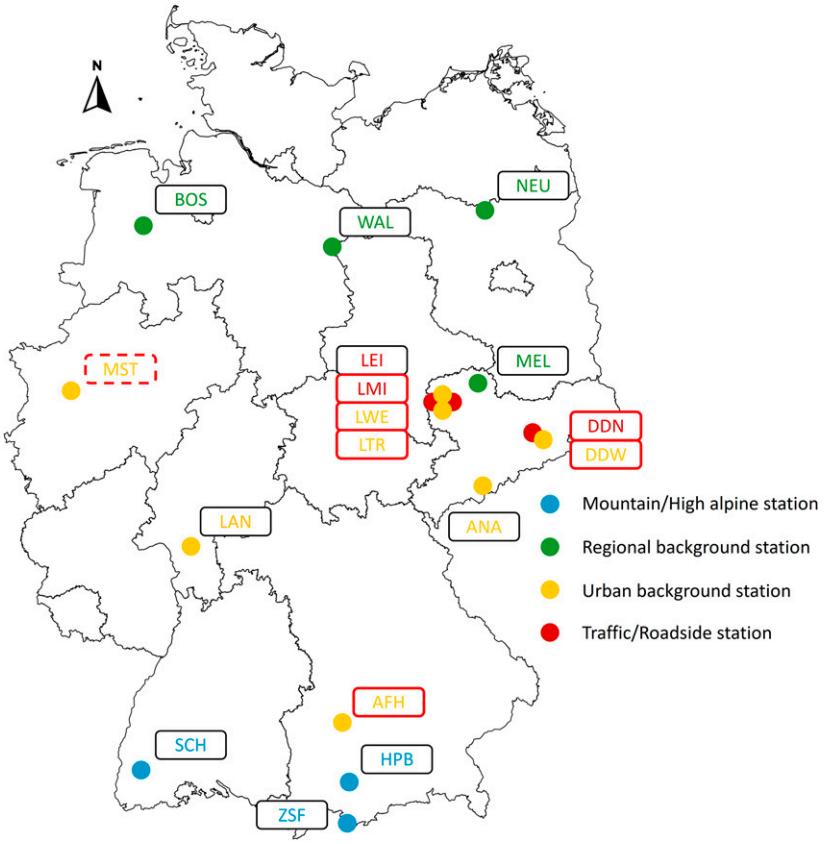

Figure 1. Location of German Ultrafine Aerosol Network stations across Germany and classification according to station type. Stations used for this analysis are highlighted with red boxes (dashed for sensitivity analysis). Map adapted from Birmili and colleagues, 2016 (18), and Sun and colleagues, 2019 (19).

Statistical Analysis

We conducted a two-stage modeling approach. In the first stage, we calculated station-specific associations between air pollutants and cause-specific mortality using Poisson regression models allowing for overdispersion. We adjusted for the following confounders: time trend, day of the week, vacation periods, public holidays, air temperature, and relative humidity. Effects of high and low temperatures were added separately to the model according to Stafoggia and colleagues (2013) (16). We used cubic regression splines for time trends (four degrees of freedom per year) and meteorological parameters (three degrees of freedom) to account for nonlinear confounding. We analyzed associations between air pollutants and mortality using different aggregated lags. Specifically, we assessed immediate (0–1 d after exposure [lag0–1]), delayed (2–4 d and 5–7 d after exposure [lag2–4 and lag5 –7, respectively]) and overall effects (lag0–7). In the second stage, station-specific estimates were pooled using a novel multilevel meta-analysis that accounts for hierarchical structures, including random terms for cities and stations (17). We tested for heterogeneity between the station-specific estimates and obtained the corresponding P value and I^2 statistic. All results are presented as a percent change per interquartile range increase in the respective air pollutant concentration to compare the relative health effects across pollutants. A detailed description is provided in the online supplement.

On an exploratory basis, we conducted several further analyses. We compared the effects between urban background and traffic-related stations. Two-pollutant models were calculated if the Spearman correlation coefficient was less than 0.7. We assessed potential effect modifications by sex (male vs. female) and age ($<$75 yr vs. $\geq$75 yr) in stratified analyses. Seasonal differences (October to March vs. April to September) were analyzed using an interaction term between the air pollutant and season. We conducted several sensitivity analyses to test the robustness of our results (e.g., different model parameters, confounding variables, and measurement stations) and also provide the results of the main models using a fixed increment in air pollution concentration.

Detailed information on the station characteristics (e.g., location and station operator, environmental data, and measurement devices) has been published elsewhere (18, 19) and is provided in the online supplement, together with a detailed description of mortality data and statistical methods.

