Aus dem

Institut für Epidemiologie

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Umwelt (GmbH), Neuherberg, Deutschland

Ambient Air Pollution and its Effects on Mortality and Hospital Admissions: A Comprehensive Analysis of Ultrafine Particles, Various Particle Sizes, and Temporal Patterns

Dissertation

zum Erwerb des Doktorgrades der Humanbiologie

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität München

vorgelegt von

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aus

München

Jahr

2024

Mit Genehmigung der Medizinischen Fakultät der

Ludwig-Maximilians-Universität München

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Tag der mündlichen Prüfung:	16.10.2024

Für meine Familie.

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List of abbreviations

µg	Microgram
µm	Micrometer
AAQD	Ambient air quality directive
AcMP	Accumulation model particle
AiMP	Aitken mode particle
AJRCCM	American Journal of Respiratory and Critical Care Medicine
AQG	Air quality guideline
BC	Black carbon
BfUL	Staatliche Betriebsgesellschaft für Umwelt und Landwirtschaft
CI	Confidence interval
cm^3	Cubic centimeter
EHLRS	Environmental Health and Lung Research School
EI	Environment International
EPA	United States Environmental Protection Agency
EU	European Union
EURO 6	European emission standard: EURO 6
GUAN	German Ultrafine Aerosol Network
HEI	Health Effects Institute
HELENA	Helmholtz Graduate School Environmental Health
HMGU	Helmholtz Munich
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
ISEE	International Society for Environmental Epidemiology
km^2	Square kilometer
LfULG	Saxon State Office for Environment, Agriculture, and Geology
LMU	Ludwig-Maximilians-University
m^3	Cubic meter
MCC	Multi-Country Multi-City Collaborative Research Network
MPSS	Mobility particle size spectrometer
MRI	Magnet resonance imaging
NAKO	German National Cohort
nm	Nanometer
NPF	New particle formation
NO_2	Nitrogen dioxide
NH_3	Ammonia

NuMP	Nucleation mode particle
O_3	Ozone
PI	Principal investigator
PM	Particulate matter
$PM_{2.5}$	Particulate matter with an aerodynamic diameter ≤ 2.5 µm
PM_{10}	Particulate matter with an aerodynamic diameter ≤ 10 µm
PNC	Particle number concentration
PNSD	Particle number size distribution
PSC	Particle surface area concentration
RDC	Research Data Centre of the Federal Statistical Office and Statistical Offices of the Federal States
SAP	Statistical analysis plan
SO_2	Sulfur dioxide
SO_4^{2-}	Sulfate
TAC	Thesis Advisory Committee
TLPH	The Lancet Planetary Health
TROPOS	Leibniz Institute for Tropospheric Research
UA	University of Augsburg
UFP	Ultrafine particle
UK	United Kingdom
US	United States
WHO	World Health Organization
WML	White matter lesion

Abstract (English)

The harmful effects of ambient air pollution on public health have been investigated in many epidemiological studies over the past decades. These investigations have established consistent associations with morbidity and mortality, making air pollution one of today's most important environmental risk factors. For this reason, national and international air quality standards have been set for common pollutants, such as particulate matter (PM) and nitrogen dioxide (NO_2). The World Health Organization (WHO) revised its recommendations in 2021 based on the latest scientific evidence and lowered the existing limits for PM and NO_2. However, the evidence only allows limits to be set for a selection of pollutants. For example, although toxicological studies indicate relatively consistent associations with health-related effects, the epidemiological evidence for the smallest size fraction of PM, the ultrafine particles (UFP, particles with a diameter ≤ 100 nm), has been assessed as heterogeneous and, therefore, insufficient for setting limit values.

This dissertation aims to examine the health effects of unregulated UFP and the time-varying effects of regulated air pollutants based on the limitations and recommendations of the 2021 WHO air quality guidelines. In this context, the associations between the number concentration of UFPs and size-fractioned particle number concentrations (e.g., size fractions 10 – 20 nm, 20 – 30 nm, 30 – 50 nm, 50 – 70 nm, 70 – 100 nm, nucleation mode particles [10 – 30 nm, NuMP], Aitken mode particles [30 – 100 nm, AiMP], and accumulation mode particles [100 – 800 nm, AcMP]) on cause-specific mortality and hospital admissions were investigated in three German cities. Furthermore, an international, multi-country, multi-city dataset was analyzed regarding the potential time-varying effects of PM and NO_2 on cardiovascular and respiratory mortality.

Increased UFP concentrations were associated with an increased risk of respiratory mortality five to seven days after UFP exposure. Moreover, the smallest UFP sub-fraction, the NuMP, showed an increased risk of respiratory mortality compared to larger particles. The effects were independent of other particle fractions, although the additional adjustment for NO_2 led to wider confidence intervals and insignificant results. Comparable results were observed for warm and cold seasons and different age groups, although larger effects were found for women.

The number concentrations of UFP did not show a clear association with cause-specific hospital admissions. The results suggested a delayed pattern of respiratory hospital admissions two to four days after exposure. However, larger particle size fractions showed consistent and pronounced effects on hospital admissions, especially the UFP sub-fraction of AiMP but also AcMP. The findings indicated a higher risk for children as well as in cold seasons, while the

risk for men and women was comparable. No significant change was observed after adjusting for particulate pollutants, and null findings were observed after adjusting for NO_2.

The analysis of time-varying associations showed mostly constant mortality effect size estimates per unit increase over the study period between 1995 and 2016, especially for NO_2 and PM_{10} (PM with a diameter of ≤ 10 µm). However, there was a significant temporal trend with increased effect sizes in the association between $PM_{2.5}$ (PM with a diameter of ≤ 2.5 µm) and cardiovascular mortality. Two pollutant models showed constant effect sizes for PM models with NO_2 adjustment and increasing effect size estimates over time for NO_2 models with adjustment for PM. Stronger associations were found in the (North) American and Western Pacific regions than in Europe, with moderate heterogeneity overall.

This dissertation adds to the literature with evidence from two multi-center analyses of UFP on hospital admissions and mortality. The results suggest that UFP may specifically affect the respiratory system, with particle size potentially playing a role. However, further research is needed to confirm these findings and establish a more conclusive understanding of the evidence. Furthermore, the findings suggest that although air pollution concentrations have decreased in recent decades, the associated mortality effect size estimates have not changed. Particle size, sources, chemical composition, and temporal changes in air pollutants warrant further and more in-depth research. In conclusion, the 2021 updated WHO air quality guidelines are important for improving air quality and reducing adverse health effects. Therefore, it is important to translate these recommendations into effective legislation and to expand research projects on still open questions.

Zusammenfassung (German)

Die gesundheitsschädlichen Auswirkungen der umweltbedingten Luftverschmutzung wurden in den letzten Jahrzehnten in einer Vielzahl epidemiologischer Studien untersucht. Dabei konnten konsistente Zusammenhänge mit Morbidität und Mortalität identifiziert werden, so dass Luftschadstoffe heute den wichtigsten umweltbedingten Risikofaktor darstellen. Aus diesem Grund wurden auf nationaler und internationaler Ebene Richt- und Grenzwerte für bestimmte Schadstoffe wie Feinstaub (PM) und Stickstoffdioxid (NO_2) festgelegt, um deren schädliche Auswirkungen auf die öffentliche Gesundheit zu reduzieren. Die Weltgesundheitsorganisation (WHO) hat ihre Empfehlungen zur Luftqualität 2021 auf Basis des aktuellen Forschungsstands überarbeitet und gleichzeitig die bestehenden Richtwerte für PM und NO_2 herabgesetzt. Die Evidenz erlaubte nur die Festlegung von Richtwerten für eine Auswahl an Schadstoffen. Beispielsweise wurde die epidemiologische Datenlage für die kleinste Fraktion der partikulären Luftschadstoffe, die ultrafeinen Partikel (UFP, Partikel mit einem Durchmesser ≤ 100 nm), als heterogen und unzureichend für die Empfehlung von Richtwerten bewertet, obwohl toxikologische Studien konsistent auf einen relevanten Zusammenhang mit gesundheitlichen Auswirkungen hindeuten.

Diese Dissertation hat zum Ziel, die gesundheitlichen Auswirkungen unregulierter ultrafeiner Partikel sowie die zeitvariierenden Effekte regulierter Luftschadstoffe zu untersuchen. Dabei wurde in drei deutschen Städten ausgewertet, wie sich die Anzahlkonzentration der UFP und bestimmter Größenfraktionen (z. B. Größenfraktionen 10 – 20 nm, 20 – 30 nm, 30 – 50 nm, 50 – 70 nm, 70 – 100 nm, Partikel im Nukleations-Modus [10 – 30 nm, NuMP], Partikel im Aitken-Modus [30 – 100 nm, AiMP] Partikel im Akkumulations-Modus [100 – 800 nm, AcMP]) auf die ursachenspezifische Mortalität und Krankenhauseinweisungen auswirkten. Darüber hinaus wurde ein internationaler multizentrischer Datensatz hinsichtlich zeitvariierender Effekte von PM und NO_2 auf die kardiovaskuläre und respiratorische Mortalität analysiert.

Die Untersuchung der UFP-Konzentrationen hinsichtlich der ursachenspezifischen Sterblichkeit zeigte eine Zunahme des respiratorischen Sterblichkeitsrisikos fünf bis sieben Tage nach UFP-Exposition. Darüber hinaus wiesen besonders Partikel der kleinsten UFP-Unterfraktion, die NuMP, im Vergleich zu größeren Partikeln ein erhöhtes Risiko für respiratorische Mortalität auf. Die Effekte waren unabhängig von anderen partikulären Luftschadstoffen, wenngleich die zusätzliche Berücksichtigung von NO_2 zu weiteren Konfidenzintervallen und insignifikanten Ergebnissen führte. Die Ergebnisse waren vergleichbar zwischen der warmen und kalten Jahreshälfte sowie zwischen den Altersgruppen, wobei für Frauen größere Effekte festgestellt werden konnten.

Anzahlkonzentrationen von UFP zeigten keinen eindeutigen Zusammenhang mit ursachenspezifischen Krankenhauseinweisungen. Die Ergebnisse deuteten auf ein verzögertes Muster von respiratorischen Krankenhauseinweisungen zwei bis vier Tage nach der Exposition hin. Des Weiteren zeigten größere Partikelfraktionen konsistente Auswirkungen auf die Krankenhauseinweisungen, insbesondere AiMP und AcMP. Die Ergebnisse zeigten sowohl ein höheres Risiko für Kinder als auch in der kalten Jahreshälfte, während das Risiko für Männer und Frauen vergleichbar war. Eine weitere Adjustierung für partikuläre Schadstoffe änderte die Ergebnisse nicht; die Adjustierung für NO_2 führte zu Null-Ergebnissen.

Die Untersuchung von zeitvariierenden Effekten ergab überwiegend konstante Effektschätzer für die ursachenspezifische Mortalität über den Studienzeitraum zwischen 1995 und 2016 für NO_2 und PM_{10} (PM mit einem Durchmesser von ≤ 10 µm). Dennoch zeigte sich ein signifikanter Trend mit erhöhtem Effektschätzer in der Assoziation zwischen $PM_{2.5}$ (PM mit einem Durchmesser von ≤ 2.5 µm) und kardiovaskulärer Mortalität. Die Ergebnisse der Zwei-Schadstoff Modelle zeigten konstante Effektschätzer für PM bei Adjustierung für NO_2 und einen Anstieg der Effektschätzer über die Zeit für NO_2 bei gleichzeitiger Adjustierung für PM. Die Auswertung der räumlichen Heterogenität ergab stärkere Assoziationen in den (nord-)amerikanischen und westpazifischen Regionen als in Europa, bei insgesamt moderater Heterogenität.

Diese Dissertation erweitert die Literatur um Evidenz aus zwei multizentrischen Analysen zu den Auswirkungen von UFP auf Krankenhauseinweisungen und Mortalität. Es zeigte sich, dass UFP insbesondere auf das respiratorische System wirken können und dass die Partikelgröße eine Rolle spielt. Dennoch wird deutlich, dass weitere Untersuchungen notwendig sind, um die beobachteten Ergebnisse zu bestätigen und ein konsistentes Bild der Evidenz zu erhalten. Zudem zeigen die Ergebnisse dieser Dissertation, dass die Konzentrationen einiger Luftschadstoffe in den letzten Jahrzehnten zwar zurückgegangen sind, dass sich die damit verbundenen Effektschätzer des Mortalitätsrisikos jedoch nicht verändert haben. Forschungsbedarf besteht hinsichtlich der Partikelgröße, ihrer Quellen, der chemischen Zusammensetzung und der zeitlichen Veränderungen der Luftschadstoffe. Insgesamt stellen die überarbeiteten Luftqualitätsrichtlinien der WHO von 2021 einen wichtigen Schritt zur Verbesserung der Luftqualität und zur Verringerung gesundheitsschädlicher Auswirkungen dar. Dennoch gilt es, einerseits, diese Empfehlungen in wirksame Gesetzgebung umzusetzen sowie, andererseits, das Wissen durch Forschungsvorhaben zu offenen Fragestellungen zu erweitern.

1. Introduction and scientific background

1.1 Air pollution and its relevance to public health, legislative frameworks, and the economy

Today, ambient air pollution has been identified as one major threat to human health. The first epidemiological studies of adverse associations with morbidity and mortality date back to episodes of severe air pollution in Europe, such as the London smog of 1952, and North America (1-3). Following concerns and evidence about the health risks of ambient air pollution, the World Health Organization (WHO) issued 1987 its first international evidence-based recommendations, so called air quality guidelines (AQGs), to guide the reduction of human exposure to harmful levels of air pollutants (4). However, these guideline values were not intended to separate harmful from nonharmful concentrations but instead represent the best scientific judgment, which still requires periodic review and reassessment with evidence evolving (4).

Over the past few decades, the evidence of the detrimental health effects of air pollutants has become increasingly robust. Studies on long- and short-term effects of particulate matter (PM) (5-8) or nitrogen dioxide (NO_2) (7, 9-11) have shown effects on (cause-specific) mortality endpoints as well as hospital admissions, ultimately building the basis for national and international public health regulations on these pollutants. Generally, air pollution significantly impacts the burden of disease and the public health of societies, e.g., as observed in changes in overall mortality, as well as the economy. For instance, ambient long-term exposure to PM with a diameter of 2.5 µm or less ($PM_{2.5}$) and NO_2 led to approximately 379,000 and 54,000 premature deaths, respectively, in the European Union (EU)-28 countries in 2018 (12). Although some parts of the world have observed reductions in premature mortality, such as the EU-28 region (e.g., -13 % for $PM_{2.5}$ compared to 2009 (12)), there has been a significant global increase in the risk of ambient PM pollution between 1990 and 2019 (13). In addition, ambient air pollution has emerged as the leading environmental risk factor over the same period, accounting for 2.92 million (11.3 % of all female deaths) and 3.75 million (12.2 % of all male deaths) deaths globally in 2019 (13).

Furthermore, air pollution can adversely affect a country's economic performance beyond the health sector, such as reduced labor force productivity or crop yields (12). For example, a 1 µg/m^3 increase in $PM_{2.5}$ concentration was significantly associated with a 0.8 % reduction in economic activity (measured as gross domestic product per capita) (14). Furthermore, in over 60 % of cases, a year-to-year variation in $PM_{2.5}$ concentrations greater than 1 µg/m^3 was observed, meaning that changes of ± 1 µg/m^3 between years are typical and the related effects relevant (14).

In 2021, the WHO updated its recommendations according to the latest evidence by reducing the recommended target values for several air pollutants, such as $PM_{2.5}$ (15). In the best-case scenario, AQGs lead to changes in legislation aimed at reducing emissions. These changes may result in alterations to pollution sources, the air pollution mixture, and its composition. It is therefore of interest whether this is accompanied by changes in associated health effects. In addition, there are limitations, as some air pollutants, namely ultrafine particles (UFP, particles with a diameter ≤ 100 nm ≙ 0.1 µm), have inconclusive evidence that prevented the formulation of AQG values. Additionally, epidemiological research on the short- and long-term health effects of regulated air pollutants often assumes a constant risk throughout the study period. Consequently, AQGs based on these studies are also based on these assumptions, and additional research and systematic evaluations will be necessary in the future.

1.2 Ambient particulate air pollution: composition, characteristics, and health impacts

Ambient air pollution is a heterogeneous and complex aerosol mixture of particulate and gaseous components. These substances can originate naturally from sources such as wildfires, volcanic eruptions, or atmospheric reactions or can be produced by anthropogenic activities such as biomass burning, vehicle/traffic emissions, or industrial processes (8, 10). In addition, they can be emitted directly into the air (primary pollution) or formed secondarily by chemical reactions and microphysical processes from precursor substances (e.g., sulfur dioxide, SO_2, or ammonia, NH_3) (12). However, individuals are exposed to various air pollutants, and addressing this problem is beyond individual control and requires action by regional, national, and international authorities (16). Furthermore, it is essential for epidemiological research to differentiate pollutants, their sources, and composition, as well as to assess the associated health effects to develop appropriate interventions and policy measures to reduce health risks and improve the quality of life of populations.

Unlike gaseous pollutants, PM consists of solid and liquid droplets of various sizes suspended in the air and is typically measured by gravimetric analysis of its total mass per unit volume of air. Subsequently, particles can be further classified into fine PM based on their aerodynamic diameter, with diameters of 2.5 µm or less for $PM_{2.5}$, and 10 µm or less for PM_{10}. In addition, there are much smaller particles, such as UFP, which contribute only marginally to the total mass concentration of PM and are, therefore, not well reflected in PM mass measurements (17). Instead, they can be more accurately characterized by measuring their particle number concentration (PNC) per unit of air volume. For instance, a measured mass concentration of 10 µg/m^3 can be represented either by one or a few particles of size 2.5 or 10 µm, or by several

million particles in the ultrafine range (e.g., particles of size 0.02 µm ≙ 20 nm) (17-19). UFP can be further and more generally classified according to their formation processes, such as nucleation or condensational growth via coagulation (17). The smallest size mode, the nucleation mode (< 0.03 µm ≙ < 30 nm), is mainly formed by atmospheric nucleation and particle growth from gaseous precursors but is also directly affected by traffic emissions (20). Particles in the Aitken mode (30 nm – 100 nm), the accumulation mode (100 nm – ~500/1,000 nm), or in the largest coarse mode (~500/1,000 nm – 10,000 nm) are either directly emitted or formed through condensational growth and coagulation from various types of precursors or mechanical or re-suspended material, with varying lifetimes and characteristics in the atmosphere (17, 21, 22). However, these modes are rather schematic subdivisions of the overall particle size distribution and do not indicate precise threshold definitions.

Figure 1 illustrates the disparities in normalized particle concentrations between particle mass (displayed in red) and particle number (displayed in blue) relative to particle size and displays the modes of different particle size fractions. As shown, the smallest particles have the highest particle number concentrations in ambient air (e.g., nucleation mode particles dominate in terms of particle numbers). In contrast, larger particle size fractions are primarily responsible for particle mass concentrations.

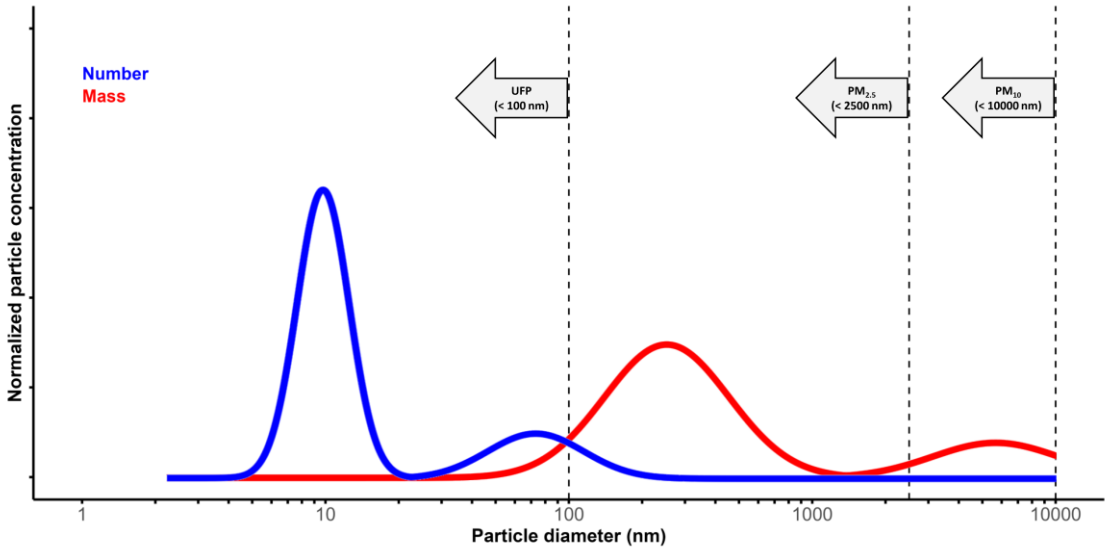

Figure 1: Schematic representation of particle number concentration (blue) and particle mass concentration (red) in relation to particle size. Figure adapted from Health Effects Institute (HEI) Review Panel on Ultrafine Particles, 2013 (17); own illustration.

Due to their small particle size, UFP have unique properties distinguishing them from larger PM. First, the particles can reach the lowest parts of the respiratory system, such as the alveolar region, where they may deposit due to diffusional and thermal motion, rather than

gravitational settling as larger particles (23-25) and can even translocate beyond the lungs into circulation (23, 26, 27). Second, UFP have a larger surface area and higher surface reactivity than other particles of the same mass, allowing them to absorb chemical compounds and thus increase their toxic and hazardous potential (19, 28). Finally, slower and less effective clearance of smaller particles from the lung has been observed, contributing to adverse health effects and further to size-dependent differences (17, 24, 26).

To understand the link between particulate air pollution and health effects, it is necessary to consider both the unique particle characteristics and potential biological pathways. It can be hypothesized that factors such as different particle sizes or characteristics, and therefore changing depositional patterns in the respiratory tract, may contribute to different health risks (29). In general, three biological pathways have been hypothesized to explain how particulate air pollution affects human health. Alone or in combination, these pathways can promote adverse health effects. For example, I) Particles may deposit in the pulmonary tree, leading to alterations in the autonomic nervous system activity through stimulation of alveolar sensory receptors (24). These changes frequently constitute the most immediate response to air pollution exposure (30, 31) and may affect the balance between sympathetic and parasympathetic activation (29). II) Air pollutants are taken up by macrophages, which may trigger subclinical inflammation in the lungs, involving pro-inflammatory and pro-oxidative mediators, which may ultimately result in systemic inflammation if the particle dose, reactivity, and lack of clearance are sufficient (24, 29, 31). III) The smallest particles can translocate from the alveoli through the epithelia to extrapulmonary regions and eventually into the circulation, directly affecting and interacting with the cardiovascular system (24, 26, 27, 29).

However, current monitoring and regulatory standards inherently assume that the risk of UFP is adequately addressed through the monitoring and regulation of larger PM. Although epidemiological studies on the health effects of UFP have grown over the past decades, evidence is still insufficient to recommend evidence-based guideline values (15) because the comparability across studies and the overall available data is limited (8). However, ample evidence from exposure science allowed to formulate four so-called good practice statements to guide authorities towards measurements and reductions of ambient UFP concentrations (15):

1. Measure ambient UFPs in terms of number concentration within a size range of ≥ 10 nm without an upper limit restriction.
2. Integrate UFP monitoring into existing air quality monitoring, including real-time size-segregated PNC measurements at selected stations alongside other airborne pollutants and PM characteristics.

3. Distinguish between low (< 1,000 particles/cm^3 for 24-hour mean) and high (> 10,000 particles/cm^3 for 24-hour mean) PNC to guide UFP emission control priorities.
4. Apply advanced science and technology to improve UFP exposure assessment for epidemiological studies and UFP management.

1.3 Advancements in air pollution epidemiology: temporal variations and ultrafine air pollution

The 2021 WHO AQGs represent an important and ambitious update to the previous 2005 WHO AQGs, reflecting the significant impact of air pollution on global health (32) and incorporating evidence from low-level air pollution studies in North America (33-35) and Europe (36, 37) to establish the updated values. However, further investigation and thorough analysis are required in certain areas. For instance, analyzing the changes over time in the health impacts of regulated air pollutants or gathering additional epidemiological evidence on exposures of emerging interest, such as UFPs.

In recent decades, the average concentrations of $PM_{2.5}$ and NO_2 have consistently decreased in some areas of the world, such as Europe and North America, although increases have been observed in other regions (12, 15). These reductions may be partially attributed to stricter air pollution mitigation policies in some countries. Studies conducted in Japan, China, the Netherlands, Switzerland, South Korea, Greece, and Italy have reported mixed results when examining the associations between these pollutants and mortality or morbidity over time. Some studies reported a decrease in effect size estimates (38-40), while others showed no temporal changes (39, 41, 42) or increasing effect sizes (38-41, 43-45). In addition, studies have reported temporal trends in associations between air pollutants and hospitalizations (46, 47). Generally, these analyses were predominantly conducted in individual cities or countries, which hampers the generalizability of the findings. Furthermore, study comparisons are limited because of variations in study methodology, study populations, and predominant exposure mixtures. Therefore, examining the temporal changes in the association between mortality and different air pollutants in different cities and countries in a standardized way can provide a better understanding of how the health risk of air pollution may have changed over time.

Furthermore, the first epidemiological short-term studies of ultrafine air pollution were conducted in the Erfurt area, Germany, in the 1990s, reporting associations with mortality (48-50). More recently, results of two multi-city studies indicated weak associations between the number concentrations of UFP or total PNC and (cause-specific) mortality endpoints (51, 52). The findings suggested a delayed increase in respiratory mortality risk following UFP exposure,

although the associations were not statistically significant (51, 52). However, single-city studies (53-60) have reported somewhat mixed results, and there is heterogeneity among study results with respect to mortality endpoints, exposure settings (e.g., time window, sources), and study methods, suggesting no general and significant pattern across studies. Different particle size fractions showed only suggestive results for cause-specific mortality and smaller particle sizes (57-60), although different cut-off values were used, which affected comparability. Further studies have investigated the effects of particle number concentrations of UFP and total PNC on hospital admissions. Two multi-city studies found no clear significant association between UFP or total PNC and cause-specific hospital admissions and only suggestive prolonged effects for respiratory causes (61, 62). Further single-city analyses (53, 56, 63, 64) and size-resolved analyses (63, 64) showed mixed results and limited comparability, again mainly due to differences in study methodology and exposure settings.

Overall, UFP have gained increasing scientific interest in recent decades, and more studies have assessed their risk to human health. However, systematic reviews and meta-analyses have concluded that there is still sparse and limited comparable exposure data, considerable heterogeneity between studies, inconclusive results, and weak indications between UFP and predominantly respiratory endpoints (17, 65, 66). More multi-center, standardized, and comparable research is necessary, such as for unregulated air pollutants, which has been explicitly addressed by the WHO in 2021 (15), or for time-varying effects of the regulated air pollutants.

1.4 Research gaps and aims of the thesis

In this context and based on the recommendations of the 2021 WHO AQGs, this doctoral thesis aims to answer the following three main hypotheses. In particular, this thesis aims to investigate the possible detrimental health effects of unregulated ambient UFP and total PNC in standardized multi-center settings.

1. Are short-term exposures to ambient total number concentrations and particles in the ultrafine range associated with daily cause-specific mortality and hospital admissions?

2. Do specific particle size fractions show different associations with health effects regarding cause-specific mortality and hospital admissions?

In addition, time-varying effects of regulated air pollutants were examined to determine if and how the mortality risk changes in light of updated AQGs.

3. Do routinely monitored and regulated air pollutants exhibit temporal variations in associations with cause-specific mortality risk with regard to their changes in ambient exposure levels over time?

This cumulative thesis consists of two published manuscripts, covering the first two hypotheses:

- Schwarz M, Schneider A, Cyrys J, Bastian S, Breitner S, Peters A. Impact of Ambient Ultrafine Particles on Cause-Specific Mortality in Three German Cities. Am J Respir Crit Care Med. 2023. (**Manuscript 1**)
- Schwarz M, Schneider A, Cyrys J, Bastian S, Breitner S, Peters A. Impact of ultrafine particles and total particle number concentration on five cause-specific hospital admission endpoints in three German cities. Environment International. 2023;178:108032. (**Manuscript 2**)

Furthermore, a third manuscript, entitled ‘Temporal Variations in the Short-Term Effects of Ambient Air Pollution on Cardiovascular and Respiratory Mortality in 380 Urban Areas during a 22-Year Period’ has been submitted to a peer-reviewed journal (at the time of submission of this thesis) and is included in the appendix of this thesis, addressing the third hypothesis. (**Manuscript 3**). At the time of publication of this thesis, the third manuscript has been published. Further information regarding final version of the manuscript can be found in section 6 of this thesis.

2. Methods

The section below briefly describes each study‘s methodological framework and is divided into two parts. The first section presents the studies on the health effects of UFP (Manuscripts 1 and 2), followed by the study on temporal variations in the health effects of regulated air pollution (Manuscript 3). More detailed information can be found in the respective manuscript.

2.1 Health effects of ultrafine particles (Manuscripts 1 and 2)

The health effects assessment of UFP was based on data from three German cities: Dresden, Leipzig, and Augsburg. Daily records of cause-specific mortality and hospital admissions were collected between January 1, 2010, and December 31, 2017, according to official statistics based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (67, 68). These data are routinely and anonymously compiled in official statistics, and data access was granted through the Research Data Center of the Federal Statistical Office and Statistical Offices of the Federal States (RDC) (67, 68). We restricted the datasets to cases that lived in a city and died in the same city (based on the official residence codes and the death certificates) or were hospitalized in the same state (67, 68). Furthermore, the analyses only considered primary diagnoses and did not include scheduled or outpatient cases.

Table 1 presents the cause-specific endpoints that were analyzed:

Table 1: Cause-specific mortality and hospital admission endpoints and related ICD-10 code.

ICD-10 code	Mortality endpoints	Hospital admission endpoints
A00-R99	Natural mortality	-
I00-I99	Cardiovascular mortality	Cardiovascular disease
I00-I52	-	Heart disease
I60-I69	-	Cerebrovascular disease
J00-J99	Respiratory mortality	Respiratory disease
J12-J18 & J20-J22	-	Lower respiratory tract infections

Furthermore, cases with unknown underlying diagnoses and cases hospitalized before the study period were excluded. The final dataset also included categorized information on the age and biological sex (male/female) of the respective case.

Air pollution data for the study period were collected from six fixed monitoring stations operated by the *Staatliche Betriebsgesellschaft für Umwelt und Landwirtschaft* (BfUL) and the

Leibniz Institute for Tropospheric Research (TROPOS) for Dresden and Leipzig and by *Helmholtz Munich* (HMGU) together with the *University of Augsburg* (UA) for the Augsburg station (67, 68). Furthermore, these stations have contributed to the *German Ultrafine Aerosol Network* (GUAN), which extends the legally required monitoring of air pollution and air quality by measuring additional pollutants, such as mass concentrations of soot particles or number concentrations of particles in the ultrafine range (69-71). Four stations were classified as 'urban background', while two were classified as 'traffic/roadside' stations. These classifications were assumed to characterize the exposure scenario in a city and were considered representative of the exposure of the urban population with background concentrations (urban background) and occurring peak concentrations (traffic/roadside) (67, 68).

Figure 2 illustrates the location and station type of the included GUAN monitoring stations.

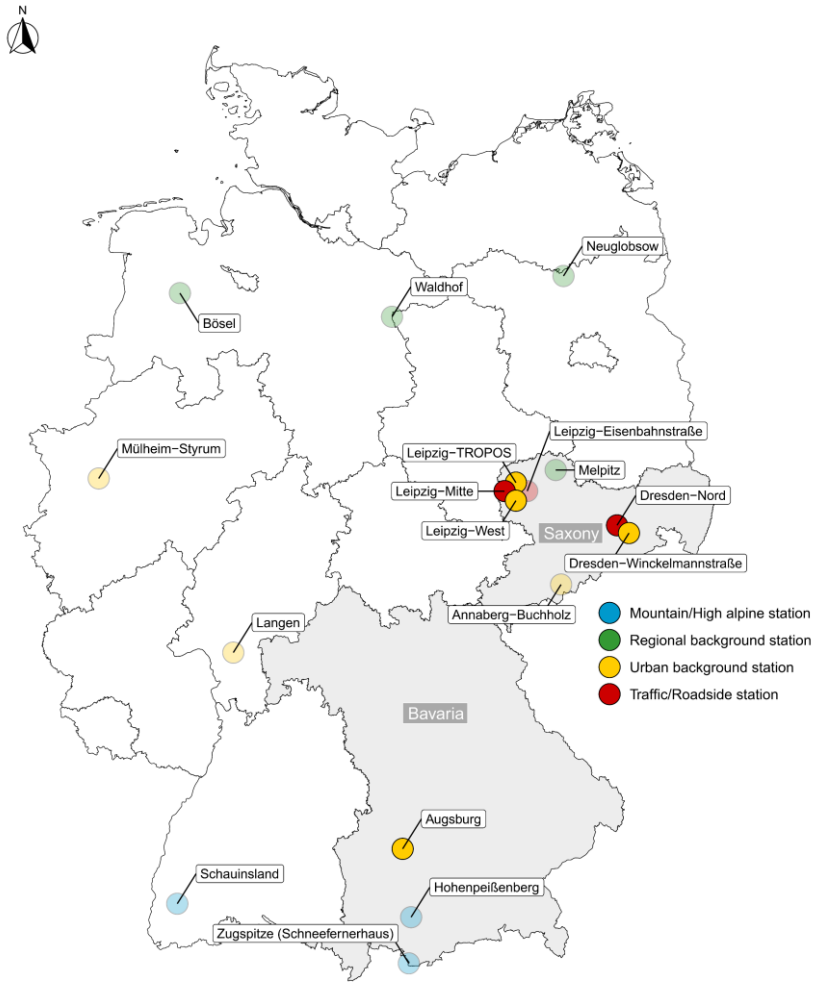

Figure 2: Map of GUAN stations across Germany. The color represents the station type. The highlighted stations were included in the analyses of this thesis (Manuscripts 1 & 2). The map is adapted from Birmili and colleagues (70) and Sun and colleagues (71); own illustration.

Particle number size distribution (PNSD) was measured at the stations using Mobility Particle Size Spectrometers (MPSS) of various modifications and configurations in the size range of 3 to 800 nm (67, 68). Additional information on the instrumentation, calibration processes, data management, and other air pollutants has been published previously (67, 68, 72-75). In general, the primary air pollutants of interest were the number concentrations of UFP and total PNC, defined in the size ranges 10 – 100 nm and 10 – 800 nm, respectively (67, 68). Additional analyses were performed on various UFP sub-fractions (e.g., size fractions 10 – 20 nm, 20 – 30 nm, 30 – 50 nm, 50 – 70 nm, 70 – 100 nm, nucleation mode particles [10 – 30 nm, NuMP], Aitken mode particles [30 – 100 nm, AiMP], and accumulation mode particles [100 – 800 nm, AcMP]). $PM_{2.5}$, NO_2, and black carbon (BC) mass concentrations were of secondary interest. Daily average concentrations of air pollutants and meteorological variables (e.g., air temperature) were calculated when $^3/_4$ of the hourly values were available (67, 68). The lagged exposure concentrations included the same day as the event (lag0) up to seven days before the event (lag7), the moving averages (lag0-1, lag2-4, lag5-7), and cumulative (lag0-7) concentrations, representing different exposure times of more immediate, delayed, and total exposure windows (67, 68).

Descriptive statistics were calculated for air pollutants, mortality, and hospital admission endpoints. Spearman correlation coefficients were calculated to assess temporal correlations. To examine the associations between daily air pollution levels and health outcomes, a two-stage modeling approach was used. In the first stage, Poisson regression models allowing for overdispersion were applied for each station, including confounders based on the literature (67, 68, 76, 77). In the second stage, station-specific estimates were then pooled using a random effects meta-analytical approach that accounted for variation within and between cities through nested hierarchical structures using random terms in the meta-models (67, 68, 78, 79). Furthermore, additional analyses were performed, such as assessing effect modification by age, biological sex, and season, and including a second air pollutant in the main model. Finally, the results were compared to several sensitivity analyses, such as modifications to model parameters, calculation of citywide exposure concentrations, or changes in the number of stations and lower cut-off values (67, 68).

2.2 Temporal variations of air pollution effects on mortality (Manuscript 3)

To examine the temporal variation of air pollution effects on cause-specific mortality, data from the *Multi-Country Multi-City Collaborative Research Network* (MCC; https://mccstudy.lshtm.ac.uk/) consortium were used. These datasets (80) consist of individual

time series for cities within the consortium, and have been regularly updated to include air pollution and mortality data for more than 620 cities in 36 countries (81). The participating consortium members were responsible for collecting air pollution and mortality data. Cause-specific mortality endpoints were collected from local authorities using the ICD-10 classification for the following endpoints: all-cause (no restrictions), natural/non-accidental (e.g., ICD-10: A00-R99), cardiovascular (e.g., ICD-10: I00-I99), and respiratory (e.g., ICD-10: J00-J99) mortality (see appendix). Air pollution and meteorological data were collected as daily mean concentrations and were generally provided by country-specific monitoring campaigns described in more detail previously (see appendix). Further adjustments were required to prepare the dataset for subsequent analyses and to improve data quality. First, the dataset was restricted to the period 1995 – 2016. Second, air pollution concentrations for an individual year were set as missing if less than $^2/_3$ of the data were available. Finally, cities were excluded if the outcome data had more than 50 % missing values or the total length of valid air pollution data was less than five years (see appendix). The final dataset comprised 380 cities or urban areas from 24 countries and the air pollutants NO_2, PM_{10}, and $PM_{2.5}$ (see appendix).

A two-stage framework was employed to investigate the associations between air pollution and cause-specific mortality (78, 79), which was further extended to examine temporal variations in the associations. In the first stage, linear quasi-Poisson regression models were fitted for each city, and a consistent confounder model was used according to previous analyses (82, 83). In the second stage, city-specific results were pooled using a multilevel random-effects meta-analysis, similar to the approach used to study the health effects of UFP, although with some modifications. Temporal variations were examined in two ways, according to the general modeling strategy. First, by applying a longitudinal multilevel meta-regression model with time as a linear term, and second, by comparing risk estimates from different time periods separately (see appendix). The study conducted secondary analyses to examine the interdependencies of a second pollutant (PM + NO_2/NO_2 + PM) in two-pollutant models and sources of heterogeneity in the longitudinal meta-regression by a set of nine meta-predictors using a multivariable meta-regression (see appendix). Finally, a series of sensitivity analyses were conducted, including changes in model parameters and variables, different inclusion/exclusion criteria, and modifications to the temperature adjustment (see appendix).

3. Results – key findings

The following section presents the key findings of the two publications and the manuscript that are part of this thesis. The structure follows the methods section by presenting the results for the studies on the health effects of UFP first (Manuscripts 1 and 2), and then the results for the study on the temporal variations in the health effects of regulated air pollution (Manuscript 3).

3.1 Health effects of ultrafine particles (Manuscripts 1 and 2)

Short-term exposure to UFP or total PNC was not consistently associated with either **natural** or **cardiovascular mortality**. However, UFP and total PNC showed both significant associations with **respiratory morality**, highest at lag5-7 (67). For example, an increase of 3,223 particles/cm^3 (representing the interquartile range of UFP concentration) was associated with a delayed increase in respiratory mortality risk of 4.46 % (95 % confidence interval [CI]: 1.52 % to 7.48 %), five to seven days after exposure (67). Furthermore, the smallest particle size fractions, the NuMP (size range: 10 nm – 30 nm), showed the largest effects on respiratory mortality, and smaller or no effects were seen for larger particle size fractions (67). The main results for respiratory mortality were independent of additional BC or $PM_{2.5}$ adjustment (e.g., UFP + $PM_{2.5}$: 4.07 % [95 % CI: 0.93 % to 7.30 %]), whereas the effect estimates got more imprecise and insignificant (wider CI's) when NO_2 was added into the models (67). Furthermore, the association between UFP and respiratory mortality was significantly stronger in women compared to men (women: 9.57 % [95 % CI: 5.35 % to 13.97 %], men: 0.45 % [95 % CI: -3.10 % to 4.13 %]), and no effect modification was seen for either age or season (67). The results of the sensitivity analyses confirmed the observed associations for respiratory mortality.

When investigating the effects of UFP and total PNC on cause-specific hospital admissions, these air pollutants did not show a clear pattern with hospital admissions. UFP exposure indicated slight increases in **cardiovascular** and **heart disease hospital admissions** on the same day and one day after UFP exposure (68). In addition, more delayed associations were seen for **respiratory hospital admissions**. For example, an interquartile range increase of 3,220 particles/cm^3 was associated with a 0.69 % (95 % CI: -0.25 % to 1.12 %) increase in the relative risk of respiratory hospital admission two to four days after exposure (68). The results for total PNC were comparable, and the largest and most consistent associations were seen for $PM_{2.5}$ (68). However, a clearer pattern was observed when different particle size fractions were analyzed. The results showed more pronounced effects for larger particle size fractions and delayed or cumulative (e.g., respiratory hospital admission, AcMP [size range:

100 nm – 800 nm], lag2-4, 1.55 % [95 % CI: 0.86 % to 2.25 %]), and more immediate patterns for smaller particle size fractions (68). The results for respiratory hospital admissions did not change and remained stable when BC or $PM_{2.5}$ was additionally added to the UFP or total PNC models. However, the effect estimates dropped to nearly zero when NO_2 was added (68). The analyses of potential effect modification showed no differences between men and women, although a slightly higher risk was seen for younger age groups and in the cold season (68). Further sensitivity analyses generally validated these results.

In summary, Figure 3 visualizes the particle size ranges where the main results of the mortality (67) and hospital admission analyses (68) are located, with regard to particle number (displayed in blue) and mass concentration (displayed in red) relative to the particle size.

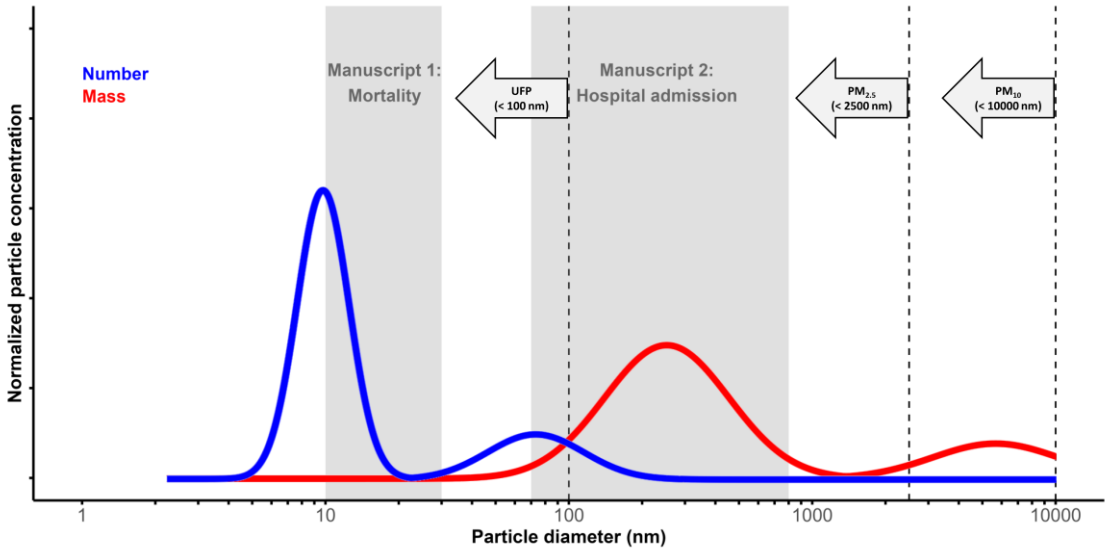

Figure 3: Schematic representation of particle number concentration (blue) and particle mass concentration (red) in relation to particle size and the main results of the mortality (67) and hospital admission analyses (68). Figure adapted from HEI Review Panel on Ultrafine Particles, 2013 (17); own illustration.

The largest associations in the mortality analysis were seen for the smaller particle size fractions (mainly dominated by particle number) and mostly for respiratory mortality (67). For the analysis of hospital admissions, mainly larger particle size fractions (less dominant in terms of particle number) were associated with hospital admissions, with the strongest and most consistent results for respiratory causes (68).

3.2 Temporal variations of air pollution effects on mortality (Manuscript 3)

Over the study period of 22 years, the average concentrations of all three studied air pollutants have decreased. For example, the median NO_2 concentration over all cities has decreased between 1995-2002 and 2009-2016 from 32.7 µg/m^3 to 22.7 µg/m^3 (see appendix). The results of the whole-period regression analyses (1995-2016) showed significant positive associations with both mortality endpoints and all three air pollutants in the model without assessment of temporal variations. For example, a 10 µg/m^3 increase in $PM_{2.5}$ was associated with a 1.07 % (95 % CI: 0.74 % to 1.39 %) increase in respiratory mortality risk (see appendix). The temporal variation analyses showed rather stable associations over the study period for NO_2 and PM_{10}. However, a significant temporal difference was observed for $PM_{2.5}$ and cardiovascular mortality (see appendix). The related relative risk increased from 0.14 % (95 % CI: -0.32 % to 0.61 %) in 1998 to 0.77 % (95 % CI: 0.35 % to 1.19 %) in 2012 (see appendix). Two-pollutant models indicated increasing effect sizes over time for NO_2 and no changes for PM fractions (see appendix). In addition, the meta-regression analysis identified stronger associations in the Western Pacific region and the Americas compared to Europe, explaining parts of the observed heterogeneity in the longitudinal analysis, although the overall heterogeneity was rather moderate (see appendix). Further secondary analyses and several sensitivity analyses did not change the overall pattern of the findings, although changes to the temperature adjustment and exclusion of US cities did show slight differences (see appendix).

4. Discussion

The discussion section should briefly describe this thesis's overarching and more general aspects, future UFP research directions based on identified knowledge gaps, and specific strengths and limitations. A more detailed discussion and further information are provided in each individual manuscript.

4.1 General aspects and key points

This thesis aimed to follow up on the discussions of the 2021 WHO AQGs and to investigate remaining open questions, such as the impact of unregulated air pollution, including the number concentration of UFP. A particular focus was on the differentiation of associations between different particle size fractions. In addition, the thesis aimed to examine temporal variations in the association between regulated air pollutants and cause-specific mortality on a large, international, and standardized scale.

The results showed that number concentrations of UFPs and total PNC were associated with respiratory mortality, whereas rather mixed results and more suggestive evidence for hospital admissions were found. These findings were generally comparable with other multi-center studies conducted in Central-Eastern (51, 61) and North/South-Western Europe (52, 62), and showed a similar delayed pattern to the first studies of UFP and mortality in the 1990s (48, 50). However, most studies did not find consistent significant results nor provide clear evidence of an association. Our multi-center studies contribute to the existing evidence and enable a more updated assessment and comparison of overall patterns. The results showed that particularly the respiratory system may be affected by UFP, although the evidence is still inconsistent (17, 65). As highlighted, differences among the studies may arise from their respective study designs (e.g., exposure assessment and assignment, study population, or statistical methods) and should be considered when drawing conclusions from the published evidence (65). In addition, the length of the time series and the data quality (e.g., a more complex and costly exposure assessment (84) may result in more missing values in UFP time series than in routinely monitored particles, which affects the power and precision of statistical analyses) prevented the examination of temporal variations in the UFP risks. Moreover, data on particle number concentrations is currently unavailable in the MCC database and temporal differences have not been analyzed. However, studies have shown decreasing UFP concentrations and related mortality risks in periods with improved air quality due to, e.g., fuel replacement from brown coal to natural gas or enhanced pollution control measures (49, 58), although more comprehensive analyses are lacking.

Furthermore, this thesis showed rather constant mortality effect size estimates between PM_{10} or NO_2 with cardio-respiratory mortality over time, although $PM_{2.5}$ showed a tendency for increasing effect size estimates with cardiovascular mortality. These findings add to the limited and mixed evidence from single-country studies reporting a decrease (38-40), an increase (38-41, 43-45), or no temporal trend (39, 41, 42) in mortality effect sizes. The heterogeneity among previous studies and the fact that the mortality effect size per unit increase did not change with decreasing air pollution levels may be explained by the complex interplay of different exposure sources and chemical compositions in multi-pollutant urban environments. This could also imply changes in toxicity, a non-linear exposure-response relationship, or different particle characteristics.

Different risk patterns were observed between mortality and hospital admission endpoints when different particle sub-fractions of UFP and PNC were analyzed, as well as between different exposure time windows. For example, smaller particle size fractions were associated with a higher risk of respiratory death, while larger particles showed no association with mortality (67). In contrast, larger particle size fractions showed a higher risk for respiratory hospital admissions, while no effects were seen for smaller particles (68). One possible explanation may be that different particle sizes could, on average, trigger different biological pathways related to different health endpoints. As reported, UFP can reach the alveoli and even translocate further across the epithelia into the interstitium (24, 26). These particles may transport toxic chemicals and therefore have an increased hazardous potential, leading to adverse effects (19). However, larger particle size fractions may remain in the airways and induce systemic inflammation or other subclinical processes; thus, the health effects may differ (24, 29, 31). However, air pollution is a significant environmental stressor that affects all so-called ‘hallmarks of environmental insults’, from the cellular or molecular level (e.g., genomic or epigenetic alterations), to the systemic and organismic level (e.g., effects on the nervous system or the microbiome) (85). Furthermore, the underlying exposure setting may also influence the results. For example, slightly larger associations were observed for respiratory mortality in urban background settings compared to traffic-related exposure settings (67). In contrast, the traffic-related setting showed a higher association with respiratory hospital admissions than the urban background setting (68), which may be explained by different prevailing exposure sources in these settings leading to, e.g., different toxicity levels.