Results

Descriptive Analysis

Total numbers and daily means of cause-specific mortality and population data are

Table 1. Description of Population and Mortality Data (2,922 Days with Valid Data)

Variable	Leipzig	Dresden	Augsburg
Mean population, 2010–2017	542,918	534,382	279,159
Total counts of natural mortality	43,250	36,106	20,712
Total counts of cardiovascular mortality	19,880	15,756	8,854
Total counts of respiratory mortality	2,559	2,143	1,426
Daily natural mortality	14.8 ± 4.1	12.4 ± 3.7	7.1 ± 2.7
Daily cardiovascular mortality	6.8 ± 2.7	5.4 ± 2.4	3.0 ± 1.7
Daily respiratory mortality	0.9 ± 1.0	0.7 ± 0.9	0.5 ± 0.7

Values are presented as mean ± SD where applicable. Population data based on official statistical yearbook of the cities: own calculations; natural mortality: *International Classification of Diseases, 10th Revision*: A00–R99; cardiovascular mortality, I00–I99; respiratory mortality, J00–J99. Source: Research Data Centre (RDC) of the Federal Statistical Office and Statistical Offices of the Federal States (Mortality Statistics [uniform directory number: 23211], survey years, 2010–2017; DOI: 10.21242/23211.2010.00.00.1.1.0 to 10.21242/23211.2017.00.00.1.1.0, own calculations).

presented in Table 1 (*see* Table E4 in the online supplement).

Station-specific descriptive statistics of air pollution and environmental data are shown in Table 2 (a more detailed overview is given in Table E5). In general, median UFP concentrations at the urban background stations were in the mid-4,000 s in particles/cm^3, except for Augsburg, where a median UFP concentration of 5,655 particles/cm^3 was observed. At the traffic-related stations, significantly increased concentrations were measured, with median UFP concentrations of 8,637 particles/cm^3 for Dresden-Nord and 10,123 particles/cm^3 for Leipzig-Mitte, respectively (Table 2).

Spearman correlation coefficients indicated mainly weak to moderate correlations between UFPs and BC, NO_2, and $PM_{2.5}$ (Table E6); UFPs and PNCs were highly correlated within stations (coefficients between 0.96 and 0.98) and moderately correlated between stations (Table E7). Compared with UFPs, higher correlations between PNCs and BC, NO_2, and $PM_{2.5}$ were observed.

Main Models/Analysis

Results of the pooled analysis are presented in Figure 2 (*see* Table E8). No clear associations were observed between UFPs or PNCs and natural or cardiovascular mortality; however, both exposures were associated with respiratory mortality. The strongest effects were seen for the delayed aggregated lags, especially lag5–7. For example, an interquartile range increase of 3,223 particles/cm^3 in UFP concentration was associated with a 4.46% (95% confidence interval [CI], 1.52% to 7.48%) increase in the relative risk of respiratory mortality. No heterogeneity was observed between station-specific estimates ($I^2 = 4.90\%$, $P = 0.385$). The results for PNCs were comparable but with smaller effect sizes. Looking at different particle size modes, we observed more pronounced effects on respiratory mortality, predominantly for the smallest subfraction, NuMPs (lag5–7, 4.49% [95% CI, 1.91% to 7.14%]) (Figure 3 and Table E9). In contrast, for natural or cardiovascular mortality, there were no changes in risk depending on particle size fractions, although NuMPs indicated a higher delayed risk for natural mortality.

The results of fixed-effects models, station-specific estimates, single-lag models, and a comparison between urban background and traffic-related stations indicated mainly higher risks for respiratory mortality at the Leipzig stations, the single lags of 3 and 6 days, and the urban background (*see* online supplement for detailed information; Figures E1–E3 and Tables E10 and E11).

Table 2. Concentrations of Air Pollution and Environmental Data per Measurement Station

Variable	LMI	LWE	LTR	DDN	DDW	AFH
Station characteristic	Traffic-related	Urban background	Urban background	Traffic-related	Urban background	Urban background
Air pollutant						
UFP (10–100 nm), particles/cm^3	10,123 (5,156)	4,520 (3,003)	4,838 (3,154)	8,637 (4,366)	4,791 (3,156)	5,655 (3,514)
PNC (10–800 nm), particles/cm^3	11,922 (5,866)	5,748 (3,482)	6,054 (3,686)	10,292 (4,975)	6,186 (3,902)	6,909 (4,017)
BC, μg/m^3	2.0 (1.3)	0.8 (0.8)	0.7 (0.8)	1.5 (1.1)	0.7 (0.8)	1.4 (1.0)
NO_2, μg/m^3	43.0 (17.0)	16.0 (11.0)	NA	33.0 (14.0)	18.0 (12.0)	17.7 (12.3)
$PM_{2.5}$, μg/m^3	13.6 (12.2)	9.6 (10.5)	NA	12.3 (11.6)	10.9 (12.3)	10.2 (10.3)
Meteorological parameter						
Temperature, °C	11.4 (12.1)	9.7 (11.7)	NA	11.3 (12.5)	11.6 (12.4)	9.9 (12.2)
Relative humidity, %	71.8 (19.6)	75.3 (18.6)	NA	70.9 (16.8)	71.8 (17.3)	79.2 (20.3)
Barometric pressure, hPa	1,016.0 (10.0)	1,016.0 (10.0)	NA	1,016.0 (10.0)	1,016.0 (10.0)	961.4 (9.0)

Values are presented as median (interquartile range).
Definition of abbreviations: AFH = Augsburg-Hochschule; BC = black carbon; DDN = Dresden-Nord; DDW = Dresden-Winckelmannstrasse; LMI = Leipzig-Mitte; LTR = Leipzig-Leibniz Institute for Tropospheric Research; LWE = Leipzig-West; NA = no data available; NO_2 = nitrogen dioxide; $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; PNC = total particle number concentrations (10–800 nm); UFP = ultrafine particles (10–100 nm).