Conducting thorough and comprehensive exposure assessments of different particle sources or chemical composition in epidemiological studies can provide valuable information. For example, two studies conducted in London, UK, and one study in three Spanish cities suggested mixed associations of particle number concentration from traffic emissions (e.g., vehicle exhaust) but also from nucleation processes with health effects (55, 56). However, we did not

explicitly analyze different exposure sources and only compared the effect estimates between urban background and traffic-related settings. As mentioned before, some differences in associated health risks between number concentrations were observable. However, this must be interpreted cautiously, because of different local influences that could not be adequately differentiated without a dedicated exposure source assessment (e.g., positive matrix factorization). For example, a large exposure study including 27 monitoring stations across Europe and the US (including four monitoring stations of our UFP analyses), covering different monitoring station types, concluded that road traffic is still a major emission source in terms of particle number (86). However, the authors reported a relevant number of cities that had high morning-midday concentrations of smaller particles (nucleation mode), which are likely influenced by factors such as photochemical nucleation but also by surface fumigation of transported air pollution from high-altitude layers (86). In addition, particles can have different chemical compositions, e.g., $PM_{2.5}$ mass consists of different components that have been shown to vary by geographical region and have undergone changes over time (8). For example, reductions in SO_2 emissions (e.g., combustion of fossil fuels) led to a decline in sulfate (SO_4^{2-}) concentrations, which is considered one of the most abundant $PM_{2.5}$ components (8). Furthermore, depending on the type of PM components (e.g., secondary aerosols, metals), different detrimental effects have been reported (87) and changes in their relative proportion to overall PM mass may modify the associated risk (88), although an explicit investigation of temporal trends in mortality risk was not conducted. In this thesis, chemical composition analyses were not conducted, and further exposure assessment was considered exploratory and relied mostly on the type of monitoring site and other parameters, such as particle size or correlations with other air pollutants. This warrants the need to include more in-depth exposure assessment (e.g., exposure sources and chemical composition) in the context of larger epidemiological studies.

Finally, it is apparent from the analyses that further research effort is needed to distinguish the effects of one pollutant from another. In each of the three analyses conducted in this thesis, including a second pollutant in the main model indicated varying influences on the results, with some combinations showing stronger effects while others exhibited weaker effects. In addition, UFP and PNC showed moderate to high temporal correlations with NO_2 in our analyses and the largest changes in the results, and Ohlwein and colleagues concluded that NO_2 may have the largest effect on point estimates compared to other pollutants (65). It is still debated whether the observed UFP effects result from the UFP number concentration per se, whether the effects may be overlaid by those of other pollutants, or rather represent specific sources such as general combustion of PM. However, studies have reported that $PM_{2.5}$ and PNC are not representative of each other, and high levels of one pollutant do not necessarily lead to

high levels of the other pollutant (89). In addition, NO_2 and UFP share mostly similar sources and temporal/spatial patterns, which may lead to higher correlations and unstable models depending on the underlying environmental setting (65, 84). Whether UFP effects are independent or a surrogate of NO_2 co-exposure or vice versa remains uncertain (90). Similar results were seen in our analyses, also with regard to monitoring station type.

4.2 Potential future UFP research directions

In addition to the varying traits of particle number and mass, two additional aspects warrant discussion and may be important and valuable for future research: particle surface area concentration (PSC) and new particle formation (NPF).

Only a few epidemiological studies have examined the associations between PSC and health outcomes, such as hospitalizations (91) or myocardial infarctions (92). It was concluded that PSC may be a more sensitive indicator of UFP risk than particle number (91) and that PSC indicated a larger and more precise risk estimate for myocardial infarction compared to PNC (92). In addition, surface area may represent a highly biologically relevant dose metric with high toxicological impact, as molecules bound to the surface may interact with body fluids and tissues (93). The surface area was also shown to have a larger association with subclinical inflammatory markers than number concentrations of UFP (94). However, the effects of PSC on mortality have shown mixed results (57, 60), and future research is needed to disentangle the effects from other particle metrics (e.g., mass and number). In addition, the simultaneous comparison of different particle metrics and their health effects is of high scientific value and should be considered in future research efforts.

Figure 4 visualizes the particle surface area concentration (displayed in green) along with the particle number (displayed in blue) and particle mass (displayed in red) in relation to particle size.

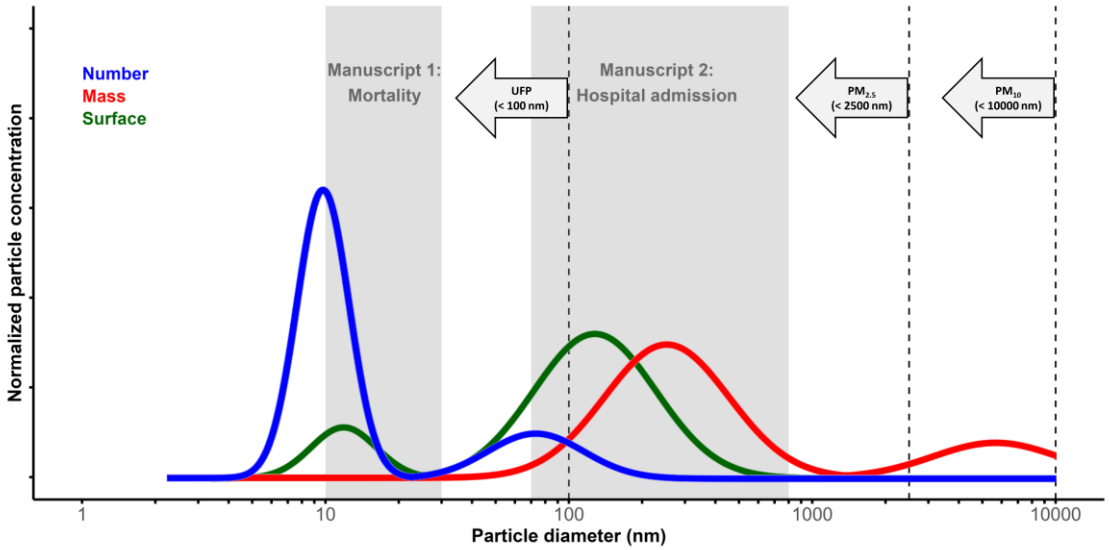

Figure 4: Schematic representation of particle number concentration (blue), particle mass concentration (red), and particle surface area concentration (green) in relation to particle size and the main results of the morality (67) and hospital admission analyses (68). Figure adapted from HEI Review Panel on Ultrafine Particles, 2013 (17); own illustration.

It can be seen that the two modes of PSC lie in the same size range as particle number and mass (and in the same region where the main results were found in the analyses), indicating that the results may be influenced by other factors or substances (e.g., chemical components on particle surface). Further research may benefit from additional consideration of PSC beyond particle number and mass, as it is not yet clear which particle metric best describes the risk of the smallest particles, especially with respect to the source of pollution.

NPF refers to the phenomenon in which molecular clusters are formed by precursor substances, such as gas-phase sulfuric acid (95). These processes occur continuously in the atmosphere, with clusters increasing in size through condensation and coagulation under favorable meteorological conditions, such as high solar irradiation, air temperature, relative humidity, and atmospheric mixing conditions (84, 95). It is hypothesized that NPF is also favored by low particle concentrations (high particle levels tend to favor condensation over NPF) and that reductions in ambient particle mass due to control measures may increase conditions conducive to NPF (84). Furthermore, NPF can likely differ in size and chemical composition from primary UFP emissions, and peaks in NPF events often coincide with high levels of other photochemical pollutants, such as ozone (O_3) (84). The significance of NPF in different environments can be determined by the strength and frequency of NPF events in a region over time (96). It can be hypothesized that these NPF events may contribute substantially to the UFP number concentration on a regional scale, and therefore may have affected our measurements. Indeed, elevated midday concentrations were observed at some urban background stations in our analyses (e.g., higher levels of the smallest particle size fractions, especially

on days with high solar irradiation), although a more specific epidemiological investigation was beyond the scope of the projects. Thus, further studies distinguishing the health effects of NPF (e.g., on NPF event days) from primary and more general UFP may be important and should be accompanied by a more in-depth analysis of emission sources, as such efforts are currently lacking for epidemiological analyses and are often limited to exposure science. In this thesis, such extensive analyses have not been conducted, but the study nevertheless shows that size-segregated measurements of particle number are an important and relevant consideration in future studies, since sources, pathways, and the related health effects may differ.

4.3 Strengths and limitations

All analyses involved a harmonized exposure and study design, state-of-the-art study methods, and have been carefully designed to meet the scientific needs and be consistent with previously published methodology. For example, size-fractioned analyses were conducted to examine whether different particle sizes have different effects, which has not been addressed in many studies but is of growing interest. In addition, the multi-center designs, large sample size, and long individual time-series data contributed to statistical power and model stability. Furthermore, the collection of exposure and outcome data was independent of each other. The routine outcome data was complete, with missing values considered to be complete at random. Finally, a comprehensive set of sensitivity analyses and further restrictions on the datasets increased the interval validity and allowed for conservative comparison of results within and across studies.

However, it is important to acknowledge certain limitations. A large number of analyses have been conducted, and some results may be due to chance. However, the analyses focused more on general patterns (e.g., overall lag patterns between exposures) than on individual significant findings. Furthermore, the ambient air contains a complex mixture of pollutants, some of which (such as UFP) exhibit large temporal-spatial variations. This could have introduced measurement error, exposure misclassification, and residual confounding, particularly when relying on single, fixed monitoring stations. Measurement error may also be a factor in the underlying cause definition of administrative datasets. However, further inspections of the data and several sensitivity analyses suggested this to be marginal. Furthermore, more detailed data on the source and chemical composition of the pollutants, which may be key factors in the toxicity and health risk of particulate air pollutants, were lacking. Finally, the analyses were conducted in Germany or more developed regions such as North America and Europe; thus, generalizations should be made with caution.

5. Conclusion and Outlook

In summary, the results of this dissertation provide evidence that ultrafine air pollution may be particularly associated with the respiratory system as seen in the investigated health endpoints of mortality and hospital admissions. However, despite the results of this thesis, further multi-center research is required to verify these findings. In addition, effects may vary by particle size and, to some extent, by exposure setting. Studies would benefit from including and comparing other particle metrics, different sources of air pollutants and chemical compositions, and additional exposures and conditions of emerging interest, such as NPF. Currently, there are plans to expand and continue the epidemiological research efforts in this field and to address the highlighted discussions of this thesis in new projects. Furthermore, the thesis shows that despite a substantial decrease in air pollution levels over the last three decades, the effect size of the associations between air pollution and mortality has not shown a proportional change. The findings highlight the need for an additional and explicit focus on temporal variations in the associated effect estimates between air pollutants and health endpoints and a potential non-linear exposure-response relationship.

The 2021 WHO air quality guidelines are an important step towards improving air quality and reducing harmful effects on health. As addressed, the utilization of emerging science and technology, such as exposure assessment and modelling, or the development and utilization of standardized procedures may facilitate comparison between studies or exposure settings and provide more detailed and highly needed data (15). However, it is necessary to translate these recommendations into effective and binding legislation at the national and international level, such as the EU ambient air quality directive (AAQD) or further emission control measures, and to expand research projects on open research questions in order to provide more consolidated evidence for future re-evaluation.

Currently, the European Union is in the process of discussing an updated AAQD that will revise the current air quality standards in the EU member states. In these negotiations, the parliament is considering the establishment of mandatory ‘monitoring supersites’ in rural and urban settings to collect more long-term data and data on pollutants of emerging concern, such as black carbon and UFP (97). Even though the proposed number of supersites is relatively low (at least one supersite per 10 million inhabitants in an urban background location and at least one supersite per 100,000 km^2 in a rural background location, with variations for member states with a smaller population and/or territory (98)), this would substantially increase the data basis in Europe, as UFP monitoring is currently mainly done through a few dedicated research efforts. Although there are currently no established air quality limits for ultrafine particles on an international level (e.g., WHO or EU), more stringent monitoring and further reduction efforts

would have significant benefits for public health and provide greater opportunities for research. One example may be an extension and/or revision of the current EURO 6 vehicle emission standards (including its technical stages), where exhaust emission measurements require a number-based approach in addition to the usual mass-based approach (99).

Finally, in 2021, the WHO published an evidence-based framework for improving ambient air quality. This framework provides guidance not only to the scientific community, but also to authorities and decision-makers at regional, national, and international levels. It also includes good practice statements for UFP, paving the way for more standardization and control of ambient ultrafine air pollution. Following the WHO AQGs in general and deriving evidence-based legislation constitute the best way to adapt mitigation measures of ambient (ultrafine) air pollution and to align public health policies accordingly.

6. Author contributions to the manuscripts and further projects

This dissertation includes two published manuscripts in the main part of the thesis and a third submitted manuscript in the appendix, for which the individual contributions are presented in the following section. Further information on each manuscript (e.g., related science communication) is provided, and additional projects are described.

During my time as a doctoral researcher within the structured doctoral program, I regularly updated the Thesis Advisory Committees (TAC) of *Ludwig-Maximilians-University Munich* (LMU) and *Helmholtz Graduate School Environmental Health* (HELENA) on the progress of the projects. Therefore, annual joint formal meetings were scheduled, in which I presented the status and results of each project to the TAC members, followed by a discussion of the research ideas, methodology, and next steps.

6.1 Manuscript 1 – 'Impact of Ambient Ultrafine Particles on Cause-Specific Mortality in Three German Cities'

The *Saxon State Office for Environment, Agriculture, and Geology* (LfULG) initiated and funded the project and its main idea, which was further scientifically developed and discussed by all participants and co-authors throughout the project.

As the first author, I was responsible for the curation and data management of the exposure data and the linkage with the routine mortality data at the RDC. Prior to this linkage, extensive pre-processing of the data was required to ensure that all necessary variables were included in the dataset and that the dataset was in the correct format. Due to the high data protection standards for mortality data in Germany, all analyses (also including the statistical analyses) were conducted at a workstation for visiting scientist at the local RDC facility. In addition, I drafted the statistical analysis plan (SAP), reviewed the current literature on the topic, and performed all statistical analyses and graphical presentations of the results. After completion of the main analyses, I drafted the manuscript and the corresponding supplement, incorporated comments from all co-authors, and submitted the manuscript to the *American Journal of Respiratory and Critical Care Medicine* (AJRCCM). In addition, I revised the manuscript based on the comments from the journal's reviewers and completed all necessary administrative tasks after its acceptance for final publication (67).

During that time, I presented preliminary results of this project in an invited online talk at the 'Statuskolloquium Luftqualität in Sachsen' and an in-person conference presentation at the

34th Annual Conference of the *International Society for Environmental Epidemiology* (ISEE) in Athens, Greece (100).

The published article includes an editorial (101) and I have been personally featured in the 'Emerging Investigators Highlight' section of the AJRCCM (https://doi.org/10.1164/rccm.207i10xliii). I gained further experience in science communication by contributing to a press release on this publication issued by HMGU (https://www.helmholtz-munich.de/en/newsroom/news-all/artikel/ambient-ultrafine-particles-very-small-and-very-dangerous) as well as by giving an interview to a local children's radio station in Munich, Germany, talking about the health effects of UFP and PM (in German: https://open.spotify.com/episode/2115BfJwW8sjIC5FDJhqGU). Finally, I contributed to two lessons on a 'Health Day' at a local high school in the Regensburg area, Germany, together with Dr. Regina Pickford (HMGU), where we taught the students about the work of environmental researchers and the relevance and recent findings in air pollution epidemiology.

The AJRCCM has an impact factor of 24.7 and is ranked 2nd/53 and 2nd/101 by *Journal Citation Indicator* in the categories 'Critical Care Medicine' and 'Respiratory System', respectively (according to *Journal Citation Reports™* 2022). The current *Altmetric Attention Score* for the publication is 97 (Altmetric.com, accessed: March 18, 2024).

6.2 Manuscript 2 – 'Impact of ultrafine particles and total particle number concentration on five cause-specific hospital admission endpoints in three German cities'

This project was also initiated and funded by the LfULG and consisted of the same scientific collaborators as the project mentioned in point 6.1.

My contributions and responsibilities as the first author consisted of all tasks from initial data management to final publication, as already mentioned in section 6.1. In brief, after extensive data management, I drafted the related SAP, updated the literature review for relevant publications on hospital admissions and morbidity outcomes, and conducted the analyses. It should be noted that these analyses were separated from the previous mortality analyses due to the data protection regulations at RDC, although the previously developed codes could be used after some adjustments to the new dataset. Following the analyses, I drafted the manuscript and online supplement, included the comments from the co-authors and submitted the manuscript to the journal *Environment International* (EI). I incorporated and revised the comments from the journal's reviewers and handled the administration after final publication (68).

After the publication, I was involved in science communication as the publication was highlighted in the Featured Publication section of HMGU (https://www.helmholtz-munich.de/en/newsroom/news-all/artikel/do-ultrafine-particles-ufps-lead-to-increased-hospital-admissions). I presented the results of this project, along with the findings of the mortality project (section 6.1), at the Kickoff Meeting of the Helmholtz Munich *Environmental Health and Lung Research School* (EHLRS) and on an EHLRS retreat with senior scientists and principal investigators (PIs).

EI has an impact factor of 11.8 and is ranked 11th/334 by *Journal Citation Indicator* in the category 'Environmental Sciences' (according to *Journal Citation Reports*^{TM} 2022).

Finally, I wrote the first version of the project-related final report, incorporated the co-author's comments, and submitted the final report to LfULG (https://www.luft.sachsen.de/ultrafeine-partikel-russ-und-gesundheit-23426.html).

6.3 Manuscript 3 (Appendix) – 'Temporal Variations in the Short-Term Effects of Ambient Air Pollution on Cardiovascular and Respiratory Mortality in 380 Urban Areas during a 22-Year Period'

The *Multi-Country Multi-City Collaborative Research Network* is an international consortium focused on research on environmental stressors, climate, and health (https://mccstudy.lshtm.ac.uk/). At its core is a large multi-center dataset to which each participating institution contributes with country-specific data and is responsible for data collection and quality.

I was involved in a subproject using the MCC dataset by reviewing the literature on temporal variations in mortality risk, drafting the SAP together with co-authors, and further project-related data management and data cleaning, such as an extended inclusion and exclusion catalog to meet the required format of the dataset. In addition, I analyzed the final dataset, including the visual presentation of the results, wrote a summary report for the MCC consortium and drafted the first version of the manuscript and the online supplement afterwards. I then incorporated all the comments and suggestions from the co-authors. At the time of the thesis submission, the manuscript was submitted to the *The Lancet Planetary Health* (TLPH) journal.

At the time of thesis submission, an abstract was accepted as an in-person conference contribution at the 5th ISEE Europe Young and Early Career Researchers Conference in Rennes, France.

TLPH has an impact factor of 25.7 and is ranked 3rd/334 by *Journal Citation Indicator* in the category 'Environmental Sciences' and 7th/400 in the category 'Public, Environmental & Occupational Health' (according to *Journal Citation Reports™* 2022).

At the time of publication of this thesis, the final version of the manuscript has been published in TLPH (https://doi.org/10.1016/S2542-5196(24)00168-2).

6.4 Further projects

Besides the projects and publications included in this thesis, I was further involved in several other projects focusing on the health effects of air pollution.

Together with Prof. Dr. Dr. Svenja Caspers and her PhD student Tatiana Miller (*Forschungszentrum Jülich*, Germany), we examined how long-term concentrations of air pollution (e.g., $PM_{2.5}$ or NO_2) are associated with white matter lesion (WML) numbers and volumes and their spatial distribution patterns in the brain. Firstly, this project entailed the comparison of different machine learning approaches for WML segmentation as part of Tatiana Miller's PhD thesis. In brief, WMLs were segmented automatically for 30,000 magnet resonance images (MRIs) of participants of the German National Cohort (NAKO) (102). Secondly, we then linked the segmented individual brain volumes of the NAKO participants with the air pollution data at the individual home addresses. Together with Margarethe Woeckel (MD student at HMGU), I drafted the SAP, did initial data cleaning and curation of the datasets, and started the epidemiological analyses.

Furthermore, I was involved in a conceptual project together with colleagues from the *Leibniz Research Institute for Environmental Medicine* (PI: Dr. Tamara Schikowski), *Heinrich-Heine-University Düsseldorf* (PI: Prof. Dr. Barbara Hoffmann), and the *Institute and Policlinic for Occupational and Social Medicine* (PI: Prof. Dr. Andreas Seidler). In brief, this consortium aimed to propose different epidemiological study designs for the investigation of UFP emissions from airplanes/airports and their health effects on the population in the Frankfurt region, Germany. In this project, I was mainly responsible for compiling all necessary and required information regarding time-series analyses and drafting the related deliverables, as well as incorporating the suggestions and comments into the final report. The project was completed as scheduled in autumn 2023 and a proposal for a subsequent study is planned for the following call for applications.

Finally, I contributed to a paper draft of Dr. Alexandra Schneider (HMGU) on the comparison of two analytical methods to identify the solubility of $PM_{2.5}$ components and their related associations with subclinical inflammatory markers using data from a prospective panel study

conducted by the *United States Environmental Protection Agency* (EPA) in Chapel Hill, North Carolina, USA. I updated the literature review on the topic and revised the first manuscript draft.

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Manuscript 1

Title:	Impact of Ambient Ultrafine Particles on Cause-Specific Mortality in Three German Cities
Authors:	Maximilian Schwarz, Alexandra Schneider, Josef Cyrys, Susanne Bastian, Susanne Breitner, and Annette Peters
Year:	2023
Journal:	American Journal of Respiratory and Critical Care Medicine
Status:	Published
Volume:	207
Page:	1334 – 1344
DOI:	https://doi.org/10.1164/rccm.202209-1837OC
Publishing license:	Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (CC BY-NC-ND 4.0 DEED; https://creativecommons.org/licenses/by-nc-nd/4.0/)
Journal Impact Factor:	24.7 (according to *Journal Citation Reports™* 2022)
Rank by Journal Impact Factor:	3/35 in the category ’Critical Care Medicine’ and 3/66 in the category ‘Respiratory System’ (according to *Journal Citation Reports™* 2022)

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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).

(Received in original form October 7, 2022; accepted in final form March 3, 2023)

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Supported by grants from the Saxon State Office for Environment, Agriculture and Geology, Dresden, Germany.

Author Contributions: S. Bastian, A.S., J.C., S. Breitner, A.P., and M.S. involved in conceptualization of the study design. M.S. and S. Breitner analyzed the data and drafted the first version of the manuscript. S. Bastian, A.S., and J.C. provided assistance with the methodological framework. All authors read the manuscript and contributed to the final version.

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 207, Iss 10, pp 1334–1344, May 15, 2023

Originally Published in Press as DOI: 10.1164/rccm.202209-1837OC on March 6, 2023
Internet address: www.atsjournals.org

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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)

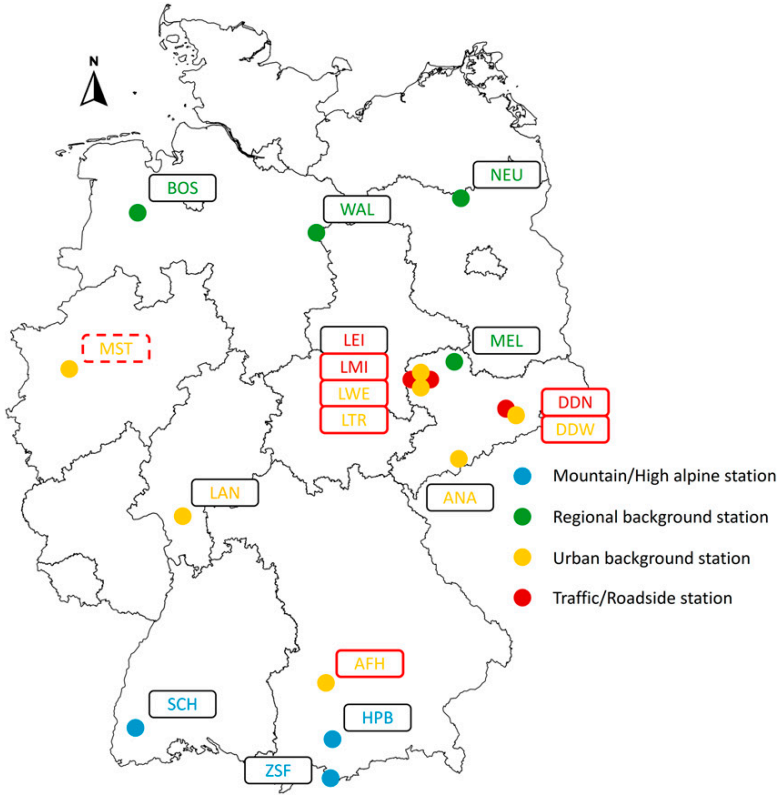

Figure 1. Location of German Ultrafine Aerosol Network stations across Germany and classification according to station type. Stations used for this analysis are highlighted with red boxes (dashed for sensitivity analysis). Map adapted from Birmili and colleagues, 2016 (18), and Sun and colleagues, 2019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

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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).