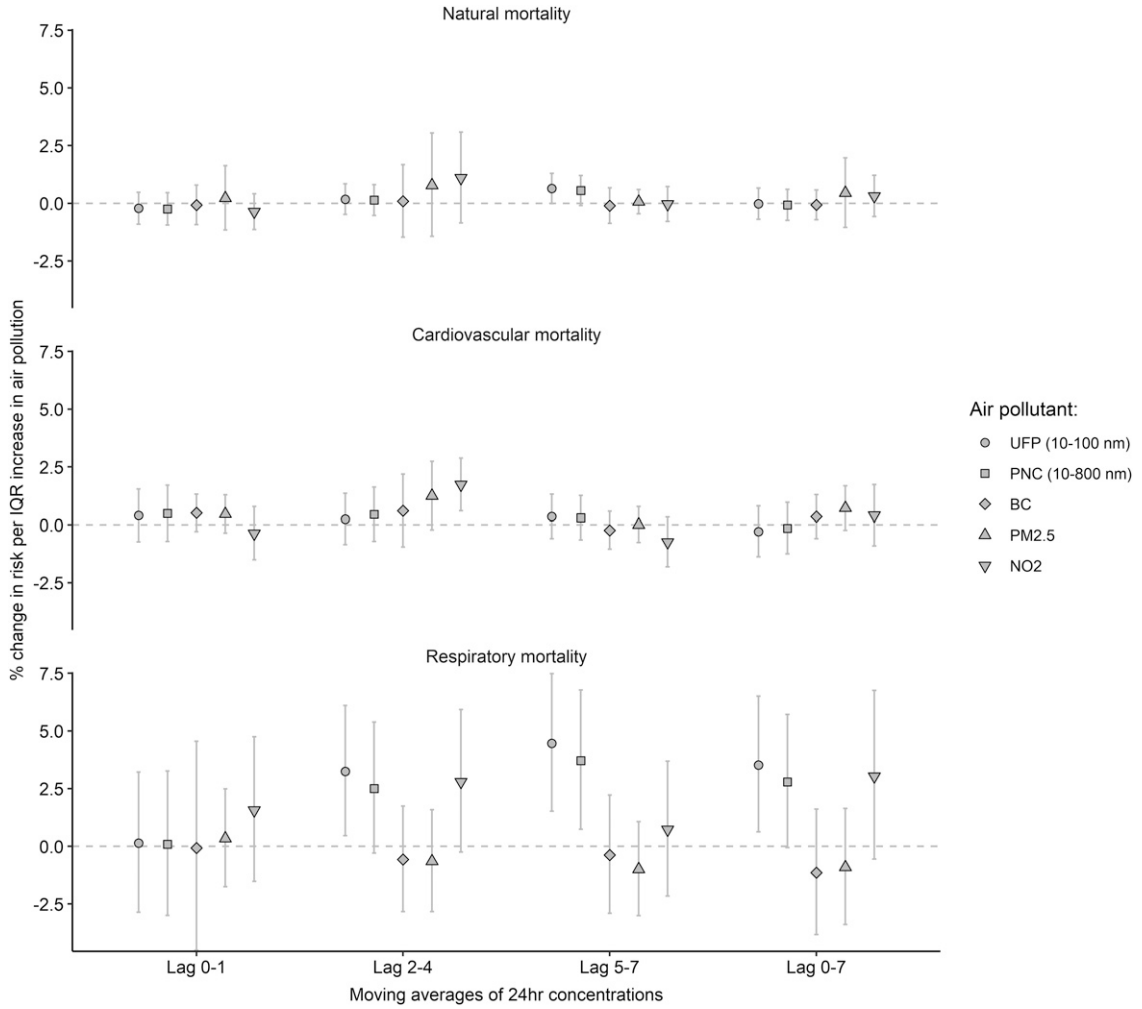

Figure 2. Percent change in relative risk and 95% confidence interval per interquartile range (IQR) increase in air pollution concentration for natural (top), cardiovascular (middle), and respiratory mortality (bottom). The *x*-axis shows the 24-hour moving average lag concentrations of air pollutants. The *y*-axis represents the percent change of risk per IQR increase in air pollution concentration (difference between the 75th and 25th percentiles; corresponds to the spread of the middle 50% of the data). Standardization by IQR facilitates comparison between different pollutants. The shape of the estimates displays the type of pollutant. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates. BC = black carbon; NO_2 = nitrogen dioxide; $PM_{2.5}$ = particulate matter ⩽2.5 μm in aerodynamic diameter; PNC = total particle number concentrations (10–800 nm); UFP = ultrafine particles (10–100 nm).

BC was not associated with any mortality outcome (*see* Table E8). The results rather indicated null effects with no distinct pattern. For $PM_{2.5}$ and NO_2, the largest effects on natural or cardiovascular mortality were observed for the aggregated average lag2–4, although substantial heterogeneity was observed for natural mortality. An increase in NO_2 of 11.00 μg/m^3 was associated with a 1.73% (95% CI, 0.60% to 2.88%) higher risk of cardiovascular death ($I^2 = 0.0\%$, $P = 0.669$). There were no significant associations with respiratory mortality for $PM_{2.5}$ or NO_2, although the effect estimates for NO_2 were all positive (*see* Table E8).