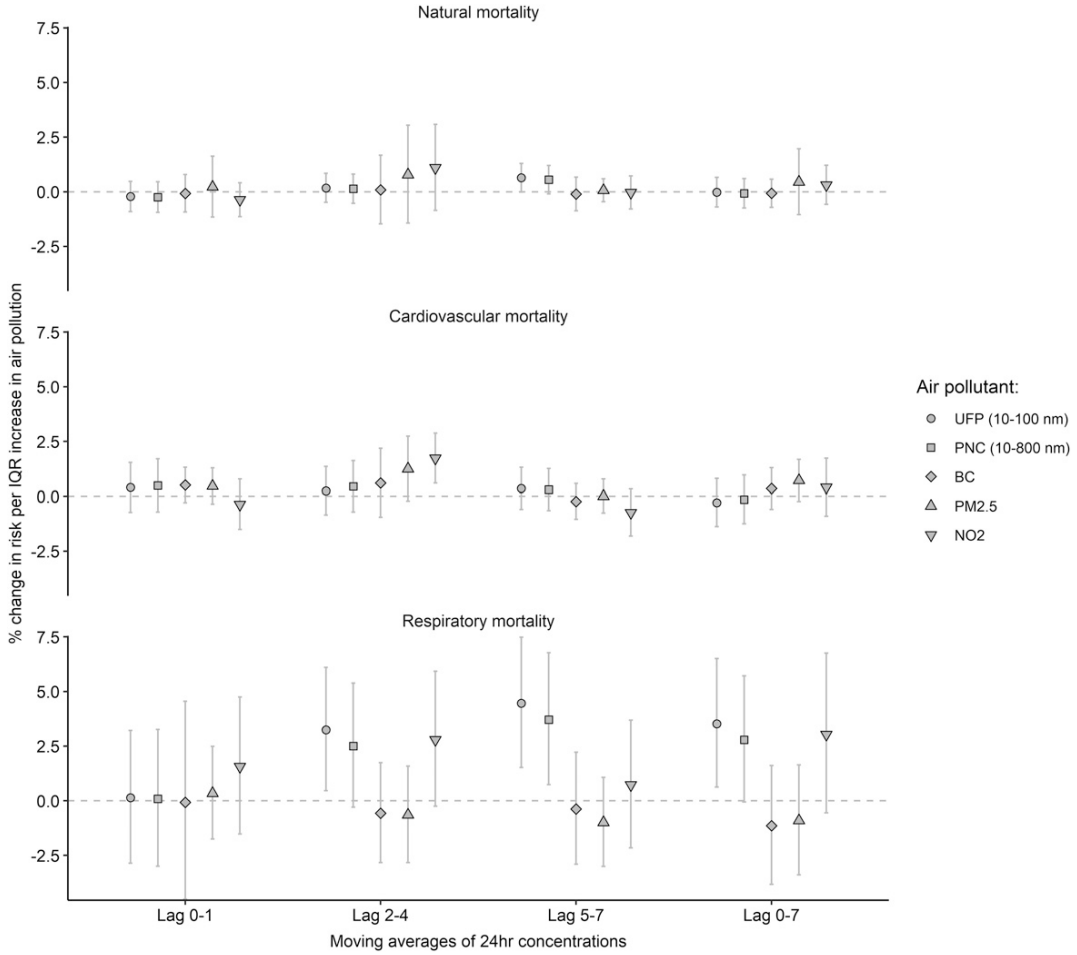

Figure 2. Percent change in relative risk and 95% confidence interval per interquartile range (IQR) increase in air pollution concentration for natural (top), cardiovascular (middle), and respiratory mortality (bottom). The *x*-axis shows the 24-hour moving average lag concentrations of air pollutants. 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 $\mu g/m^3$ 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

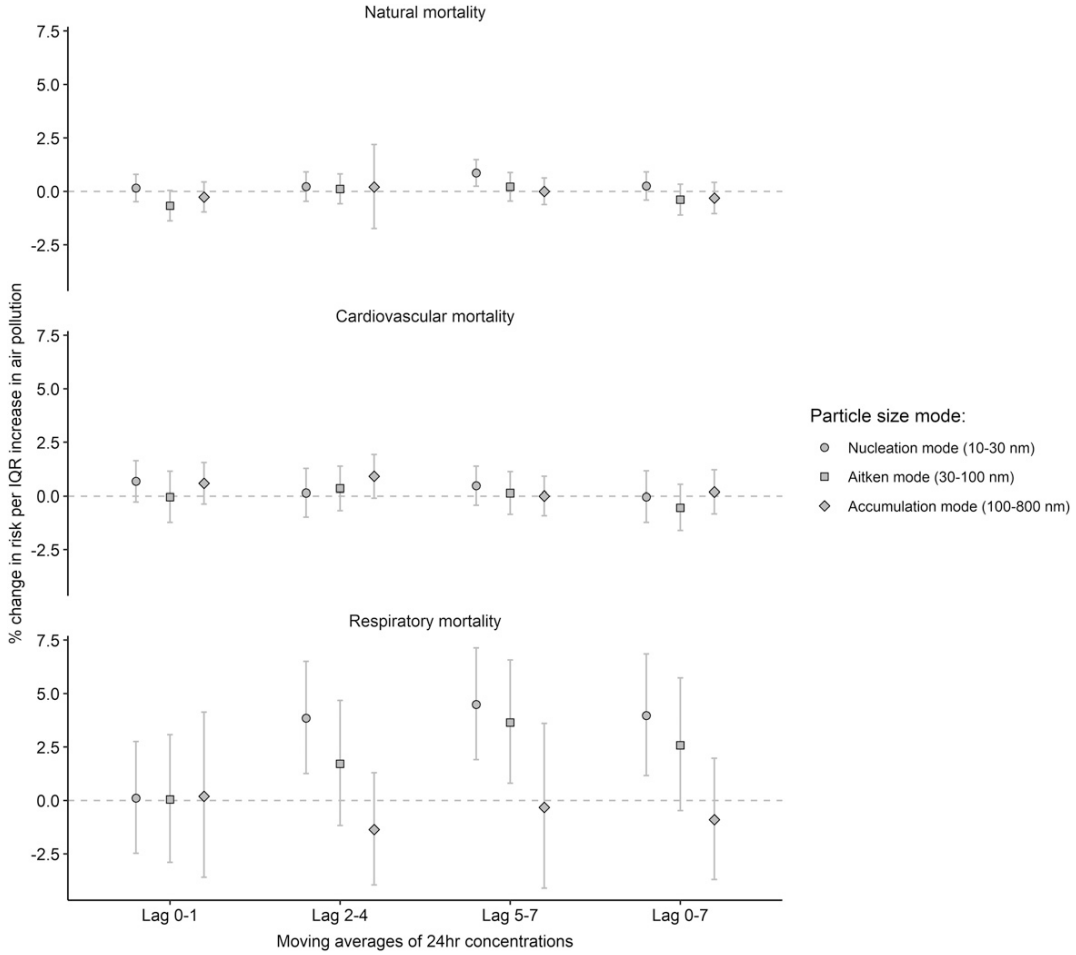

Figure 3. Percent change in relative risk and 95% confidence interval per interquartile range (IQR) increase in air pollution concentration for natural (top), cardiovascular (middle), and respiratory mortality (bottom). The *x*-axis shows the 24-hour moving average lag concentrations of air pollutants. 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

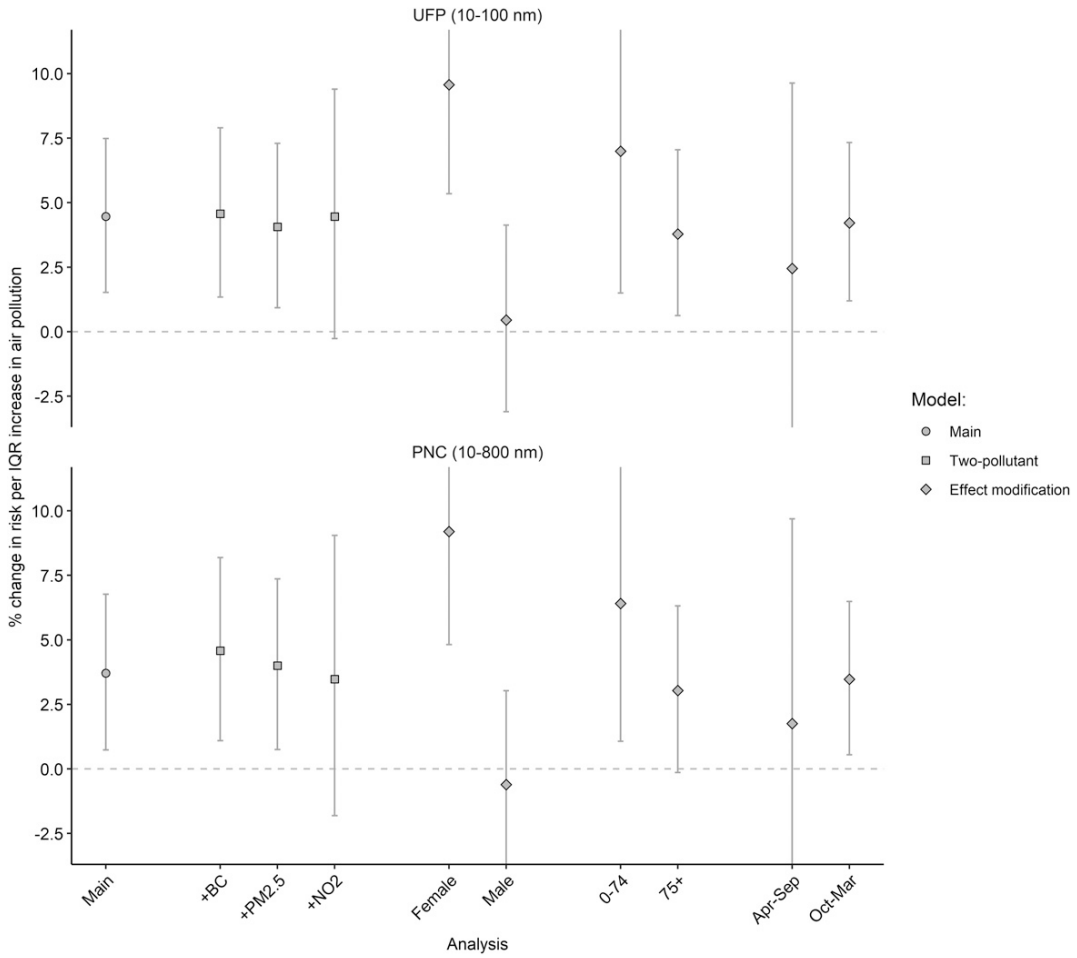

Figure 4. Percent change in relative risk and 95% confidence interval per interquartile range (IQR) increase in concentration of particles in the ultrafine range (10–100 nm; UFPs; top panel) and total particle number concentrations (10–800 nm; PNCs; bottom panel) for respiratory mortality (5–7 d after 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 $\leqslant$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

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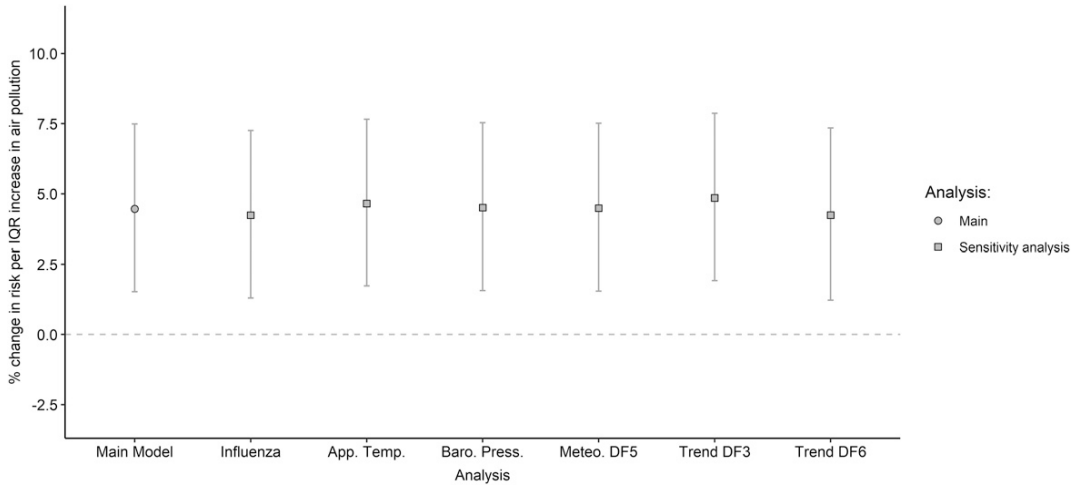

Figure 5. Percent change in relative risk and 95% confidence interval per interquartile range (IQR) increase in concentration of particles in the ultrafine range (10–100 nm; UFPs) for respiratory mortality (5–7 d after UFP exposure). The *x*-axis shows the results of the main model (dots) and different 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

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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. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Karen Meyer (Research Data Centre [RDC] of the Federal Statistical Office and Statistical Offices of the Federal States, Fürth, Germany) and Dana Leenders (IT service provider of North Rhine-Westphalia, Düsseldorf, Germany) for support with the mortality data; Christoph Asbach and Heinz Kaminski (Institute of Energy and Environmental Technology [IUTA], Duisburg, Germany) and North Rhine-Westphalia State Agency for Nature, Environment and Consumer Protection (LANUV) (Essen, Germany) for providing exposure data for Mülheim-Styrum; Maik Merkel (Leibniz Institute for Tropospheric Research [TROPOS], Leipzig, Germany) for providing data of Leipzig-TROPOS; Andrea Hausmann and Gunter Löschau (Saxon State Office for Environment, Agriculture and Geology) for advice with the study concept; Simonas Kecorius (Helmholtz Munich) for helpful discussions on the topic; and the editors and unknown reviewers for their thoughtful comments and suggestions on the manuscript. Source for mortality data: 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).

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Impact of ambient ultrafine particles on cause-specific mortality in three German cities

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ONLINE DATA SUPPLEMENT

Supplementary Methods:

Mortality and Population Data:

We collected data on daily cause-specific mortality for the three German cities Dresden, Leipzig, and Augsburg. This information is compiled routinely and anonymously for each death in Germany using the International Statistical Classification of Diseases and Related Health Outcomes (ICD-10). We accessed the raw dataset through a workstation for visiting scientists at the Research Data Centre (RDC) of the Federal Statistical Office and Statistical Offices of the Federal States ([Mortality Statistics (EVAS 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). During data handling, only cases that lived and died in the same city were considered for further analysis. Linkage was done using official residency codes and information from the official death certificates. In addition, only primary diagnoses were considered. Furthermore, the dataset comprised information on the age (seven age categories) and sex (male, female) of the individual case. Based on ICD-10 codes, we calculated mortality counts for each day of the study period between January 1st, 2010, and December 31st, 2017. The three mortality endpoints were natural- (ICD-10: A00-R99), cardiovascular- (ICD-10: I00-I99), and respiratory mortality (ICD-10: J00-J99). Informed consent or approvals were not required because mortality data are collected routinely and anonymously in official statistics. Population data was retrieved from official statistical yearbooks of the examined cities.

Environmental Data:

This project aimed to quantify the effects of air pollution on cause-specific mortality in Germany. Therefore, we selected six measurement stations that were part of the former multicenter and multi-institutional German Ultrafine Aerosol Network (GUAN). This project targeted the scientific investigation of atmospheric aerosol effects and covered a large number of pollutants and exceeded the legally regulated air quality measurements (e.g., measurement of soot particles and particle counts in the ultrafine size range) (1). We selected the monitoring stations based on the following criteria:

1. Focus on stations of urban background and traffic-related environments to obtain representative exposure profiles since most people in Germany live in comparable

exposure settings (→ Exclusion of stations in rural/regional and mountain/alpine areas).

2. Exclusion of cities with a low population (N low for mortality endpoints) (→ e.g., exclusion of the cities “Langen” and “Annaberg”).
3. Keep cities with good comparisons of the measurement devices (→ Station “Mülheim-Styrum” as sensitivity analysis).

One station, “Leipzig-Eisenbahnstraße”, was excluded because of a different underlying exposure setting (local street canyon) that is not comparable to the other stations and does not represent the average population exposure of the city. Four of the selected stations were considered as urban background stations and representative of most of the urban population (LWE: Leipzig-West; LTR: Leipzig-TROPOS; DDW: Dresden-Winckelmannstr.; AFH: Augsburg Hochschule). It was assumed that most of the population was exposed to comparable air pollution concentrations. To better capture the effects of peak concentrations, we also included two stations of the category traffic-related (LMI: Leipzig-Mitte; DDN: Dresden-Nord). Pronounced diurnal cycles and the highest numbers of traffic-related pollutants were reported at these stations (1). The measurement stations in Saxony (cities of Leipzig and Dresden) were operated by the BfUL (Betriebsgesellschaft für Umwelt und Landwirtschaft Saxony, in cooperation with TROPOS (for particle number size distributions (PNSD) measurements)) and the Augsburg station was operated by Helmholtz Munich in cooperation with the University of Augsburg/WZU. Further information on the GUAN project (e.g., concept, other stations, etc.) can be found elsewhere (1-3). Supplement Table E1 gives a short overview of some station characteristics in our analysis.

Supplement Table E1: Description of station characteristics.

City	Station name	Abbr.	Type	Operator	Station characteristics
Leipzig	L-Mitte	LMI	Traffic-related	LfULG/BfUL	Distance to road: ~5 m, DTV: ~45,000, intersection
Leipzig	L-West	LWE	Urban background	LfULG/BfUL	Park area with trees
Leipzig	L-TROPOS	LTR	Urban background	TROPOS	On the roof of a three-story building, park
Dresden	DD-Nord	DDN	Traffic-related	LfULG/BfUL	Distance to road: ~9 m, DTV: ~19,400, train station square

Dresden	DD-Winckelmannstr.	DDW	Urban background	LfULG/BfUL	Backyard with park and parking lot
Augsburg	A-Hochschule	AFH	Urban background	HMGU/University Augsburg	On the premises of the AFH, major road: ~100 m

Information based on Pausch A & Mühlner M. 2020; Löschau et al. 2017; Cyrys et al. 2008 (4-6); Abbr.: abbreviation; L: Leipzig; TROPOS: Leibniz Institute for Tropospheric Research; DD: Dresden; A: Augsburg; LfULG: Saxon State Office for Environment, Agriculture and Geology; BfUL: Betriebsgesellschaft für Umwelt und Landwirtschaft Saxony (in cooperation with TROPOS for particle number size distributions); HMGU: Helmholtz Zentrum Munich; DTV: daily traffic volume; AFH: University of Applied Sciences Augsburg.

Air pollution concentrations of primary interest were particle number concentrations of particles in the ultrafine range (10-100nm, UFP) and total particle number concentrations (10-800nm, PNC). Furthermore, nucleation mode particles (NuMP, 10-30nm), Aitken mode particles (AiMP, 30-100nm), and accumulation mode particles (AcMP, 100-800nm) were included into the analysis as additional pollutants to get a better overview of different size distributions and thus specific origins/sources. Of secondary interest, we measured nitrogen dioxide (NO_2), black carbon (BC), and mass concentrations of particulate matter with an aerodynamic diameter $\leq$ 2.5µm ($PM_{2.5}$).

Measurement of PNSD was conducted by mobility particle size spectrometers (MPSS, TROPOS-design (manufacturer)) in different configurations across the measurement stations. Briefly, this device measures PNSD continuously in the size range between 3-800nm on a high time-resolution of 5-20 minutes via a differential mobility analyzer (DMA, TROPOS-design (manufacturer)) and condensation particle counter (CPC, models 3010/3025/3772, TSI Inc.). Further information on devices as well as quality assurance, calibration processes, and data management have been published elsewhere (7-10). $PM_{2.5}$ mass concentrations were measured by tapered element oscillating microbalance (TEOM, model 1400a incl. FDMS 8500, Rupprecht & Patashnick Co., and TEOM model 1405, Thermo Fisher Scientific Inc.) for the Augsburg station and high-volume samplers (HVS, model DHA-80, DIGITEL Elektronik AG) at the other stations. To correct the loss of the volatile fractions of particulate mass, both TEOMs in Augsburg were equipped with a Filter Dynamics Measurement System (FDMS model 8500b, Thermo Fisher Scientific Inc.). Further information on the pollutants $PM_{2.5}$ and NO_2 can be found online in the database of the German Environmental Agency (https://www.env-it.de/stationen/public/open.do). BC mass concentrations were measured by multiangle absorption photometers (MAAP, Model 5012, Thermo Scientific) for all stations except

Augsburg, where an aethalometer (Type 8100, Thermo Fisher Scientific Inc.) was used. For BC, more information can be found elsewhere (1, 2). Supplement Table E2 and Figure 1 gives a short overview of device characteristics at the stations.

For air pollutants and environmental data (e.g., air temperature, relative humidity, and barometric pressure), when applicable, hourly and daily means were calculated if 75% of the data was available. We did not impute missing values in the main analysis. Based on daily averages, we calculated lagged exposure concentrations for single lags as well as for multiday average lags. Single lags included concentrations of the exact day (lag0) up to seven days prior to the event time point (lag7). In addition, average lag concentrations comprised immediate (lag0-1), delayed (lag2-4 & lag5-7), and overall effects (lag0-7).

Supplement Table E2: Description of measurement devices per station.

Station	Type	Height of inlet above ground	Mobility particle size spectrometer	Size range	Thermo-denuder	BC instrument	BC cut-off
LMI	Portable cabin	4m	TDMPSS – TROPOS-design	5-800nm	no	MAAP	PM_{10}
LWE	Portable cabin	4m	TDMPSS – TROPOS-design	10-800nm	no	MAAP	PM_{10}
LTR	Portable cabin	~16m	TDMPSS – TROPOS-design	5-800nm	yes	MAAP	PM_{10}
DDN	Portable cabin	4m	TMPSS – TROPOS-design	5-800nm	no	MAAP	PM_1*
DDW	Portable cabin	4m	MPSS – TROPOS-design	10-800nm	no	MAAP	PM_1
AFH	Portable cabin	4m	TDMPSS – TROPOS-design	5-800nm	yes	Aethalometer	$PM_{2.5}$

Table adapted from Birmili 2016 (1); Further information on the type of mobility particle size spectrometer can be found by Sun 2019 (3); BC: black carbon; LMI: Leipzig-Mitte; LWE: Leipzig-West; LTR: Leipzig-TROPOS; DDN: Dresden-Nord; DDW: Dresden-West; AFH: Augsburg-Hochschule; TDMPSS: Thermodenuder Mobility Particle Size Spectrometer; TROPOS: Leibniz Institute for Tropospheric Research; TMPSS: Tandem Mobility Particle Size Spectrometer; MPSS: Mobility Particle Size Spectrometer; MAAP: Multiangle Absorption Photometer; PM_{10}: Particulate matter with an aerodynamic diameter $\geq$ 10µm; $PM_{2.5}$: Particulate matter with an aerodynamic diameter $\geq$ 2.5µm; PM_1: Particulate matter with an aerodynamic diameter $\geq$ 1µm.

*: Station DDN: PM_{10} inlet until Feb. 12, 2012, afterwards PM_1 inlet.

Since at the station LTR only PNSD and BC were available, all analyses regarding $PM_{2.5}$ and NO_2 did not include the station LTR. For the remaining analyses, confounder model

adjustment (e.g., air temperature data) included data of LWE, the other urban background station in Leipzig. Correlations between air pollutants were high between the two stations. No data on NO_2 was measured at the Augsburg station (AFH). Therefore, we used data of another station (A-LfU: Augsburg - Bavarian State Office for Environment) with the same exposure class and with good correlations between other variables.

Statistical Analysis:

Descriptive statistics were calculated for counts/numbers of cause-specific mortality (e.g., mean, standard deviation) and air pollution and environmental data (e.g., number of days with complete data (N), median, interquartile range (IQR), minimum, and maximum). We investigated temporal variations using the Spearman correlation coefficient and considered values of ≥ 0.7 as high correlations.

In order to investigate the association between air pollution and cause-specific mortality, we followed a two-stage modelling approach of station-specific and pooled estimates.