Two-pollutant models and effect modification analysis are reported based on the combination of pollutant, lag structure, and mortality endpoint, for which the strongest effects were found in the main analysis. The results are presented in Figure 4 and Table E12. The UFP effects on respiratory mortality 5–7 days after exposure remained rather unchanged after additional adjustment for BC or $PM_{2.5}$, indicating an independent effect (e.g., UFP + $PM_{2.5}$, 4.07% [95% CI, 0.93% to 7.30%]), whereas further adjustment for NO_2 led to wider CIs. For PNCs, a similar pattern was found. However, it should be noted that, for NO_2, the results for the Leipzig-Mitte station were excluded from the pooled estimates because of high Spearman correlation coefficients, leading to more imprecise results.

Associations between respiratory mortality and UFPs 5–7 days after exposure were significantly stronger in women, with a 9.57% (95% CI, 5.35% to 13.97%) increase in risk, compared with 0.45% (95% CI, −3.10% to 4.13%) in men (Figure 4 and Table E12). No substantial effect modifications were seen

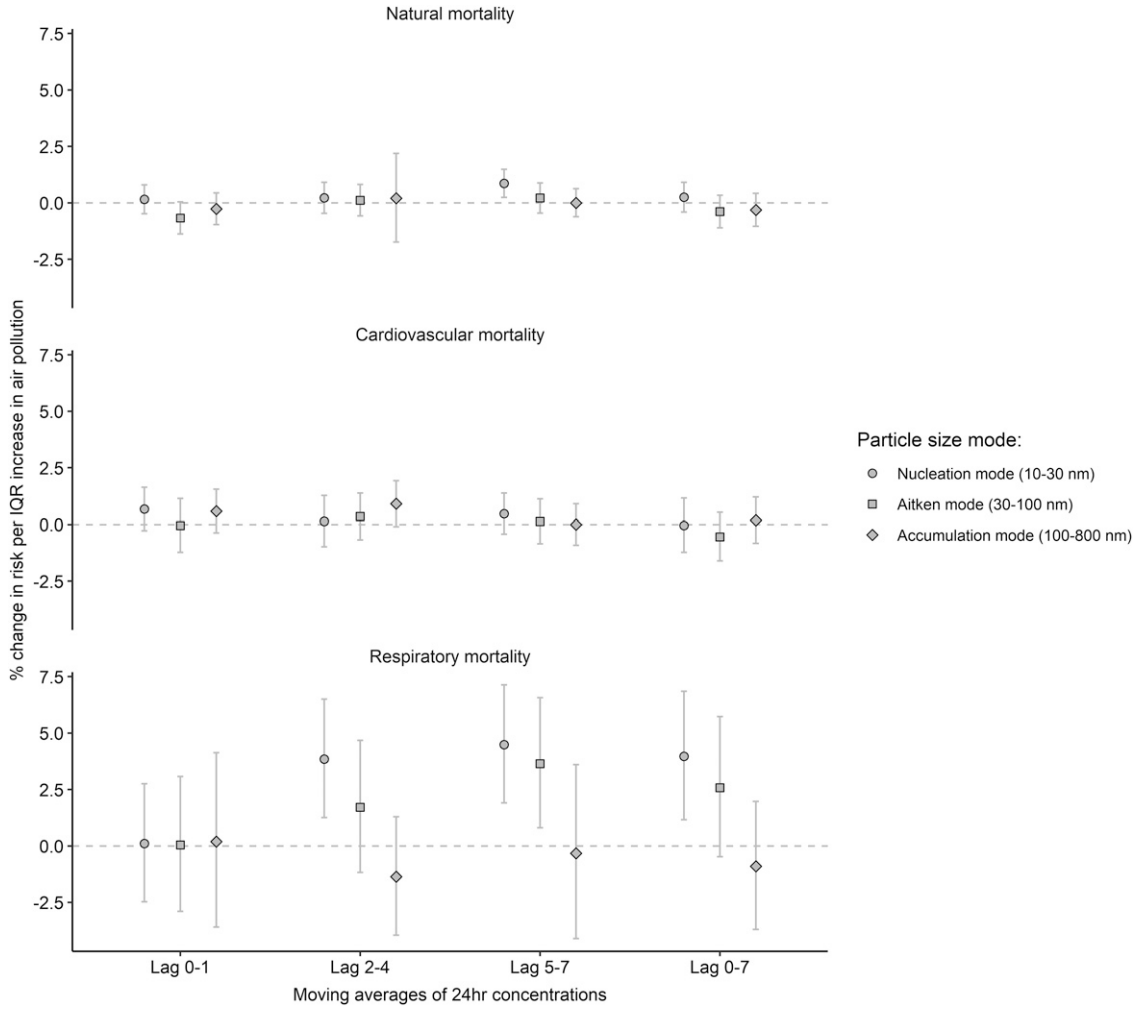

Figure 3. Percent change in relative risk and 95% confidence interval per interquartile range (IQR) increase in air pollution concentration for natural (top), cardiovascular (middle), and respiratory mortality (bottom). The *x*-axis shows the 24-hour moving average lag concentrations of air pollutants. The *y*-axis represents the percent change of risk per IQR increase in air pollution concentration (difference between the 75th and 25th percentiles; corresponds to the spread of the middle 50% of the data). Standardization by IQR facilitates comparison between different pollutants. The shape of the estimates displays the type of pollutant by particle size mode. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates.

for age and season. Generally, PNCs showed similar results.