In the first stage, we calculated Poisson regression models allowing for overdispersion. We set up a general confounder model, which was used for each station-specific model. The selection of covariates was based on literature as well as our previous UFIREG-project, which assessed effects of air pollution in Central Europe (11). The following variables were included in the model:

- Time trend (represented as date order, continuous)
- Indicator variable for day of the week (Monday-Sunday, categorical)
- Indicator variable for public holidays (dummy-variable, continuous)
- Indicator variable for vacation (dummy-variable, continuous)
- Relative humidity (continuous)
- Influence of high temperature (continuous)
- Influence of low temperature (continuous)

The effects of high and low temperature were modelled according to prior work by Stafoggia et al. 2013 (12). Briefly, with this method, we modelled effects of high and low temperature separately and therefore accounted for different lag structures of high and low temperatures

on health outcomes (12). In order to adjust for non-linear confounding and long-term/seasonal variations, we included cubic regression splines for time trend (four degrees of freedom (DF) per year) and meteorological parameters (three DF). We considered changes in population number including a log-offset into our models. As mentioned before, we used lagged exposures to assess effects of air pollution on mortality. Thus, we focused primarily on immediate (lag0-1), delayed (lag2-4, lag5-7), and overall (lag0-7) effects, and secondarily analyzed single lags from lag0 to lag7. We decided to use single and average lag models instead of distributed lag models (DLM) because of loss of statistical power due to missing data for exposure data and low count numbers for some mortality endpoints.

In the second stage, station-specific estimates were pooled using a novel multilevel meta-analytical approach for environmental research, published by Sera and colleagues (13, 14). This method accounts for nested geographical hierarchical structures including random structures for the cities and the stations within a city (14). This method was chosen to account for heterogeneity/variation between cities and stations. Restricted maximum likelihood (REML) estimation was applied in the models. In addition, we conducted the same analysis using a fixed-effects model approach as an additional/sensitivity analysis. Furthermore, we tested for heterogeneity among the station-specific estimates and presented the corresponding p-value as well as the I^2 test statistic. In this regard, we considered $I^2 > 50\%$ and $p < 0.05$ as significant and as substantial heterogeneity.

Further analyses were conducted on an exploratory basis. We compared the pooled results between urban background and traffic-related stations to evaluate differences in risks according to the underlying exposure profiles/settings. For two-pollutant models, effect modification analysis, and the sensitivity analyses, we mainly focused on the combination of mortality endpoint, average lag, and air pollutant with the largest effects within the main analysis but also provided some additional information in supplementary tables and figures.

We investigated potential effect modification of age, sex, and season. We therefore stratified the dataset by age (< 75 years vs. $\geq$ 75 years) and sex (male vs. female) and analyzed the strata using the general modeling strategy. Differences between season (warm period: April - September, cold period: October - March) were investigated by including an interaction term into the models.

To determine whether the effects of air pollutants act independently, we performed two-pollutant analyses when the Spearman correlation coefficients between the two pollutants were less than 0.7. Therefore, the second pollutant was added as another linear term into the main model.

Sensitivity Analyses:

We performed several sensitivity analyses to test the robustness of the main results by variation of model parameters as well as using alternate models and variables. The following analyses have been conducted:

1. We changed the DF for time trend (three and six DF per year).
2. We changed the DF for meteorological variables from three to five.
3. Temperature effects were accounted by replacing relative humidity and air temperature by apparent temperature (15, 16). We used the following formula to calculate apparent temperature: *at = -2.653 + (0.994 * temp) + (0.0153 * (dp*dp))* with *at* = apparent temperature, *temp* = air temperature, and *dp* = dew point.
   Dew point temperature (*dp*) was calculated in the following way:
   $$\frac{1}{\frac{1}{temp + 241.413} - \frac{log_{10}(\frac{rh}{100})}{1{,}838.675}} - 241.413$$
   with *temp* = air temperature and *rh* = relative humidity
4. We additionally adjusted for barometric pressure in the main model.
5. We considered influenza epidemics in the main model. Data on influenza epidemics are publicly available at the Robert Koch Institute database "SurvStat@RKI 2.0" (https://survstat.rki.de/default.aspx) and were downloaded for the three cities in our analyses. The influenza variable was added as a linear term into the main model.
6. We used alternate definitions of UFP and PNC variables using a different lower cut-off value. We changed the lower cut-off values from 10nm to 20nm (UFP: 20-100nm, PNC: 20-800nm). This was driven by the potentially increasing measurement uncertainties at the lower end of the particle size distribution published by Wiedensohler et al. 2012 (9).
7. We extended our main analysis with data from another urban background monitoring station of GUAN. The station "Mülheim-Styrum" (MST) is located in North Rhine-

Westphalia, in the North-West of Germany (Figure 1) and represents air pollution data for the Ruhr area including the three cities of Mülheim, Oberhausen, and Essen. This area comprises of approximately one million inhabitants and is influenced by a mix of residential-, industrial-, and traffic exposures (17). The station included a mobile container, operated by the Institute of Energy and Environmental Technology (IUTA) and a measurement station by the regional air quality measurement network provided by the State Agency for Nature, Environment and Consumer Protection (LANUV). Instrumentation at MST included a scanning mobility particle sizer (SMPS/MPSS, TSI model 3936) that measured PNSD in the size range of 13.8-750nm (1, 17). BC was measured by an aethalometer and NO_2 according to the standard method (chemiluminescence, https://www.env-it.de/stationen/public/open.do). No data on $PM_{2.5}$ was available for MST. More information about station characteristics and instrumentation have been published elsewhere (1, 17, 18) and a short overview of the measured air pollutants, environmental data, and cause-specific mortality is presented in Supplement Table E3.

Mortality data was collected via the IT service provider of North Rhine-Westphalia according to the data handling process of the main analysis.

We decided to use MST only as a sensitivity analysis due to the following facts:

a. PNSD in a different size range (13.8-750nm vs. 10-800nm).
b. Data on BC concentrations only available for 783 days (loss of statistical power, especially for the two-pollutant models).
c. No data on $PM_{2.5}$ (inconsistency regarding two-pollutant models).
d. No data on age and sex (inconsistency regarding effect modification analysis).

8. We calculated city-specific average exposure concentrations and imputed missing values. Therefore, we used an adapted version of the APHEA approach, according to Berglind et al. 2009 (19), and followed the main analysis procedure for the three city-specific estimates.
9. We considered a fixed increment in air pollution concentration for the main results to facilitate comparison between studies. We used standardized increments according to the literature of 10,000 particles/cm^3 (e.g., UFP particle number concentrations), 1 µg/m^3 (e.g., BC mass concentrations), and 10 µg/m^3 (e.g., particulate matter and nitrogen dioxide mass concentrations).

10. Finally, we checked the exposure response functions of the station-specific estimates for any deviations from linearity by replacing the linear term in the main model with a cubic regression spline with three DF. To compare the differences between the models, we used a likelihood-ratio test and compared differences and slopes visually.

Supplement Table E3: Description of air pollution, environmental, and mortality data for the station Mülheim-Styrum.

Variable	Median (IQR)	N_{days}
Air pollution		
UFP (10-100nm, n/cm^3)	8,817 (5,024)	2,593
PNC (10-800nm, n/cm^3)	10,860 (5,770)	2,593
BC (µg/m^3)	0.9 (0.76)	783
NO_2 (µg/m^3)	27.68 (17.19)	2,826
$PM_{2.5}$ (µg/m^3)	-*	-*
Meteorological parameter		
Air temperature (°C)	11.43 (6.92)	2,915
Relative humidity (%)	77.89 (12.67)	2,915
Barometric pressure (hPa)	-*	-*
Mortality (counts)		
Natural (ICD-10: A00-R99)	32.27 (6.33)†	94,299‡
Cardiovascular (ICD-10: I00-I99)	11.33 (3.68)†	33,100‡
Respiratory (ICD-10: J00-J99)	3.03 (1.95)†	8,849‡

IQR: Interquartile range; N_{days}: Number of days with valid data; UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); BC: Black carbon; NO_2: Nitrogen dioxide; $PM_{2.5}$: Particulate matter with an aerodynamic diameter $\geq$ 2.5µm; °C: Degree Celsius; hPa: hectopascal; ICD-10: International Statistical Classification of Diseases and Related Health Outcomes (10th revision); No data on $PM_{2.5}$ was available at the station Mülheim-Styrum.

*: No data available.
†: Mean (Standard deviation).
‡: Total number of cases.

All results are presented as percent change per IQR increase in air pollution concentration ((exp(beta*IQR)-1)*100) and corresponding 95% confidence intervals (CI). The IQR represents a variable's dispersion (or spread) by using the range for the middle 50% of the data, equal to the difference between the 75th and 25th percentiles. This standardization method is commonly used in epidemiological contexts to allow and facilitate the comparison of relative health effects of different pollutants. This method was preferred over fixed-unit standardization increments because one study objective was to compare the results and

effect sizes between different pollutants. It is still an open question for UFP whether different particle size fractions have different health effects. However, the main results are also shown with a fixed increment as a sensitivity analysis in the supplement. Results with p values < 0.05 were considered statistically significant.

Data management as well as the analysis and visualization were conducted using RStudio version 1.3.1335/1.4.1106 with R version 3.6.1/4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) and the packages *mgcv* and *ggplot2*. The pooled analysis was performed using the R package *mixmeta*.

Supplementary Results:

No substantial changes in risk estimates were observed when fixed-effects models were used instead of random-effects models, although the confidence intervals narrowed slightly using fixed-effects (Supplement Figure E1). Results of station-specific estimates for UFP and PNC, as well as single-lag models mainly indicated higher risks for respiratory mortality, especially at the urban background stations Leipzig-West (LWE) and Leipzig-TROPOS (LTR; Supplement Table E10) as well as for the single lags 3 and 6 (Supplement Figure E2). Furthermore, the comparison between urban background and traffic-related stations indicated similar effects (Supplement Table E11 and Supplement Figure E3). Nevertheless, UFP showed slightly higher risks for respiratory mortality at the urban background stations, whereas for natural mortality, risks were higher at traffic-related stations.

Sensitivity Analyses:

Sensitivity analyses were again primarily done for the air pollutant, average lag, and mortality endpoint, for which the strongest associations were found in the main models.

1. Changing the DF for time trend resulted in no major differences from the main model (Figure 5).
2. Changing the DF for meteorological parameters resulted in comparable results (Figure 5).
3. Replacing temperature and relative humidity by apparent temperature did not change the results (Figure 5).
4. Additional adjustment for barometric pressure resulted in no changes from the main model (Figure 5).
5. Additional adjustment for influenza epidemics showed comparable results (Figure 5).
6. Using an alternate definition of UFP (20-100nm) and PNC (20-800nm) resulted in no major differences from the main model analysis (Supplement Table E9).
7. Extending our main analysis by another urban background station indicated comparable, albeit lower, results (Supplement Table E9).
8. Using city-specific averages showed decreased estimates for respiratory mortality (Supplement Figure E4).

9. Using a different standardization method (e.g., percent change in risk per 10,000 particles increase in UFP concentration) led to larger effect estimates with wider confidence intervals. The direction and significance of the results were not affected because the initial model results (the beta value of the model) were only scaled differently. For example, an increase of 10,000 particles in the ultrafine range (UFP, lag 5-7) resulted in a 14.51% [95% CI: 4.81%; 25.10%] increase in respiratory mortality (Supplement Figures E5-E7 and Supplement Tables E13-E14).
10. Exposure response functions did not show any deviations from the linearity assumption (Supplement Figure E8).

Supplementary Tables:

Supplement Table E4: Description of population and mortality data, stratified by sex. N = 2,922 days.

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
Male	20,133	16,623	9,630
Female	23,117	19,483	11,082
Total counts of cardiovascular mortality	19,880	15,756	8,854
Male	8,086	6,483	3,764
Female	11,794	9,273	5,090
Total counts of respiratory mortality	2,559	2,143	1,426
Male	1,397	1,163	767
Female	1,162	980	659
Mean daily natural mortality (SD)	14.8 (4.1)	12.4 (3.7)	7.1 (2.7)
Mean daily cardiovascular mortality (SD)	6.8 (2.7)	5.4 (2.4)	3.0 (1.7)
Mean daily respiratory mortality (SD)	0.9 (1.0)	0.7 (0.9)	0.5 (0.7)

N: Number of days with valid data; SD: standard deviation; Population data based on official statistical yearbook of the cities; own calculations; Natural mortality: ICD-10: A00-R99; Cardiovascular mortality: ICD-10: I00-I99; Respiratory mortality: ICD-10: J00-J99. Source: Research Data Centre (RDC) of the Federal Statistical Office and Statistical Offices of the Federal States ([Mortality Statistics (EVAS 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).

Supplement Table E5: Station-specific descriptive statistics of air pollutants and meteorological parameters.

Variable	N_{days}	Mean	SD	P_{25}	Median (P_{50})	P_{75}	IQR
UFP (10-100nm, n/cm^3)							
LMI	2,279	10,747	4,172	7,843	10,123	12,999	5,156
LWE	1,787	5,126	2,619	3,299	4,520	6,302	3,003
LTR	2,668	5,469	2,881	3,581	4,838	6,735	3,154
DDN	2,287	9,128	3,436	6,684	8,637	11,050	4,366
DDW	2,211	5,341	2,754	3,426	4,791	6,582	3,156
AFH	2,392	6,366	3,621	4,101	5,655	7,615	3,514
PNC (10-800nm, n/cm^3)							
LMI	2,279	12,590	4,692	9,321	11,922	15,187	5,866
LWE	1,787	6,265	2,886	4,208	5,748	7,690	3,482
LTR	2,668	6,703	3,231	4,515	6,054	8,201	3,686
DDN	2,287	10,912	3,924	8,134	10,292	13,109	4,975
DDW	2,211	6,714	3,184	4,478	6,186	8,380	3,902
AFH	2,392	7,668	4,113	5,071	6,909	9,088	4,017
BC (µg/m^3)							
LMI	2,499	2.3	1.2	1.5	2.0	2.8	1.3

LWE	2,067	1.0	0.9	0.5	0.8	1.3	0.8
LTR	2,807	1.0	1.0	0.4	0.7	1.2	0.8
DDN	2,693	1.8	1.0	1.1	1.5	2.2	1.1
DDW	2,057	0.9	0.7	0.4	0.7	1.2	0.8
AFH	2,644	1.7	1.0	1.1	1.4	2.0	1.0
NO_2 (µg/m^3)							
LMI	2,886	44.0	12.7	35.0	43.0	52.0	17.0
LWE	2,896	17.6	8.9	11.0	16.0	22.0	11.0
LTR*	0	-	-	-	-	-	-
DDN	2,874	34.2	10.4	27.0	33.0	41.0	14.0
DDW	2,890	20.2	9.5	13.0	18.0	25.0	12.0
AFH†	2,212	19.8	10.2	12.5	17.7	24.8	12.3
$PM_{2.5}$ (µg/m^3)							
LMI	2,891	17.5	13.0	9.1	13.6	21.2	12.2
LWE	2,885	13.5	12.0	5.9	9.6	16.4	10.5
LTR*	0	-	-	-	-	-	-
DDN	2,900	16.2	12.6	8.2	12.3	19.8	11.6
DDW	2,892	15.1	12.9	6.6	10.9	18.9	12.3
AFH	2,922	13.0	10.3	6.1	10.2	16.4	10.3
Air temperature (°C)							
LMI	2,911	11.7	8.0	5.9	11.4	18.0	12.1
LWE	2,919	9.9	7.7	4.3	9.7	16.0	11.7
LTR*	0	-	-	-	-	-	-
DDN	2,915	11.4	8.1	5.3	11.3	17.8	12.5
DDW	2,922	11.6	8.0	5.6	11.6	18.0	12.4
AFH	2,803	9.9	7.9	3.6	9.9	15.9	12.2
Relative humidity (%)							
LMI	2,909	70.9	12.6	61.2	71.8	80.8	19.6
LWE	2,905	74.2	12.2	65.0	75.3	83.6	18.6
LTR*	0	-	-	-	-	-	-
DDN	2,915	70.6	11.4	62.2	70.9	79.0	16.8
DDW	2,922	70.8	11.4	62.2	71.8	79.5	17.3
AFH	2,803	77.8	12.7	68.1	79.2	88.4	20.3
Barometric pressure (hPa)							
LMI	2,911	1,015.8	8.1	1,011.0	1,016.0	1,021.0	10.0
LWE	2,919	1,016.1	8.3	1,011.0	1,016.0	1,021.0	10.0
LTR*	0	-	-	-	-	-	-
DDN	2,915	1,016.2	8.2	1,011.0	1,016.0	1,021.0	10.0
DDW	2,922	1,016.0	8.0	1,011.0	1,016.0	1,021.0	10.0
AFH	2,803	961.0	7.4	956.8	961.4	965.8	9.0

N_{days}: Number of days with valid data; SD: Standard deviation; P_{25}: 25th percentile; P_{50}: 50th percentile; P_{75}: 75th percentile; IQR: Interquartile range; UFP: Particle number concentration of particles in the ultrafine range (10-100nm); LMI: Leipzig-Mitte; LWE: Leipzig-West; LTR: Leipzig-TROPOS; DDN: Dresden-Nord; DDW: Dresden-Winckelmannstr.; AFH: Augsburg-Hochschule; PNC: Total particle number concentration (10-800nm); BC: Black carbon; NO_2: Nitrogen dioxide; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≥ 2.5µm; °C: Degree Celsius; hPa: hectopascal.

*: No data at this station available.

†: NO_2 data for Augsburg measured at station A-LfU instead of AFH

Supplement Table E6: Spearman correlation coefficients of station-specific air pollutants and meteorological parameters.

Variable	UFP (10-100nm, n/cm³)	PNC (10-800nm, n/cm³)	BC (µg/m³)	NO_2 (µg/m³)*	$PM_{2.5}$ (µg/m³)	Temp. (°C)	Rel hum. (%)
Leipzig-Mitte							
PNC (10-800nm, n/cm³)	**0.98**						
BC (µg/m³)	0.59	0.69					
NO_2 (µg/m³)	**0.73**	**0.77**	**0.73**				
$PM_{2.5}$ (µg/m³)	0.28	0.40	**0.72**	0.50			
Temperature (°C)	0.09	0.08	-0.11	-0.08	-0.30		
Relative humidity (%)	-0.13	-0.14	0.18	-0.05	0.14	-0.62	
Barometric pressure (hPa)	0.18	0.20	0.16	0.15	0.25	-0.10	-0.02
Leipzig-West							
PNC (10-800nm, n/cm³)	**0.96**						
BC (µg/m³)	0.22	0.40					
NO_2 (µg/m³)	0.18	0.30	**0.78**				
$PM_{2.5}$ (µg/m³)	0.09	0.30	**0.86**	0.67			
Temperature (°C)	0.42	0.36	-0.26	-0.46	-0.32		
Relative humidity (%)	-0.47	-0.42	0.24	0.31	0.19	-0.55	
Barometric pressure (hPa)	0.12	0.16	0.19	0.21	0.25	-0.08	-0.03
Leipzig-TROPOS							
PNC (10-800nm, n/cm³)	**0.96**						
BC (µg/m³)	0.31	0.49					
NO_2 (µg/m³)	-†	-†	-†				
$PM_{2.5}$ (µg/m³)	-†	-†	-†	-†			
Temperature (°C)	-†	-†	-†	-†	-†		
Relative humidity (%)	-†	-†	-†	-†	-†	-†	
Barometric pressure (hPa)	-†	-†	-†	-†	-†	-†	-†
Dresden-Nord							
PNC (10-800nm, n/cm³)	**0.98**						
BC (µg/m³)	0.53	0.65					
NO_2 (µg/m³)	0.63	0.64	0.68				
$PM_{2.5}$ (µg/m³)	0.14	0.30	0.66	0.32			
Temperature (°C)	0.07	0.04	-0.24	-0.25	-0.34		
Relative humidity (%)	-0.20	-0.19	0.17	0.15	0.19	-0.58	
Barometric pressure (hPa)	0.20	0.21	0.06	0.04	0.20	-0.08	-0.01
Dresden-Winckelmannstr.							
PNC (10-800nm, n/cm³)	**0.96**						
BC (µg/m³)	0.33	0.50					
NO_2 (µg/m³)	0.28	0.39	**0.79**				
$PM_{2.5}$ (µg/m³)	0.21	0.41	**0.87**	0.66			

Temperature (°C)	0.35	0.27	-0.33	-0.43	-0.35		
Relative humidity (%)	-0.40	-0.35	0.28	0.33	0.16	-0.53	
Barometric pressure (hPa)	0.19	0.22	0.23	0.25	0.25	-0.16	0.01
Augsburg-Hochschule							
PNC (10-800nm, n/cm^3)	**0.98**						
BC (µg/m^3)	0.57	0.67					
NO_2 (µg/m^3)*	0.37	0.48	**0.78**				
$PM_{2.5}$ (µg/m^3)	0.57	0.62	**0.80**	0.66			
Temperature (°C)	0.09	0.06	-0.21	-0.29	-0.47		
Relative humidity (%)	-0.28	-0.26	0.17	0.09	0.19	-0.57	
Barometric pressure (hPa)	0.20	0.22	0.16	0.19	0.13	-0.01	-0.11

UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); BC: Black carbon; NO_2: Nitrogen dioxide; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≥ 2.5µm. Temp.: Temperature; °C: Degree Celsius; Rel. hum.: relative humidity; hPa: hectopascal. Number printed in bold indicate high correlation (≥ ± 0.7).

*: NO_2 data for Augsburg measured at station A-LfU instead of AFH.
†: No data at this station available.

Supplement Table E7: Spearman correlation coefficients of particle in the ultrafine range (UFP, 10-100nm) and total particle number concentration (PNC, 10-800nm).

Variable	Leipzig-Mitte	Leipzig-West	Leipzig-TROPOS	Dresden-Nord	Dresden-Winckelmannstr.
UFP (10-100nm, n/cm^3)					
Leipzig-West	0.62				
Leipzig-TROPOS	**0.70**	**0.85**			
Dresden-Nord	0.56	0.47	0.57		
Dresden-Winckelmannstr.	0.51	0.67	0.68	0.66	
Augsburg-Hochschule	0.44	0.30	0.43	0.38	0.39
PNC (10-800nm, n/cm^3)					
Leipzig-West	0.65				
Leipzig-TROPOS	**0.72**	**0.88**			
Dresden-Nord	0.60	0.50	0.60		
Dresden-Winckelmannstr.	0.56	**0.71**	**0.73**	**0.70**	
Augsburg-Hochschule	0.47	0.35	0.46	0.42	0.45

UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); Number printed in bold indicate high correlation (≥ ± 0.7)

Supplement Table E8: Percent change in relative risk and 95% confidence interval per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollutants and cause-specific mortality. Standardization by IQR facilitates comparison between different pollutants. Results of the pooled main analysis, stratified by air pollutant, average lag, and mortality endpoint. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates.

Variable	IQR	NM [95% CI]	CVM [95% CI]	RM [95% CI]
UFP				
lag0-1	3,420	-0.22% [-0.90%; 0.48%]	0.40% [-0.74%; 1.54%]	0.14% [-2.85%; 3.22%]
lag2-4	3,220	0.17% [-0.49%; 0.84%]	0.24% [-0.85%; 1.35%]	**3.24% [0.46%; 6.10%]**
lag5-7	3,223	0.64% [-0.01%; 1.29%]	0.35% [-0.60%; 1.32%]	**4.46% [1.52%; 7.48%]**
lag0-7	2,804	-0.02% [-0.70%, 0.66%]	-0.29% [-1.38%; 0.81%]	**3.52% [0.63%; 6.51%]**
PNC				
lag0-1	3,978	-0.25% [-0.94%; 0.45%]	0.49% [-0.72%; 1.71%]	0.09% [-2.99%; 3.27%]
lag2-4	3,744	0.14% [-0.53%; 0.81%]	0.44% [-0.72%; 1.62%]	2.50% [-0.29%; 5.38%]
lag5-7	3,747	0.55% [-0.10%; 1.20%]	0.30% [-0.65%; 1.27%]	**3.71% [0.74%; 6.77%]**
lag0-7	3,221	-0.07% [-0.74%; 0.60%]	-0.15% [-1.25%; 0.97%]	2.79% [-0.05%; 5.72%]
BC				
lag0-1	0.90	-0.07% [-0.93%; 0.79%]	0.51% [-0.29%; 1.32%]	-0.07% [-4.50%; 4.56%]
lag2-4	0.88	0.09% [-1.47%; 1.67%]	0.60% [-0.96%; 2.19%]	-0.57% [-2.83%; 1.75%]
lag5-7	0.88	-0.10% [-0.87%; 0.66%]	-0.23% [-1.05%; 0.58%]	-0.37% [-2.90%; 2.22%]
lag0-7	0.77	-0.07% [-0.72%; 0.58%]	0.35% [-0.60%; 1.31%]	-1.14% [-3.83%; 1.62%]
$PM_{2.5}$†				
lag0-1	10.78	0.23% [-1.15%; 1.62%]	0.46% [-0.36%; 1.29%]	0.35% [-1.75%; 2.49%]
lag2-4	10.32	0.78% [-1.43%; 3.04%]*	1.25% [-0.22%; 2.74%]	-0.65% [-2.83%; 1.58%]
lag5-7	10.32	0.07% [-0.46%; 0.60%]	0.01% [-0.76%; 0.78%]	-0.99% [-3.01%; 1.07%]
lag0-7	9.10	0.45% [-1.05%; 1.97%]	0.72% [-0.23%; 1.68%]	-0.90% [-3.39%; 1.64%]
NO_2†‡				
lag0-1	11.80	-0.36% [-1.14%; 0.41%]	-0.37% [-1.51%; 0.78%]	1.56% [-1.52%; 4.74%]
lag2-4	11.00	1.10% [-0.85%; 3.08%]*	**1.73% [0.60%; 2.88%]**	2.79% [-0.24%; 5.92%]
lag5-7	11.00	-0.04% [-0.79%; 0.72%]	-0.74% [-1.81%; 0.34%]	0.72% [-2.16%; 3.69%]
lag0-7	9.16	0.31% [-0.58%; 1.21%]	0.40% [-0.91%; 1.74%]	3.04% [-0.56%; 6.76%]

IQR: Interquartile range; NM: Natural mortality (ICD-10 code: A00-R99); CI: Confidence interval; CVM: Cardiovascular mortality (ICD-10 code: I00-I99); RM: Respiratory mortality (ICD-10 code: J00-J99); UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); BC: Black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter $\geq$ 2.5µm; NO_2: Nitrogen dioxide. Numbers printed in bold indicate statistical significance ($p < 0.05$).