Sensitivity Analysis

Sensitivity analyses were again done for selected combinations of pollutant, lag structure, and mortality endpoints. Overall, changing several model parameters, adjusting for additional variables, or using alternative definitions of UFPs and PNCs or city-specific exposures resulted in only minor changes in the UFP effect estimates (Figures 5 and E4 and Table E9). For the main analyses, an alternative standardization method with fixed increments resulted in larger effect estimates but also in wider CIs. However, the direction and significance of the estimates were not affected (Figures E5–E7 and Tables E13 and E14). Additional inclusion of a different urban background station in the pooled analysis generated comparable, albeit lower, effects, still indicating a higher risk for respiratory mortality (*see* the online supplement and Table E9). Finally, the exposure–response functions for UFPs (lag5–7) and respiratory mortality indicated no significant deviations from linearity (Figure E8).

Discussion

This time-series analysis found delayed associations between UFPs and PNCs and respiratory mortality. The strongest effects were seen for UFPs with a delay of 5–7 days. Consistently, we found the strongest effect with particle number concentrations in the size range of 10–30 nm. In contrast, we found no clear effects on natural or cardiovascular mortality. For respiratory mortality, adjustment for other air pollutants such as $PM_{2.5}$ or BC indicated independent results; adjustment for NO_2 led to wider CIs and insignificant results. The findings were comparable between age groups and seasons, but more pronounced risks were observed for women.

A multicity study conducted in eight European cities (20) reported weak delayed pooled effects of PNCs that were strongest for a single lag of 6 days and respiratory