*: $I^2 > 50\%$ & $p < 0.05$.

†: Pooled analysis for this air pollution without station LTR (no data at this station available).

‡: NO_2 data for Augsburg measured at station A-LfU instead of AFH.

Supplement Table E9: Percent change in relative risk and 95% confidence interval per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollutants and cause-specific mortality. Standardization by IQR facilitates comparison between different pollutants. Results of the pooled sensitivity analysis, stratified by analysis/air pollutant, average lag, and mortality endpoint. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates.

Variable	IQR	NM [95% CI]	CVM [95% CI]	RM [95% CI]
Nucleation mode (10-30nm)				
lag0-1	1,921	0.16% [-0.48%; 0.80%]	0.68% [-0.27%; 1.63%]	0.11% [-2.47%; 2.76%]
lag2-4	1,786	0.22% [-0.47%; 0.92%]	0.14% [-0.98%; 1.28%]	**3.85% [1.26%; 6.50%]**
lag5-7	1,787	**0.86% [0.25%; 1.48%]**	0.47% [-0.43%; 1.38%]	**4.49% [1.91%; 7.14%]**
lag0-7	1,578	0.25% [-0.40%; 0.91%]	-0.04% [-1.23%; 1.17%]	**3.97% [1.17%; 6.85%]**
Aitken mode (30-100nm)				
lag0-1	1,731	-0.67% [-1.38%; 0.04%]	-0.05% [-1.23%; 1.15%]	0.04% [-2.89%; 3.07%]
lag2-4	1,630	0.12% [-0.58%; 0.82%]	0.35% [-0.68%; 1.39%]	1.71% [-1.17%; 4.68%]
lag5-7	1,630	0.22% [-0.45%; 0.89%]	0.13% [-0.85%; 1.12%]	**3.64% [0.81%; 6.57%]**
lag0-7	1,399	-0.38% [-1.10%; 0.34%]	-0.54% [-1.60%; 0.53%]	2.58% [-0.48%; 5.73%]
Accumulation mode (100-800nm)				
lag0-1	877	-0.26% [-0.97%, 0.44%]	0.58% [-0.37%; 1.55%]	0.20% [-3.59%; 4.13%]
lag2-4	829	0.21% [-1.74%; 2.19%]*	0.91% [-0.10%; 1.93%]	-1.36% [-3.95%; 1.30%]
lag5-7	830	0.00% [-0.62%; 0.63%]	-0.01% [-0.92%; 0.91%]	-0.33% [-4.10%; 3.60%]
lag0-7	704	-0.31% [-1.04%; 0.42%]	0.18% [-0.84%; 1.21%]	-0.90% [-3.70%; 1.98%]
UFP (20-100nm)				
lag0-1	2,377	-0.50% [-1.19%; 0.20%]	0.17% [-0.90%; 1.27%]	0.43% [-2.47%; 3.42%]
lag2-4	2,233	0.17% [-0.51%; 0.84%]	0.37% [-0.62%; 1.37%]	**2.98% [0.16%; 5.88%]**
lag5-7	2,234	0.47% [-0.18%; 1.13%]	0.34% [-0.62%; 1.30%]	**4.20% [1.38%; 7.10%]**
lag0-7	1,915	-0.12% [-0.80%; 0.57%]	-0.08% [-1.25%; 1.10%]	**3.44% [0.50%; 6.45%]**
PNC (20-800nm)				
lag0-1	3,090	-0.49% [-1.20%; 0.22%]	0.30% [-0.89%; 1.51%]	0.29% [-2.73%; 3.40%]
lag2-4	2,879	0.11% [-0.57%; 0.80%]	0.59% [-0.50%; 1.70%]	1.98% [-0.86%; 4.89%]
lag5-7	2,879	0.38% [-0.27%; 1.04%]	0.26% [-0.70%; 1.22%]	**3.21% [0.36%; 6.14%]**
lag0-7	2,442	-0.17% [-0.85%; 0.52%]	0.05% [-1.12%; 1.23%]	2.45% [-0.44%; 5.42%]
Extension MST UFP				
lag0-1	3,591	-0.39% [-0.95%; 0.17%]	-0.16% [-1.50%; 1.20%]	0.22% [-1.89%; 2.38%]
lag2-4	3,386	-0.09% [-0.63%; 0.45%]	0.14% [-0.70%; 1.00%]	2.07% [-0.01%; 4.20%]
lag5-7	3,389	0.33% [-0.30%; 0.97%]	0.46% [-0.37%; 1.30%]	**3.43% [0.79%; 6.13%]**
lag0-7	3,010	-0.22% [-0.76%; 0.33%]	-0.20% [-1.05%, 0.66%]	2.20% [-0.61%; 5.08%]
Extension MST PNC				
lag0-1	4,175	-0.33% [-0.89%; 0.23%]	-0.04% [-1.46%; 1.40%]	0.17% [-1.94%; 2.33%]
lag2-4	3,950	-0.02% [-0.57%; 0.52%]	0.38% [-0.48%; 1.24%]	1.65% [-0.44%; 3.77%]

lag5-7	3,951	0.39% [-0.14%; 0.93%]	0.52% [-0.31%; 1.36%]	**3.20% [0.65%; 5.83%]**
lag0-7	3,498	-0.13% [-0.68%; 0.41%]	-0.03% [-0.88%; 0.83%]	1.48% [-0.76%; 3.77%]

IQR: Interquartile range; NM: Natural mortality (ICD-10 code: A00-R99); CI: Confidence interval; CVM: Cardiovascular mortality (ICD-10 code: I00-I99); RM: Respiratory mortality (ICD-10 code: J00-J99); UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); MST: Model included data from the measurement station Mülheim-Styrum. Numbers printed in bold indicate statistical significance ($p < 0.05$).

*: $I^2 > 50\%$ & $p < 0.05$.

Supplement Table E10: Percent change in relative risk and 95% confidence interval per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in UFP/PNC and cause-specific mortality. Standardization by IQR facilitates comparison between different pollutants. Results from the station-specific analysis for the average lag5-7 and were adjusted for main model covariates.

Variable	IQR	NM [95% CI]	CVM [95% CI]	RM [95% CI]
UFP				
LMI	4,332	**1.45% [0.03%; 2.88%]**	0.70% [-1.35%; 2.78%]	5.01% [-0.92%; 11.29%]
LWE	2,687	0.67% [-1.33%; 2.71%]	0.29% [-2.64%; 3.31%]	**9.16% [0.27%; 18.84%]**
LTR	2,687	-0.01% [-1.34%; 1.33%]	-0.04% [-1.99%; 1.94%]	**8.20% [2.47%; 14.26%]**
DDN	3,804	1.12% [-0.72%; 2.99%]	0.30% [-2.39%; 3.06%]	3.08% [-4.39%; 11.14%]
DDW	2,804	0.48% [-1.30%; 2.30%]	-0.17% [-2.83%; 2.55%]	0.01% [-7.28%; 7.88%]
AFH	3,024	-0.45% [-2.29%; 1.43%]	1.00% [-1.77%; 3.85%]	2.72% [-4.31%; 10.26%]
Pooled estimate	3,223	0.64% [-0.01%; 1.29%]	0.35% [-0.60%; 1.32%]	**4.46% [1.52%; 7.48%]**
I^2 & p-value		0.00%, p = 0.753	0.00%, p = 0.992	4.90%, p = 0.385
PNC				
LMI	5,009	1.25% [-0.16%; 2.69%]	0.50% [-1.55%; 2.58%]	4.94% [-1.01%; 11.24%]
LWE	2,976	0.41% [-1.48%; 2.33%]	0.37% [-2.40%; 3.22%]	6.88% [-1.40%; 15.84%]
LTR	3,182	-0.14% [-1.49%; 1.23%]	-0.14% [-2.12%; 1.87%]	**8.02% [2.17%; 14.20%]**
DDN	4,449	1.20% [-0.68%; 3.13%]	0.25% [-2.50%; 3.08%]	1.54% [-5.96%; 9.64%]
DDW	3,408	0.50% [-1.28%; 2.32%]	-0.01% [-2.67%; 2.71%]	-1.36% [-8.47%; 6.31%]
AFH	3,456	-0.36% [-2.16%; 1.46%]	1.07% [-1.62%; 3.83%]	2.36% [-4.42%; 9.62%]
Pooled estimate	3,747	0.55% [-0.10%; 1.20%]	0.31% [-0.65%; 1.27%]	**3.71% [0.74%; 6.77%]**
I^2 & p-value		0.00%, p = 0.781	0.00%, p = 0.990	10.20%, p = 0.351

UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); IQR: Interquartile range; NM: Natural mortality (ICD-10 code: A00-R99); CI: Confidence interval; CVM: Cardiovascular mortality (ICD-10 code: I00-I99); RM: Respiratory mortality (ICD-10 code: J00-J99); LMI: Leipzig-Mitte; LWE: Leipzig-West; LTR: Leipzig-TROPOS; DDN: Dresden-Nord; DDW: Dresden-Winckelmannstr.; AFH: Augsburg-Hochschule; I^2: Test statistic for heterogeneity. Numbers printed in bold indicate statistical significance ($p < 0.05$).

Supplement Table E11: Percent change in relative risk and 95% confidence interval per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollutants and cause-specific mortality. Standardization by IQR facilitates comparison between different pollutants. Results of the pooled main analysis, stratified by air pollutant, average lag, mortality endpoint, and station characteristic. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates. Green color indicates the results for the urban background stations; black color for the traffic-related stations.

Variable	IQR	Station	NM [95% CI]	CVM [95% CI]	RM [95% CI]
UFP					
lag0-1	2,981	UB	-0.44% [-1.33%; 0.46%]	-0.03% [-1.69%; 1.65%]	1.71% [-2.20%; 5.76%]
lag2-4	2,797	UB	-0.02% [-0.89%; 0.86%]	0.18% [-1.75%; 2.14%]	**3.97% [0.35%; 7.71%]**
lag5-7	2,800	UB	0.12% [-0.73%; 0.97%]	0.22% [-1.04%; 1.48%]	4.64% [-0.17%; 9.68%]
lag0-7	2,395	UB	-0.47% [-1.48%; 0.55%]	0.16% [-1.33%; 1.67%]	**5.74% [1.47%; 10.20%]**
lag0-1	4,298	TR	0.02% [-1.14%; 1.20%]	0.91% [-0.82%; 2.66%]	-1.96% [-6.64%; 2.96%]
lag2-4	4,066	TR	0.46% [-0.81%; 1.74%]	0.21% [-1.43%; 1.86%]	2.73% [-1.94%; 7.63%]
lag5-7	4,068	TR	**1.31% [0.20%; 2.42%]**	0.55% [-1.05%; 2.18%]	4.25% [-0.35%; 9.07%]
lag0-7	3,623	TR	0.41% [-0.94%; 1.76%]	-0.60% [-2.74%; 1.59%]	2.41% [-2.13%; 7.16%]
PNC					
lag0-1	3,490	UB	-0.41% [-1.31%; 0.50%]	-0.04% [-1.99%; 1.94%]	1.74% [-2.29%; 5.93%]
lag2-4	3,253	UB	0.01% [-0.89%; 0.92%]	0.46% [-1.64%; 2.60%]	3.06% [-0.52%; 6.78%]
lag5-7	3,255	UB	0.05% [-0.78%; 0.89%]	0.25% [-0.99%; 1.50%]	3.66% [-1.27%; 8.83%]
lag0-7	2,742	UB	-0.49% [-1.73%; 0.76%]	0.41% [-1.05%; 1.88%]	4.50% [0.41%; 8.74%]
lag0-1	4,955	TR	-0.07% [-1.25%; 1.12%]	1.11% [-0.64%; 2.89%]	-2.22% [-6.96%; 2.77%]
lag2-4	4,726	TR	0.29% [-0.85%; 1.43%]	0.29% [-1.38%; 1.98%]	2.07% [-2.67%; 7.03%]
lag5-7	4,729	TR	**1.21% [0.10%; 2.34%]**	0.41% [-1.21%; 2.05%]	3.70% [-0.92%; 8.55%]
lag0-7	4,179	TR	0.20% [-0.87%; 1.29%]	-0.62% [-2.70%; 1.51%]	1.84% [-2.68%; 6.57%]
BC					
lag0-1	0.78	UB	0.20% [-0.44%; 0.84%]	0.61% [-0.32%; 1.56%]	0.29% [-3.29%; 4.00%]
lag2-4	0.75	UB	0.16% [-1.29%; 1.62%]	0.84% [-0.13%; 1.82%]	-0.60% [-3.18%; 2.05%]
lag5-7	0.75	UB	-0.32% [-1.02%; 0.38%]	-0.15% [-1.08%; 0.78%]	-0.14% [-3.61%; 3.46%]
lag0-7	0.62	UB	-0.16% [-0.87%; 0.57%]	0.41% [-0.64%; 1.47%]	-1.16% [-4.81%; 2.62%]
lag0-1	1.15	TR	-0.46% [-2.10%; 1.21%]	0.29% [-1.37%; 1.98%]	-1.63% [-7.73%; 4.87%]
lag2-4	1.15	TR	-0.41% [-2.44%; 1.66%]	0.19% [-1.45%; 1.86%]	-0.52% [-4.90%; 4.08%]
lag5-7	1.15	TR	0.08% [-1.02%; 1.19%]	-0.40% [-2.00%; 1.22%]	-0.82% [-5.08%; 3.64%]
lag0-7	1.05	TR	0.08% [-1.20%; 1.38%]	0.24% [-1.63%; 2.14%]	-1.17% [-6.56%; 4.53%]
$PM_{2.5}$†					
lag0-1	10.37	UB	0.23% [-0.84%; 1.32%]	0.52% [-0.54%; 1.59%]	0.61% [-2.16%; 3.45%]
lag2-4	9.93	UB	0.73% [-1.18%; 2.67%]*	1.34% [-0.49%; 3.20%]	-0.73% [-3.61%; 2.23%]
lag5-7	9.93	UB	0.09% [-0.61%; 0.79%]	0.13% [-0.90%; 1.16%]	-1.05% [-3.69%; 1.67%]
lag0-7	8.77	UB	0.44% [-0.93%; 1.83%]	0.84% [-0.42%; 2.12%]	-0.86% [-4.12%; 2.51%]
lag0-1	11.40	TR	-0.17% [-1.37%; 1.04%]	0.40% [-0.81%; 1.62%]	0.03% [-3.17%; 3.34%]
lag2-4	10.90	TR	0.08% [-1.64%; 1.83%]*	0.86% [-0.41%; 2.14%]	-0.55% [-3.89%; 2.90%]
lag5-7	10.90	TR	0.05% [-0.76%; 0.86%]	-0.14% [-1.32%; 1.05%]	-0.92% [-4.03%; 2.28%]

lag0-7	9.60	TR	0.03% [-1.08%; 1.16%]	0.58% [-0.88%; 2.06%]	-0.97% [-4.78%; 2.99%]
NO_2†‡					
lag0-1	10.83	UB	-0.41% [-1.52%; 0.71%]	-0.16% [-1.80%; 1.50%]	1.71% [-2.62%; 6.22%]
lag2-4	10.23	UB	1.45% [-0.48%; 3.41%]	**2.29% [0.59%; 4.02%]**	2.17% [-2.20%; 6.74%]
lag5-7	10.23	UB	-0.06% [-1.36%; 1.26%]	-0.36% [-1.94%; 1.25%]	-1.02% [-5.04%; 3.17%]
lag0-7	8.93	UB	0.28% [-1.07%; 1.65%]	0.84% [-1.17%; 2.89%]	0.50% [-4.66%; 5.94%]
lag0-1	13.25	TR	-0.34% [-1.47%; 0.79%]	-0.56% [-2.21%; 1.12%]	1.51% [-3.01%; 6.25%]
lag2-4	12.15	TR	0.45% [-1.67%; 2.61%]	1.41% [-0.17%; 3.02%]	3.44% [-0.92%; 7.99%]
lag5-7	12.15	TR	-0.06% [-1.10%; 0.99%]	-1.08% [-2.60%; 0.46%]	2.30% [-1.93%; 6.71%]
lag0-7	9.50	TR	0.34% [-0.86%; 1.56%]	0.09% [-1.68%; 1.89%]	**5.18% [0.17%; 10.43%]**

IQR: Interquartile range; NM: Natural mortality (ICD-10 code: A00-R99); CI: Confidence interval; CVM: Cardiovascular mortality (ICD-10 code: I00-I99); RM: Respiratory mortality (ICD-10 code: J00-J99); UFP: Particle number concentration of particles in the ultrafine range (10-100nm); UB: urban background; TR: traffic-related; PNC: Total particle number concentration (10-800nm); BC: Black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≥ 2.5µm; NO_2: Nitrogen dioxide. Numbers printed in bold indicate statistical significance ($p < 0.05$).

*: $I^2 > 50\%$ & $p < 0.05$.

†: Pooled analysis for this air pollution without station LTR (no data at this station available).

‡: NO_2 data for Augsburg measured at station A-LfU instead of AFH.

Supplement Table E12: Percent change in relative risk and 95% confidence interval per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in UFP (top) and PNC (bottom) and cause-specific mortality for the average lag5-7. Standardization by IQR facilitates comparison between different pollutants. Results of the two-pollutant and effect modification analysis. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates.

Analysis	IQR	NM [95% CI]	CVM [95% CI]	RM [95% CI]
UFP				
Main analysis	3,223	0.64% [-0.01%; 1.29%]	0.35% [-0.60%; 1.32%]	**4.46% [1.52%; 7.48%]**
Two-pollutant model				
+ adj. BC	3,223	0.57% [-0.15%; 1.29%]	0.50% [-0.55%; 1.57%]	**4.57% [1.34%; 7.90%]**
+ adj. $PM_{2.5}$*	3,330	**0.80% [0.06%; 1.56%]**	0.46% [-0.64%; 1.56%]	**4.07% [0.93%; 7.30%]**
+ adj. NO_2†	3,080	0.78% [-0.34%; 1.90%]	0.66% [-1.00%; 2.34%]	4.46% [-0.26%; 9.40%]
Effect modification				
Male	3,223	0.66% [-0.29%; 1.62%]	0.61% [-0.89%; 2.13%]	0.45% [-3.10%; 4.13%]
Female	3,223	0.64% [-0.24%; 1.53%]	0.20% [-1.04%; 1.46%]	**9.57% [5.35%; 13.97%]**
0-74 years	3,223	**1.44% [0.18%; 2.72%]**	1.74% [-0.47%; 4.00%]	**6.99% [1.50%; 12.79%]**
75+ years	3,223	0.28% [-0.50%; 1.06%]	0.02% [-1.03%; 1.09%]	**3.79% [0.62%; 7.05%]**

Apr.-Sep.	3,223	0.02% [-1.11%; 1.16%]	-0.22% [-1.55%; 1.14%]	2.45% [-4.26%; 9.63%]
Oct.-Mar.	3,223	**1.00% [0.13%; 1.87%]**	0.80% [-0.28%; 1.89%]	**4.22% [1.19%; 7.33%]**
PNC				
Main analysis	3,747	0.55% [-0.10%; 1.20%]	0.30% [-0.65%; 1.27%]	**3.71% [0.74%; 6.77%]**
Two-pollutant model				
+ adj. BC	3,747	0.56% [-0.21%; 1.33%]	0.54% [-0.58%; 1.68%]	**4.58% [1.09%; 8.19%]**
+ adj. $PM_{2.5}$*	3,860	**0.78% [0.01%; 1.57%]**	0.48% [-0.66%; 1.63%]	**4.00% [0.75%; 7.36%]**
+ adj. NO_2†	3,572	0.84% [-0.33%; 2.02%]	0.81% [-0.93%; 2.57%]	3.48% [-1.81%; 9.05%]
Effect modification				
Male	3,747	0.56% [-0.53%; 1.66%]	0.71% [-0.78%; 2.23%]	-0.60% [-4.11%; 3.03%]
Female	3,747	0.59% [-0.29%; 1.48%]	0.05% [-1.19%; 1.30%]	**9.20% [4.82%; 13.76%]**
0-74 years	3,747	**1.45% [0.16%; 2.76%]**	1.97% [-0.25%; 4.23%]	**6.41% [1.07%; 12.03%]**
75+ years	3,747	0.16% [-0.61%; 0.94%]	-0.09% [-1.15%; 0.98%]	3.04% [-0.14%; 6.32%]
Apr.-Sep.	3,747	-0.05% [-1.10%; 1.00%]	-0.37% [-1.68%; 0.95%]	1.76% [-5.60%; 9.69%]
Oct.-Mar.	3,747	0.88% [-0.01%; 1.77%]	0.76% [-0.30%; 1.82%]	**3.48% [0.55%; 6.49%]**

UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); IQR: Interquartile range; NM: Natural mortality (ICD-10 code: A00-R99); CI: Confidence interval; CVM: Cardiovascular mortality (ICD-10 code: I00-I99); RM: Respiratory mortality (ICD-10 code: J00-J99); Adj.: adjustment; BC: Black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≥ 2.5µm; NO_2: Nitrogen dioxide. Apr.: April; Sep.: September; Oct.: October; Mar.: March; Numbers printed in bold indicate statistical significance ($p < 0.05$).

*: Pooled analysis without station LTR (no data at this station available).

†: Pooled analysis without station LTR (no data at this station available) and LMI (Spearman correlation coefficient ≥ 0.7).

Supplement Table E13: Percent change in relative risk and 95% confidence interval per fixed-unit increase in air pollutants and cause-specific mortality. Results of the pooled main analysis, stratified by air pollutant, average lag, and mortality endpoint. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates.

Variable	Incr.	NM [95% CI]	CVM [95% CI]	RM [95% CI]
UFP				
lag0-1	10,000	-0.63% [-2.62%; 1.40%]	1.16% [-2.13%; 4.57%]	0.40% [-8.12%; 9.70%]
lag2-4	10,000	0.54% [-1.50%; 2.64%]	0.76% [-2.62%; 4.27%]	**10.41% [1.43%; 20.20%]**
lag5-7	10,000	1.99% [-0.04%; 4.06%]	1.10% [-1.85%; 4.14%]	**14.51% [4.81%; 25.10%]**
lag0-7	10,000	-0.07% [-2.46%; 2.38%]	-1.03% [-4.83%; 2.92%]	**13.15% [2.25%; 25.21%]**
PNC				
lag0-1	10,000	-0.62% [-2.36%; 1.15%]	1.23% [-1.79%; 4.34%]	0.22% [-7.35%; 8.42%]
lag2-4	10,000	0.36% [-1.42%; 2.18%]	1.19% [-1.91%; 4.39%]	6.83% [-0.78%; 15.02%]

lag5-7	10,000	1.48% [-0.27%; 3.25%]	0.82% [-1.72%; 3.42%]	**10.21% [1.98%; 19.10%]**
lag0-7	10,000	-0.22% [-2.28%; 1.88%]	-0.45% [-3.83%; 3.05%]	8.92% [-0.16%; 18.83%]
BC				
lag0-1	1	-0.08% [-1.03%; 0.87%]	0.57% [-0.32%; 1.47%]	-0.08% [-4.99%; 5.07%]
lag2-4	1	0.10% [-1.67%; 1.90%]	0.68% [-1.09%; 2.49%]	-0.64% [-3.21%; 1.99%]
lag5-7	1	-0.12% [-0.98%; 0.76%]	-0.27% [-1.19%; 0.66%]	-0.42% [-3.29%; 2.53%]
lag0-7	1	-0.09% [-0.93%; 0.75%]	0.46% [-0.77%; 1.70%]	-1.48% [-4.94%; 2.10%]
$PM_{2.5}$†				
lag0-1	10	0.21% [-1.07%; 1.51%]	0.43% [-0.33%; 1.20%]	0.32% [-1.62%; 2.31%]
lag2-4	10	0.76% [-1.39%; 2.95%]	1.21% [-0.21%; 2.66%]	-0.63% [-2.74%; 1.53%]
lag5-7	10	0.07% [-0.44%; 0.58%]	0.01% [-0.74%; 0.76%]	-0.96% [-2.92%; 1.03%]
lag0-7	10	0.50% [-1.15%; 2.17%]	0.79% [-0.26%; 1.85%]	-0.99% [-3.71%; 1.81%]
NO_2†‡				
lag0-1	10	-0.31% [-0.96%; 0.35%]	-0.31% [-1.28%; 0.66%]	1.32% [-1.29%; 4.01%]
lag2-4	10	1.00% [-0.78%; 2.80%]	**1.57% [0.55%; 2.61%]**	2.54% [-0.22%; 5.37%]
lag5-7	10	-0.03% [-0.72%; 0.65%]	-0.68% [-1.65%; 0.31%]	0.66% [-1.96%; 3.35%]
lag0-7	10	0.34% [-0.63%; 1.32%]	0.44% [-1.00%; 1.90%]	3.32% [-0.61%; 7.40%]
Nucleation mode (10-30nm)				
lag0-1	10,000	0.83% [-2.47%; 4.24%]	3.57% [-1.41%; 8.79%]	0.57% [-12.21%; 15.20%]
lag2-4	10,000	1.26% [-2.58%; 5.24%]	0.79% [-5.38%; 7.36%]	**23.55% [7.26%; 42.31%]**
lag5-7	10,000	4.92% [1.38%; 8.58%]	2.67% [-2.39%; 7.99%]	**27.85% [11.14%; 47.07%]**
lag0-7	10,000	1.62% [-2.52%; 5.93%]	-0.23% [-7.53%; 7.64%]	**27.99% [7.62%; 52.20%]**
Aitken mode (30-100nm)				
lag0-1	10,000	-3.81% [-7.70%; 0.26%]	-0.28% [-6.89%; 6.81%]	0.26% [-15.59%; 19.10%]
lag2-4	10,000	0.72% [-3.49%; 5.11%]	2.15% [-4.11%; 8.81%]	10.98% [-6.95%; 32.36%]
lag5-7	10,000	1.34% [-2.72%; 5.58%]	0.82% [-5.09%; 7.09%]	**24.57% [5.05%; 47.72%]**
lag0-7	10,000	-2.69% [-7.59%; 2.47%]	-3.81% [-10.90%; 3.85%]	19.99% [-3.35%; 48.96%]
Accumulation mode (30-100nm)				
lag0-1	10,000	-2.96% [-10.47%; 5.19%]	6.87% [-4.12%; 19.13%]	2.27% [-34.09%; 58.69%]
lag2-4	10,000	2.55% [-19.06%; 29.93%]	11.55% [-1.14%; 25.86%]	-15.22% [-38.48%; 16.82%]
lag5-7	10,000	0.03% [-7.18%; 7.81%]	-0.08% [-10.48%; 11.53%]	-3.87% [-39.64%; 53.10%]
lag0-7	10,000	-4.34% [-13.77%; 6.12%]	2.62% [-11.24%; 18.64%]	-12.09% [-41.46%; 32.02%]

Incr.: Fixed-unit increment; NM: Natural mortality (ICD-10 code: A00-R99); CI: Confidence interval; CVM: Cardiovascular mortality (ICD-10 code: I00-I99); RM: Respiratory mortality (ICD-10 code: J00-J99); UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); BC: Black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter $\geq$ 2.5µm; NO_2: Nitrogen dioxide. Numbers printed in bold indicate statistical significance ($p < 0.05$).

*: $I^2 > 50\%$ & $p < 0.05$.

†: Pooled analysis for this air pollution without station LTR (no data at this station available).

‡: NO_2 data for Augsburg measured at station A-LfU instead of AFH.

Supplement Table E14: Percent change in relative risk and 95% confidence interval per fixed-unit increase in UFP (top) and PNC (bottom) and cause-specific mortality for the average lag5-7. Results of the two-pollutant and effect modification analysis. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates.

Analysis	Incr.	NM [95% CI]	CVM [95% CI]	RM [95% CI]
UFP				
Main analysis	10,000	1.99% [-0.04%; 4.06%]	1.10% [-1.85%; 4.14%]	**14.51% [4.81%; 25.10%]**
Two-pollutant model				
+ adj. BC	10,000	1.77% [-0.47%; 4.06%]	1.57% [-1.69%; 4.95%]	**14.87% [4.21%; 26.61%]**
+ adj. $PM_{2.5}$*	10,000	**2.43% [0.16%; 4.75%]**	1.37% [-1.91%; 4.77%]	**12.71% [2.81%; 23.57%]**
+ adj. NO_2†	10,000	2.54% [-1.10%; 6.31%]	2.14% [-3.22%; 7.80%]	15.21% [-0.85%; 33.88%]
Effect modification				
Male	10,000	2.07% [-0.89%; 5.12%]	1.90% [-2.72%; 6.75%]	1.41% [-9.30%; 13.39%]
Female	10,000	2.00% [-0.74%; 4.81%]	0.62% [-3.20%; 4.59%]	**32.80% [17.55%; 50.03%]**
0-74 years	10,000	**4.54% [0.56%; 8.68%]**	5.49% [-1.46%; 12.94%]	**23.34% [4.72%; 45.26%]**
75+ years	10,000	0.87% [-1.53%; 3.33%]	0.07% [-3.18%; 3.42%]	**12.22% [1.94%; 23.54%]**
Apr.-Sep.	10,000	0.06% [-3.40%; 3.64%]	-0.66% [-4.74%; 3.59%]	7.79% [-12.65%; 33.02%]
Oct.-Mar.	10,000	**3.13% [0.42%; 5.91%]**	2.51% [-0.85%; 5.98%]	**13.67% [3.75%; 24.54%]**
PNC				
Main analysis	10,000	1.48% [-0.27%; 3.25%]	0.82% [-1.72%; 3.42%]	**10.21% [1.98%; 19.10%]**
Two-pollutant model				
+ adj. BC	10,000	1.50% [-0.55%; 3.58%]	1.46% [-1.54%; 4.54%]	**12.70% [2.94%; 23.39%]**
+ adj. $PM_{2.5}$*	10,000	**2.05% [0.03%; 4.11%]**	1.24% [-1.70%; 4.27%]	**10.70% [1.95%; 20.20%]**
+ adj. NO_2†	10,000	2.36% [-0.92%; 5.75%]	2.28% [-2.57%; 7.37%]	10.04% [-4.99%; 27.45%]
Effect modification				
Male	10,000	1.50% [-1.42%; 4.50%]	1.92% [-2.07%; 6.07%]	-1.61% [-10.61%; 8.30%]
Female	10,000	1.58% [-0.77%; 3.99%]	0.13% [-3.15%; 3.51%]	**26.47% [13.37%; 41.08%]**

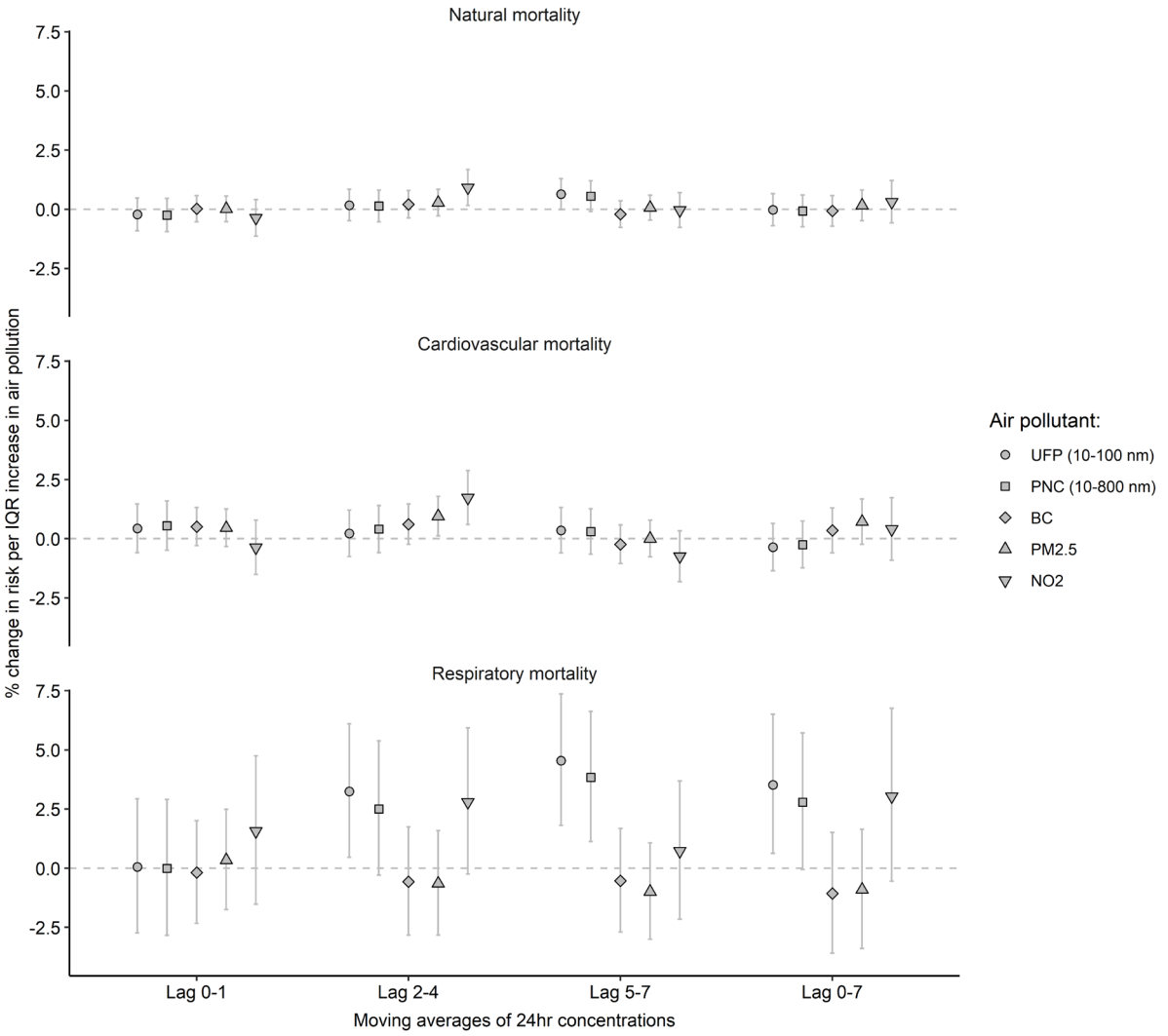
0-74 years	10,000	**3.91% [0.42%; 7.52%]**	5.33% [-0.68%; 11.70%]	**18.03% [2.89%; 35.41%]**
75+ years	10,000	0.43% [-1.63%; 2.53%]	-0.24% [-3.03%; 2.62%]	8.32% [-0.37%; 17.76%]
Apr.-Sep.	10,000	-0.14% [-2.90%; 2.69%]	-0.99% [-4.41%; 2.56%]	4.76% [-14.26%; 28.01%]
Oct.-Mar.	10,000	2.37% [-0.02%; 4.80%]	2.03% [-0.78%; 4.93%]	**9.55% [1.48%; 18.28%]**

UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); Incr.: Fixed-unit increment; NM: Natural mortality (ICD-10 code: A00-R99); CI: Confidence interval; CVM: Cardiovascular mortality (ICD-10 code: I00-I99); RM: Respiratory mortality (ICD-10 code: J00-J99); Adj.: adjustment; BC: Black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter $\geq$ 2.5µm; NO_2: Nitrogen dioxide. Apr.: April; Sep.: September; Oct.: October; Mar.: March; Numbers printed in bold indicate statistical significance ($p < 0.05$).

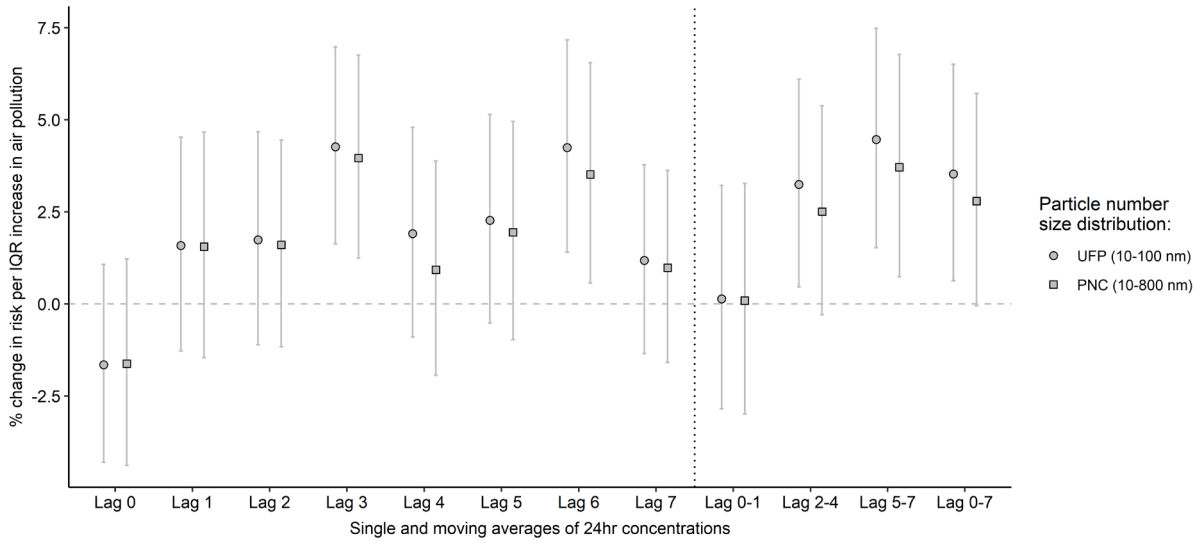
*: Pooled analysis without station LTR (no data at this station available).

†: Pooled analysis without station LTR (no data at this station available) and LMI (Spearman correlation coefficient ≥ 0.7).

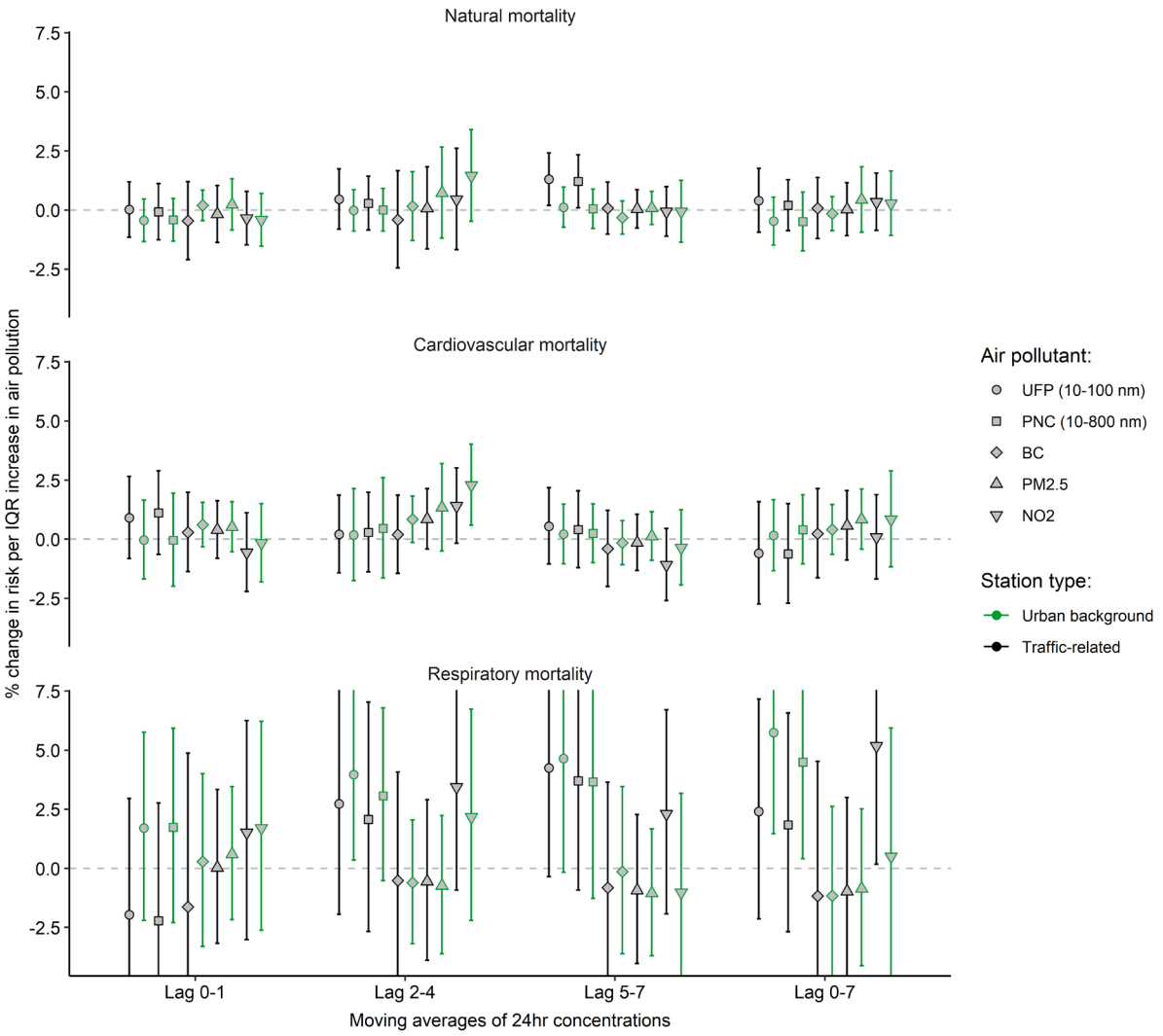
Supplementary Figures:



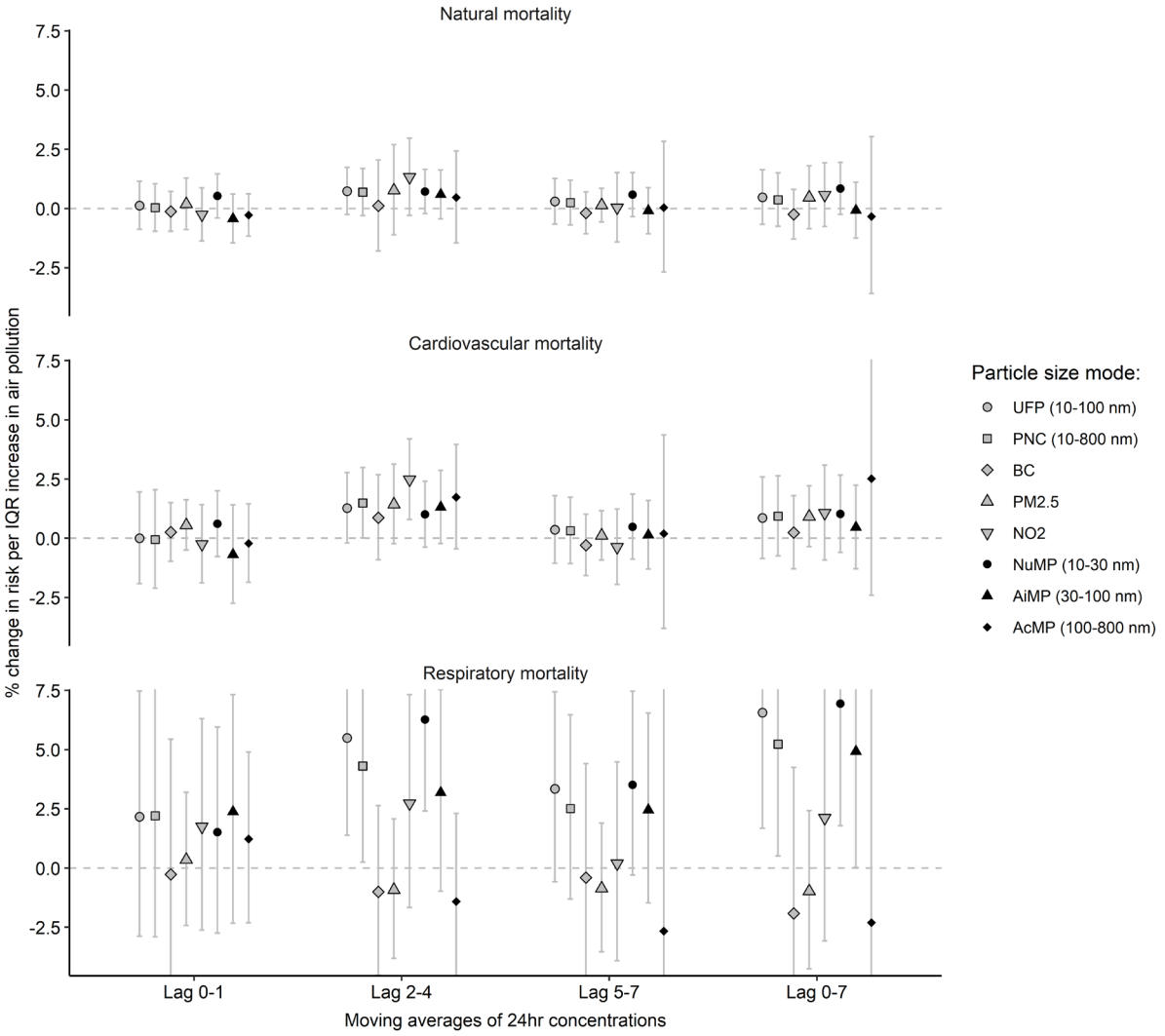
Supplement Figure E1: Percent change in relative risk and 95% confidence interval per interquartile range increase in air pollution concentration for natural- (top), cardiovascular- (middle), and respiratory mortality (bottom). The x-axis shows the 24hr moving average lag concentrations of air pollutants. The y-axis represents the percent change of risk per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollution concentration. 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 fixed-effects models and were adjusted for main model covariates.



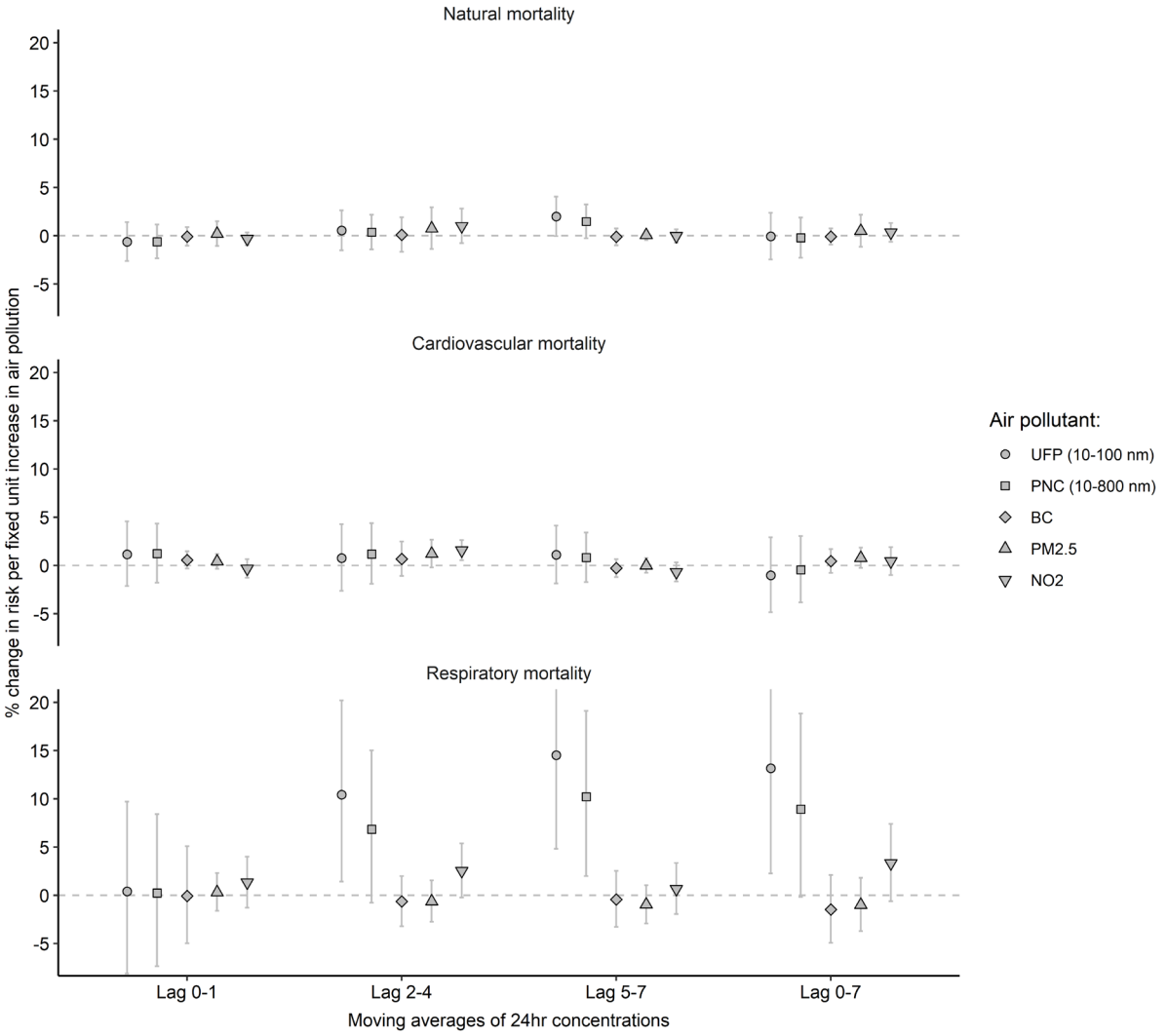
Supplement Figure E2: Percent change in relative risk and 95% confidence interval per interquartile range increase in air pollution concentration for respiratory mortality. The x-axis shows the single and average lags of air pollutants. The y-axis represents the percent changes of risk per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollution concentration. Standardization by IQR facilitates comparison between different pollutants. The shape of the estimates displays the type of pollutant. All estimates represent the pooled multilevel random-effects analysis of the measurement stations and were adjusted for main model covariates.