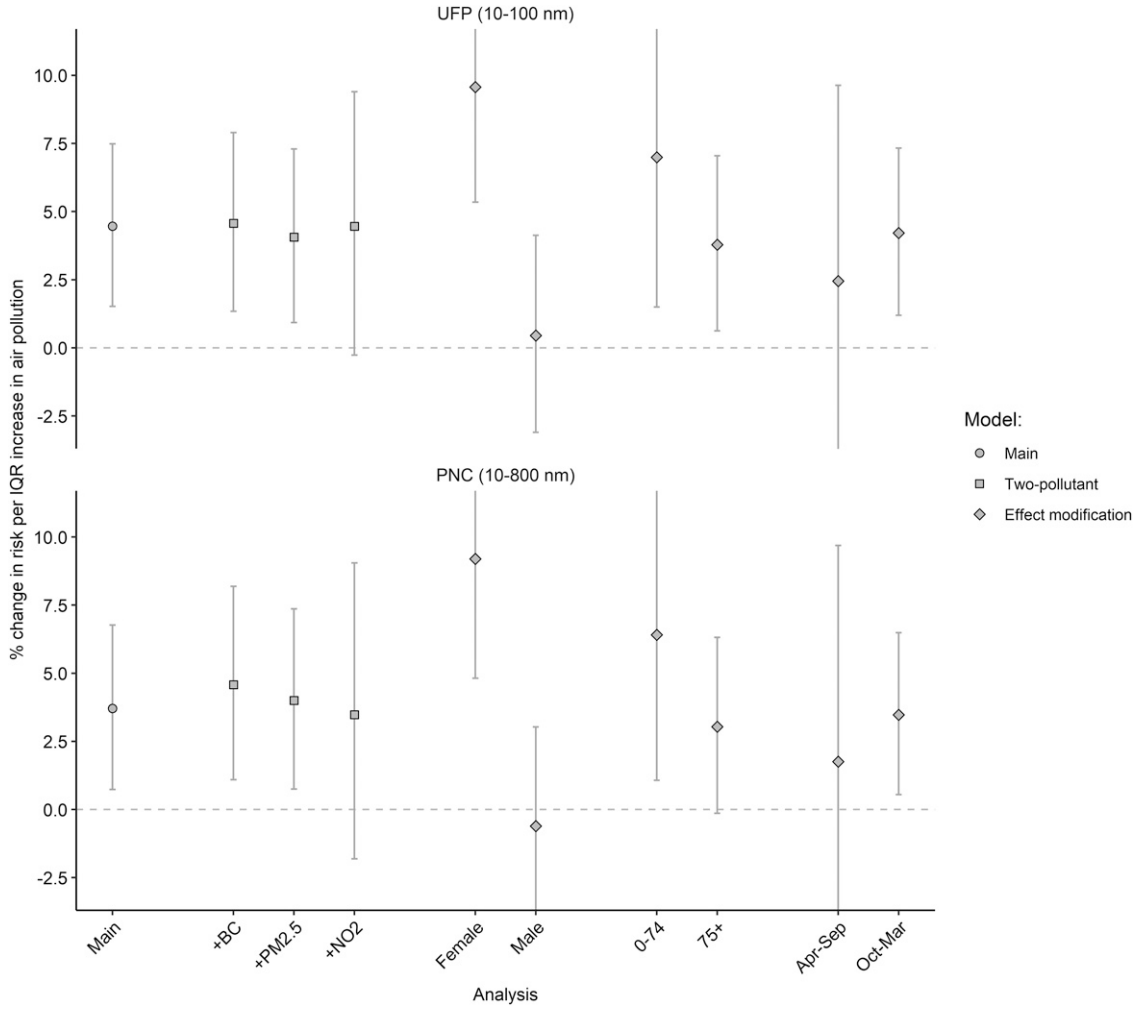

Figure 4. Percent change in relative risk and 95% confidence interval per interquartile range (IQR) increase in concentration of particles in the ultrafine range (10–100 nm; UFPs; top panel) and total particle number concentrations (10–800 nm; PNCs; bottom panel) for respiratory mortality (5–7 d after UFP exposure). The *x*-axis shows the results for the main (dots), two-pollutant (rectangles), and effect-modification analyses (diamonds). The *y*-axis represents the percent change of risk per IQR increase in air pollution concentration (difference between the 75th and 25th percentiles; corresponds to the spread of the middle 50% of the data). Standardization by IQR facilitates comparison between different pollutants. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates. It should be noted that, for the two-pollutant models for $PM_{2.5}$ and nitrogen dioxide (NO_2), the station Leipzig-Leibniz Institute for Tropospheric Research was not included in the model (no air pollution data). Additionally, the Leipzig-Mitte station was not included in the NO_2 model because Spearman correlation coefficients were greater than 0.7. BC = black carbon; $PM_{2.5}$ = particulate matter $\leq$2.5 μm in aerodynamic diameter.

mortality. These findings are consistent with our results, as we found increased risks for respiratory mortality at single lags of 3 and 6 days. In contrast to our results, Stafoggia and colleagues observed higher effect estimates for natural and cardiovascular mortality. However, the authors pointed out null effects after removing the most influential station from the pooled analysis (20). Another study conducted in five central and western European cities, including Augsburg and Dresden, Germany (21), found positive, albeit insignificant, pooled delayed effects for respiratory mortality after exposure to UFPs or PNCs (e.g., UFP lag2–5 and respiratory mortality: 8.5% [95% CI, −4.8% to 23.7%] per 2,750 particles/cm^3). The effects were independent of $PM_{2.5}$; natural and cardiovascular mortality were not associated with UFPs or PNCs (21). Although differences exist between this previous study and our study (e.g., lag structures and lower cutoff values in the UFP definition), we observed comparable results. Furthermore, the CIs indicated a higher degree of precision in our study, probably due to the substantially longer time series. In a single-station analysis in the German Ruhr area, Hennig and colleagues reported higher risks for respiratory mortality following lag2 (3.50% [95% CI, −0.77% to 7.95%]) and lag6 (4.51% [95% CI, 0.37% to 8.81%]) exposures to UFPs (22). However, no clear pattern was found for average lag effects (22). As a sensitivity analysis, we included the Mülheim-Styrum monitoring station used by Hennig and colleagues in our main model. Despite some methodological differences (*see* online supplement), the UFP effects on

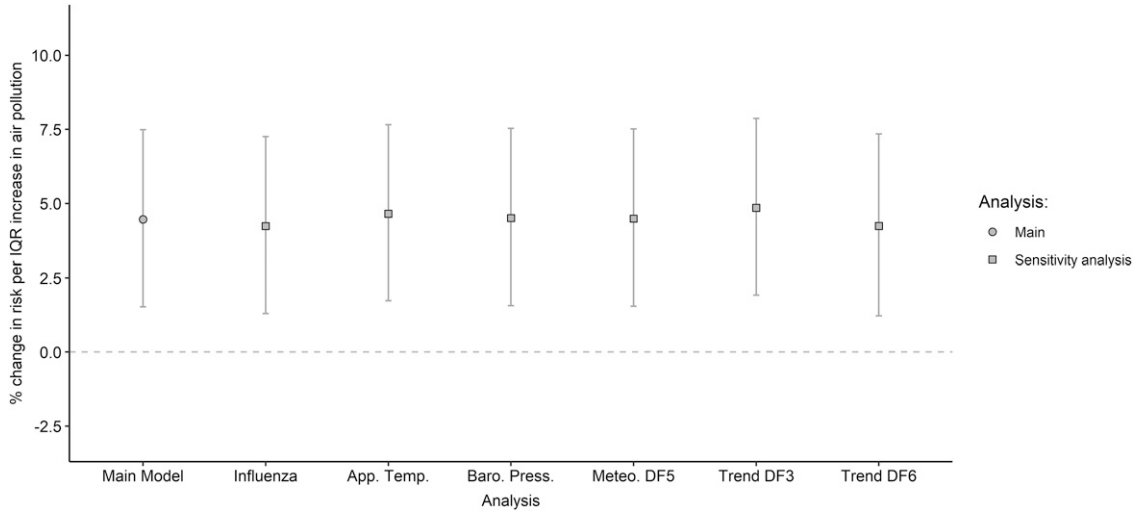

Figure 5. Percent change in relative risk and 95% confidence interval per interquartile range (IQR) increase in concentration of particles in the ultrafine range (10–100 nm; UFPs) for respiratory mortality (5–7 d after UFP exposure). The *x*-axis shows the results of the main model (dots) and different sensitivity analysis (rectangles). The *y*-axis represents the percent change of risk per IQR increase in air pollution concentration (difference between the 75th and 25th percentiles; corresponds to the spread of the middle 50% of the data). Standardization by IQR facilitates comparison between different pollutants. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates. App. Temp. = Apparent Temperature; Baro. Press. = Barometric Pressure; DF = Degrees of Freedom; Meteo. = Meteorology.

respiratory mortality slightly decreased but remained robust. Finally, our results are consistent with those from the extensively studied, highly polluted area of Erfurt, Germany, where the initial epidemiological short-term studies in the 1990 s found evidence of an association between UFPs and cardio-(respiratory) mortality (10, 11, 23).

Three combined main pathways are thought to promote the adverse health effects of particulate air pollution, and especially UFPs, on health (24). First, smaller particles, and especially UFPs, can translocate from the alveolar space by entering the endothelial cells and the lung interstitium. It has been demonstrated that they translocate to epithelial cells and eventually into the circulation, potentially causing direct adverse effects along the way (24, 25). When in the blood, they can reach other lung areas and distant nonpulmonary regions and organs. As a result of their large surface area relative to the unit mass and their surface reactivity, chemical compounds can be more easily absorbed and transported, leading to further damage (7). Second, a series of subclinical systemic reactions can be induced from the lung, e.g., the release of proinflammatory and prooxidative mediators (24, 26). These can lead to local and systemic inflammatory processes and trigger prothrombotic effects, a procoagulation state, and epithelial and endothelial dysfunction (24, 26). Third, particles that deposit in the pulmonary tree can directly stimulate neuronal reflexes, leading to changes in pulmonary and cardiac autonomic regulation (24). These alterations in autonomic tone involve multiple reflex arcs and are often the most immediate response to exposure to air pollution (27). Although epidemiological studies to date can only provide suggestive evidence on mortality, clinical relevance is given because UFP effects may induce endpoints such as impaired lung function (28) and systemic inflammation (12) or affect morbidity, particularly respiratory health in younger people (13).

Few studies reported on potential effect modification (e.g., age, sex, or season), showing mixed results. Findings from one systematic review (12) and two aforementioned short-term analyses (20, 22) observed increased UFP effects in the warmer season. In contrast, the results reported by Lanzinger and colleagues (21) and the present study indicated a slightly increased risk in the cold season. A possible explanation could be a different exposure mixture or a smaller influence of Germany's more temperate climatic conditions (22). Higher risk estimates for elderly people have been reported previously (20, 21). We observed no significant effect modification by age, although higher risks were observed in the younger age group. Our study showed that women had a significantly increased risk of respiratory mortality. Similar, although insignificant, findings were reported by Lanzinger and colleagues for respiratory mortality (21) and by Stafoggia and colleagues for natural mortality (20). Differences in air pollution effects between men and women have been extensively studied, although the findings remain uncertain, and some studies reported larger effects in women (29). Several factors have been hypothesized that could affect and explain these differences. Biological (i.e., sex) factors could include, for example, different levels of hormones and cytokines (e.g., high-sensitivity C-reactive protein as a marker for systemic inflammation) or a higher total deposition fraction of UFPs in the lungs of women (30–32). On the contrary, socioeconomic (i.e., gender) factors could explain different underlying exposure patterns, societal roles, and health behavior in general (e.g., differences in smoking prevalence or physical activity) (33). For respiratory deaths, further examination of our data showed that women were substantially older (more were aged $\geqslant$85 yr) than men, that there were no major differences in underlying causes of death or by station or city, and that the effects did not change when the analysis was further stratified by particle size fraction (data not shown). However, the results did not change when the analysis was additionally stratified

by age. A more detailed investigation of other potentially influential factors was not possible with the available data set, and any causal conclusions would be highly speculative, beyond the scope of the present paper, and unable to be adequately supported by the evidence from our analysis because of the absence of important variables and the study design itself. In summary, even though the observed associations may be partially explained by sex and gender differences, larger data sets and prospective longitudinal analyses that explicitly address sex and gender differences in UFPs are needed to clarify our findings further.

An ongoing debate concerns whether the effects of UFPs occur independently from $PM_{2.5}$. Different sources, temporal-spatial patterns, and atmospheric urban environments result in almost no relationship between UFPs and $PM_{2.5}$ and limited representativeness between the two quantities (34). UFPs are assumed to be more associated with traffic-related air pollutants such as nitrogen oxides, carbon monoxide, and BC (8). We found evidence for independent effects of UFPs after adjustment for $PM_{2.5}$ or BC. The inclusion of NO_2 led to more imprecise and insignificant results. Similar to our results, a recent review concluded that NO_2 adjustment had greater effects on the point estimates than adjustments for other pollutants (12). High correlations between UFPs and NO_2 could lead to multicollinearity or methodological issues, resulting in unstable models and biased effect estimates (12). As a result, there remains uncertainty about independent effects when UFPs are adjusted for additional NO_2 coexposure (which may originate from similar sources, e.g., traffic emissions), but also vice versa (5, 35). Source-specific and chemical-composition analyses included in the context of large epidemiological studies could help to further clarify this issue. In addition, spatiotemporal modeling of short-term UFP exposures or the inclusion of multiple monitoring stations per area unit could contribute to a more comprehensive estimate of population-representative UFP exposures. Accounting for the high spatial variability remains challenging and will require a greater focus in the future, especially for long-term studies. Although quantification of UFP risk based on number concentration was recommended by the WHO in 2021, there is still no national or international consensus on what constitutes the most important dimension of UFPs, and standard methods still do not exist (14). Furthermore, without adequate characterization of the UFP source or chemical composition, it remains unclear whether the effects are the result of UFP number concentration *per se* or represent a marker of combustion PM. Comparing the health effects and related biological plausibility of different UFP exposure metrics (e.g., particle number or surface area) and a more detailed characterization of UFPs (with regard to their sources and chemical composition) would contribute to a better and more holistic picture of UFP risk. For example, Schmid and Stoeger have identified surface area as a highly relevant biological/toxicological dose metric because it may better represent the area where molecules on the particle surface interact with body tissues or fluids (36). However, depending on the mode of action, other metrics could be more biologically effective for health, so aerosol exposure monitoring should optimally include multiple dose metrics simultaneously (36). In our analysis, we had the opportunity to assess the link between UFPs and mortality using background and traffic-related stations. UFPs exhibited higher risks for respiratory mortality at urban background stations; NO_2 exhibited higher risks at traffic-related stations. Contrarily, traffic-related stations showed higher risks for natural mortality after UFP exposure. Generally, urban background stations are considered to better reflect the exposure concentrations of the average urban population. Nevertheless, we included traffic-related stations to better capture daily peak concentrations and to evaluate potential differences on an exploratory basis. This differentiation may also be valuable for future research to understand more about the differences in risk between station types (and also within cities) in the context of prevailing exposures (e.g., NO_2). In addition, to date, regulatory air-quality monitoring has focused on mass concentrations of fine PM (e.g., $PM_{2.5}$ and PM_{10}) and gaseous pollutants (e.g., NO_2 and O_3), inherently assuming that the health effects of UFPs are well represented by monitoring these pollutants. Given the growing body of literature and our findings, it would not be sufficient to use current monitoring standards to assess PM risk adequately.

Strengths and Limitations

Our study represents a carefully designed multicity study over eight consecutive years with a harmonized exposure design for all included stations and standardized outcome data collection. The monitoring stations and equipment were incorporated into the German multiinstitutional GUAN, which ensured routine maintenance and standardized calibration processes to measure particle number size distribution through its operators. In addition, for two cities, we included traffic-related stations in the pooled analysis to also capture the effects of peak concentrations to better represent the exposure situation in these urban areas. Therefore, we are among the first to compare different risk estimates between these two exposure settings in a multicity epidemiological context. We thoroughly adjusted for meteorological variables and time trends to rule out the possibility that the detected associations resulted from meteorological influences or seasonal differences. Additional sensitivity analyses indicated that our final effect estimates seemed to be conservative and robust to variations in the models.

This study has several limitations to acknowledge. First, we did not have source-specific information on particles. As a result, we could only assume potential sources using different size modes. Second, unlike $PM_{2.5}$, UFPs have been reported to exhibit high variability in space (6), which might lead to exposure misclassification (or measurement error), especially when a single station is used to represent the exposure risk for an entire city (6). In this study, we did not statistically correct for possible measurement error, so the effect estimates may be affected toward or away from the null (37). However, we included additional stations for Dresden and Leipzig to better capture the spatial variation in UFP concentrations. Moreover, Cyrys and colleagues (38) have shown, for Augsburg, Germany, that a carefully chosen urban background station can adequately capture the temporal variation of UFPs across the city. However, we included only six stations from three cities, so our analysis may lack statistical power (e.g., when comparing risks between station types). Third, we performed several analyses and cannot rule out the possibility that some results were observed by chance. In addition, despite careful model selection, residual confounding could be present, especially for additional NO_2 adjustment, because the real-world exposure environment is a complex mixture of particles and gases that may originate from the same sources. Fourth, the number of

deaths, especially respiratory mortalities, was rather low, and the resulting effect estimates might be affected, especially when examining effect modification. Nevertheless, the CIs generally did not show large uncertainty, and the inclusion of additional respiratory deaths from the Ruhr area did not substantially change the results. Last, our study was conducted only in Germany, so the results may not be easily transferable to other regions. Different meteorological or climatic conditions can affect the concentration of pollutants in the environment. For example, wind speed and rain can lead to dilution or leaching of particles in the air. In addition, new particle formation from precursor substances of UFPs can occur in areas with high solar irradiation. This highlights the need for multicity studies with different meteorological or climatic conditions.

Conclusions

In summary, the pooled results of our time-series study indicated an increased risk for respiratory mortality after exposure to UFPs. In particular, delayed effects were seen for multiday averages and corroborated findings from high-pollution settings. No consistent associations were found for cardiovascular or natural mortality. The study highlights that longer time series with more monitors per city of high-quality UFP measurements are needed to overcome the inconsistency in the available evidence. It also highlights that multiple measurements with a classification of particle size fractions, chemical composition, and emission source are needed to further substantiate the impact of UFPs as called for by the good practice statements for UFPs published by the WHO in 2021 (14). In general, focusing our policies on eliminating combustion might be the most health-protective air pollution mitigation approach. ■

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