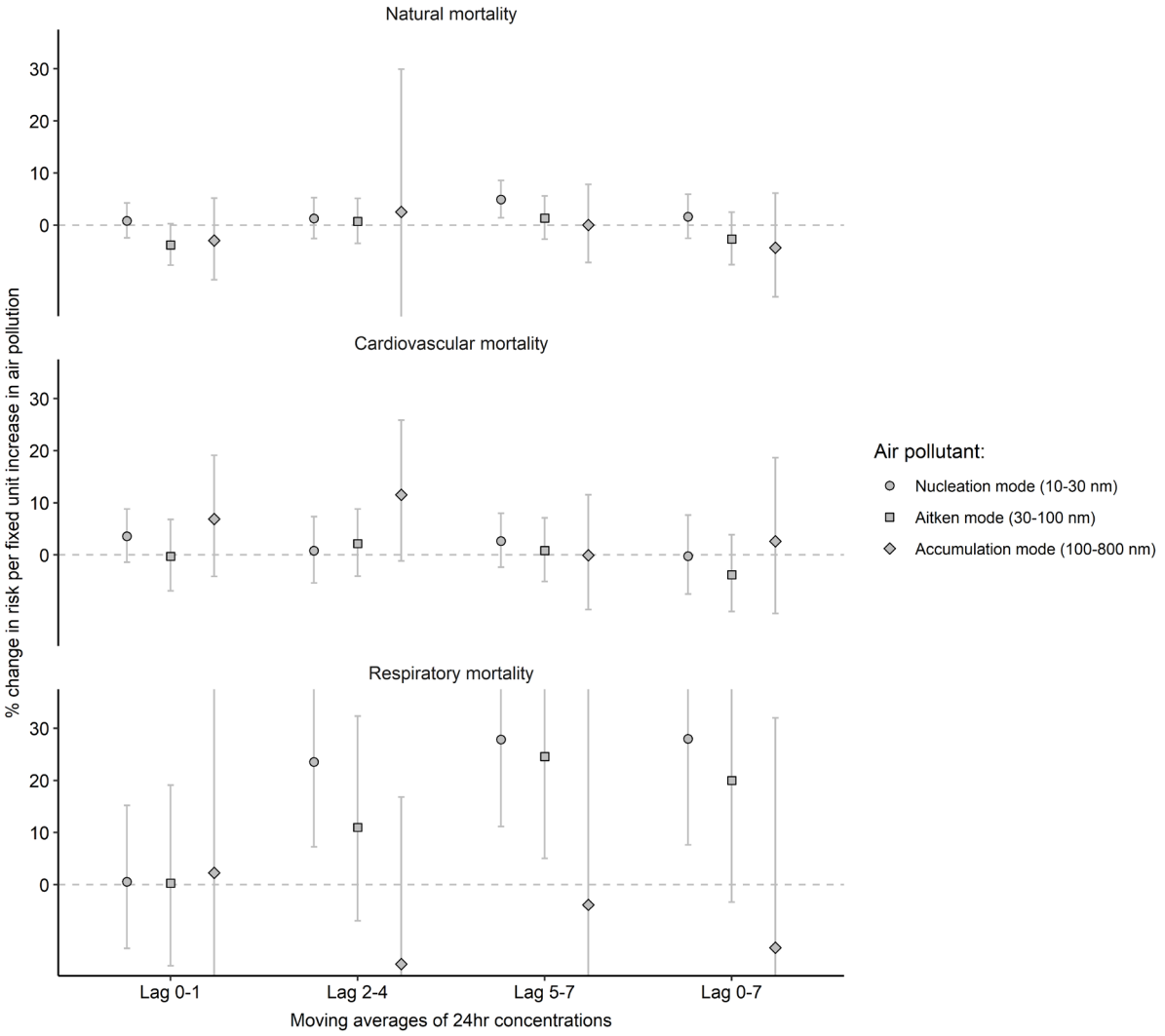
Supplement Figure E3: Percent change in relative risk and 95% confidence interval per interquartile range increase in air pollution concentration for natural- (top), cardiovascular- (middle), and respiratory mortality (bottom) and separated by station type. The x-axis shows the 24hr moving average lag concentrations of air pollutants. The y-axis represents the percent change of risk per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollution concentration. Standardization by IQR facilitates comparison between different pollutants. The shape of the estimates displays the type of pollutant. Estimates for urban background stations are displayed in green and estimates for traffic-related stations are displayed in black. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates.



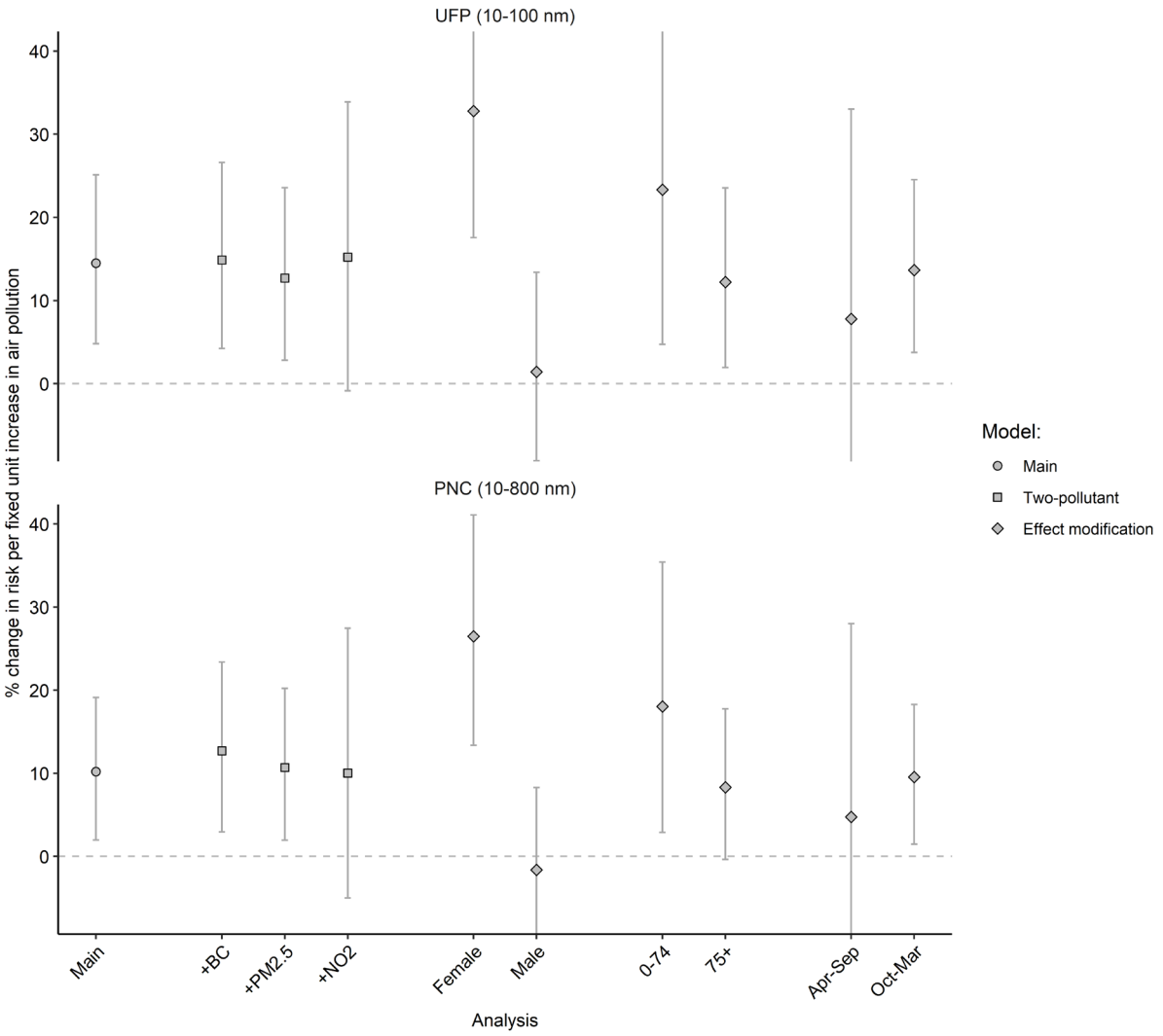
Supplement Figure E4: Percent change in relative risk and 95% confidence interval per interquartile range increase in air pollution concentration for natural- (top), cardiovascular- (middle), and respiratory mortality (bottom). The x-axis shows the 24hr moving average lag concentrations of air pollutants. The y-axis represents the percent change of risk per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollution concentration. Standardization by IQR facilitates comparison between different pollutants. The shape of the estimates displays the type of pollutant. Estimates are pooled using city-specific exposure concentrations according to the APHEA protocol. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates.



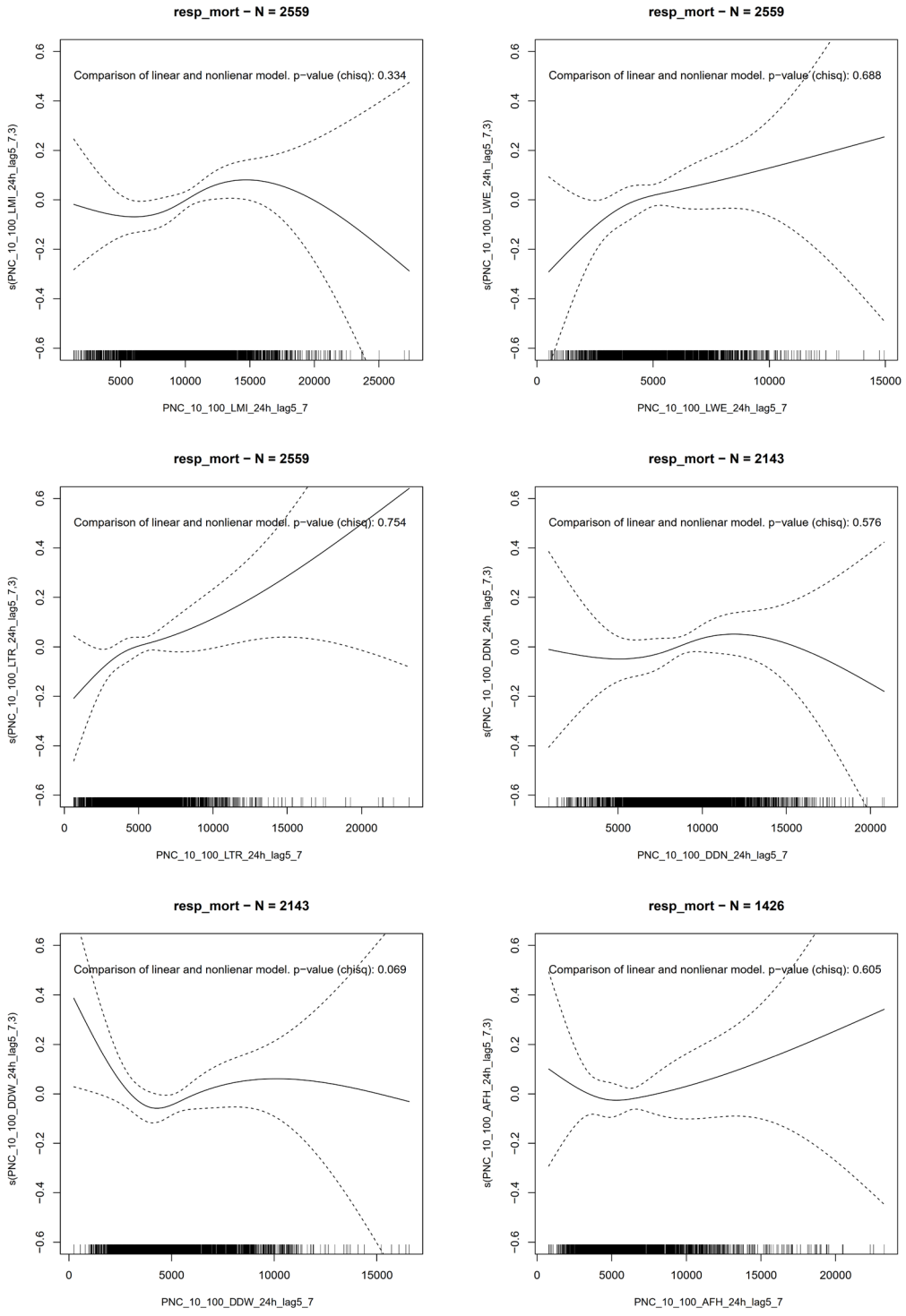
Supplement Figure E5: Percent change in relative risk and 95% confidence interval per fixed-unit increase in air pollution concentration for natural- (top), cardiovascular- (middle), and respiratory mortality (bottom). The x-axis shows the 24hr moving average lag concentrations of air pollutants. The y-axis represents the percent change of risk per fixed increment increase in air pollution concentration. We used standardized increments according to the literature of 10,000 particles/cm^3 (UFP and PNC), 1 µg/m^3 (BC), and 10 µg/m^3 ($PM_{2.5}$ and NO_2). 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.



Supplement Figure E6: Percent change in relative risk and 95% confidence interval per fixed-unit increase in air pollution concentration for natural- (top), cardiovascular- (middle), and respiratory mortality (bottom). The x-axis shows the 24hr moving average lag concentrations of air pollutants. The y-axis represents the percent change of risk per fixed increment increase in air pollution concentration. We used standardized increments according to the literature of 10,000 particles/cm^3. 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.



Supplement Figure E7: Percent change in relative risk and 95% confidence interval per fixed-unit increase in concentration of particles in the ultrafine range (10-100nm; UFP; top panel) and total particle number concentration (10-800nm; PNC; bottom panel) for respiratory mortality (lag5-7). The x-axis shows the results for the main (displayed as dot), two-pollutant (displayed as rectangle), and effect modification analysis (displayed as diamond). The y-axis represents the percent change of risk per fixed increment increase in air pollution concentration. We used standardized increments according to the literature of 10,000 particles/cm^3. 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 $PM_{2.5}$ and NO_2, the station Leipzig-TROPOS was not included in the model (no air pollution data). Additionally, the station Leipzig-Mitte was not included in the NO_2 model because Spearman correlation coefficients were above 0.7.



Supplement Figure E8: Exposure-response analysis for Leipzig-Mitte (top left), Leipzig-West (top right), Leipzig-TROPOS (middle left), Dresden-Nord (middle right), Dresden-Winckelmannstr. (bottom left), and Augsburg (bottom right). Smooth functions with three degrees of freedom (represented by black lines) were used for respiratory mortality (lag5-7) and particle number concentration for particles in the ultrafine range (UFP, 10-100nm). Dotted lines indicate 95% confidence intervals. The models were adjusted for main model covariates.

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Manuscript 2

Title:	Impact of ultrafine particles and total particle number concentration on five cause-specific hospital admission endpoints in three German cities
Authors:	Maximilian Schwarz, Alexandra Schneider, Josef Cyrys, Susanne Bastian, Susanne Breitner, and Annette Peters
Year:	2023
Journal:	Environment International
Status:	Published
Volume:	178
Page:	108032 – 999999
DOI:	https://doi.org/10.1016/j.envint.2023.108032
Publishing license:	Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (CC BY-NC-ND 4.0 DEED; https://creativecommons.org/licenses/by-nc-nd/4.0/)
Journal Impact Factor:	11.8 (according to *Journal Citation Reports™* 2022)
Rank by Journal Impact Factor:	17/275 in the category ‘Environmental Sciences’ (according to *Journal Citation Reports™* 2022)

Environment International 178 (2023) 108032

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Impact of ultrafine particles and total particle number concentration on five cause-specific hospital admission endpoints in three German cities

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ARTICLE INFO

Handling Editor: Dr. Hanna Boogaard

Keywords:
Ambient air pollution
Ultrafine particles
Particle number concentrations
Particulate matter
Hospital admission
Morbidity

ABSTRACT

Introduction: Numerous studies have shown associations between daily concentrations of fine particles (e.g., particulate matter with an aerodynamic diameter ≤2.5 μm; $PM_{2.5}$) and morbidity. However, evidence for ultrafine particles (UFP; particles with an aerodynamic diameter of 10–100 nm) remains conflicting. Therefore, we aimed to examine the short-term associations of UFP with five cause-specific hospital admission endpoints for Leipzig, Dresden, and Augsburg, Germany.

Material and methods: We obtained daily counts of (cause-specific) cardiorespiratory hospital admissions between 2010 and 2017. Daily average concentrations of UFP, total particle number (PNC; 10–800 nm), and black carbon (BC) were measured at six sites; $PM_{2.5}$ and nitrogen dioxide (NO_2) were obtained from monitoring networks. We assessed immediate (lag 0–1), delayed (lag 2–4, lag 5–7), and cumulative (lag 0–7) effects by applying station-specific confounder-adjusted Poisson regression models. We then used a novel multi-level meta-analytical method to obtain pooled risk estimates. Finally, we performed two-pollutant models to investigate interdependencies between pollutants and examined possible effect modification by age, sex, and season.

Results: UFP showed a delayed (lag 2–4) increase in respiratory hospital admissions of 0.69% [95% confidence interval (CI): −0.28%; 1.67%]. For other hospital admission endpoints, we found only suggestive results. Larger particle size fractions, such as accumulation mode particles (particles with an aerodynamic diameter of 100–800 nm), generally showed stronger effects (respiratory hospital admissions & lag 2–4: 1.55% [95% CI: 0.86%; 2.25%]). $PM_{2.5}$ showed the most consistent associations for (cardio-)respiratory hospital admissions, whereas NO_2 did not show any associations. Two-pollutant models showed independent effects of $PM_{2.5}$ and BC. Moreover, higher risks have been observed for children.

Conclusions: We observed clear associations with $PM_{2.5}$ but UFP or PNC did not show a clear association across different exposure windows and cause-specific hospital admissions. Further multi-center studies are needed using harmonized UFP measurements to draw definite conclusions on the health effects of UFP.

1. Introduction

Over the last decades, numerous epidemiological studies have investigated the effects of ambient air pollution on adverse health effects. Especially gaseous pollutants such as nitrogen dioxide (NO_2) or ozone (O_3), and particulate matter (PM) have been associated with mortality (Chen and Hoek 2020; Orellano et al., 2020) and morbidity (Atkinson et al., 2014; Brunekreef et al., 2021). Since the 1990s, the smallest size fraction of ambient particulate air pollution, the ultrafine particles (UFP), have been hypothesized to differ in risk from larger particle size fractions (HEI Review Panel on Ultrafine Particles, 2013; Stone et al., 2017). However, only a few epidemiological studies have investigated the effects of UFP on cause-specific hospital admissions.

UFP have been conventionally classified as particles with an aerodynamic diameter ≤100 nm (=0.1 μm) and originate in urban air mainly from motor traffic exhaust, several nucleation processes, and

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https://doi.org/10.1016/j.envint.2023.108032
Received 3 April 2023; Received in revised form 7 June 2023; Accepted 9 June 2023
Available online 15 June 2023

combustion in general (Morawska et al., 2008; Vu et al., 2015). They can be emitted directly as primary particles by combustion processes in, e.g., engines or formed as secondary particles by photochemical processes and condensation of gaseous precursors such as cooling exhaust gases (Morawska et al., 2008; Vu et al., 2015). Due to their small particle size, UFP have different physical characteristics than fine PM (PM with an aerodynamic diameter of $\leq$2.5 μm; $PM_{2.5}$). For example, they highly contribute to the particle number concentration but only marginally to total particle mass and exhibit a greater spatial variation than fine PM (HEI Review Panel on Ultrafine Particles 2013; Stone et al., 2017). Furthermore, UFP can reach the smallest regions of the respiratory tract, the alveoli. They have a high deposition efficiency and a slower respiratory tract clearance than larger particles (HEI Review Panel on Ultrafine Particles, 2013; Stone et al., 2017). Toxicological studies reported a high surface reactivity and large surface area per unit mass, enabling UFP to absorb chemical substances more easily; thus, UFP might be more hazardous than PM (Kwon et al., 2020).

To date, regulatory air quality monitoring focuses on $PM_{2.5}$ or PM_{10} (PM with an aerodynamic diameter of $\leq$10 μm) and some gaseous pollutants (e.g., NO_2 and O_3) and does not include separate monitoring of UFP. Scientific and legislative challenges result from the complexity of involved processes, the more elaborate and costly measurement techniques, and the lack of standardized measurements (Cassee et al., 2019). Furthermore, no legal monitoring obligation (due to the lack of limit values for UFP) could prompt continuous measurements of UFP at network monitoring stations (Cassee et al., 2019). As a result, UFP are measured only at a few measurement stations over a longer time.

Although the overall evidence is still conflicting and insufficient, there is evidence that suggests an effect of UFP or total particle number concentrations (PNC) on cause-specific mortality (HEI Review Panel on Ultrafine Particles, 2013; Ohlwein et al., 2019) and morbidity (HEI Review Panel on Ultrafine Particles, 2013; Samoli et al., 2020; Stone et al., 2017). Moreover, two recent systematic reviews on hospital admissions identified children as a susceptible subgroup. In particular, children with respiratory diseases might be more vulnerable to the effects of UFP exposure, and asthma exacerbation may play an important role (da Costa e Oliveira et al., 2019; Li et al., 2019). However, so far, only three larger multi-city epidemiological studies have investigated the effects of UFP on hospital admissions. Lanzinger and colleagues found the highest associations with respiratory hospital admissions for a 6-day average in UFP concentration (Lanzinger et al., 2016). Samoli and colleagues reported no association between UFP and respiratory hospital admissions, although suggestive effects were seen among younger people (0–14 years) (Samoli et al., 2020). Similar results were reported by Lin and colleagues for modeled UFP concentrations associated with cardiovascular hospital admissions in New York State, USA (Lin et al., 2022).

A recent study analyzed the adverse health effects of UFP in terms of cause-specific mortality in three German cities between 2010 and 2017 that reported a delayed increased risk of respiratory mortality following UFP exposure (Schwarz et al., 2023).

Here, we investigated the association of daily ambient UFP concentrations and PNC with cause-specific hospital admissions, using data from the same project including multiple monitoring stations per city. In addition, we assessed the effects of particle size sub-fractions within the range of 10–800 nm. Further, we performed two-pollutant models to examine whether UFP and PNC showed effects independent of other pollutants. We also assessed whether age, sex, and season modified the effects of UFP and PNC on hospital admissions.

2. Material and methods

2.1. Hospital admission data

We retrieved daily counts of hospital admissions for the study period January 1, 2010, to December 31, 2017, for the three German cities Dresden, Leipzig, and Augsburg from official statistics. Only the primary diagnosis at hospital discharge was considered. The following five hospital admission endpoints were included according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10 codes): cardiovascular diseases (I00-I99), heart diseases (I00-I52), cerebrovascular diseases (I60-I69), respiratory diseases (J00-J99), and lower respiratory tract infections (LRTI; J12-J18 & J20-J22). The raw data set was accessed via a workstation for visiting scientists at the Research Data Centre (RDC) of the Federal Statistical Office and Statistical Offices of the Federal States ([Hospital Statistics (EVAS 23131)], survey years [2010–2017], DOI: 10.21242/23131.2010.00.02.1.1.0 to 10.21242/23131.2017.00.02.1.1.0, own claculations). We selected only individuals who lived in the cities of Dresden, Leipzig, or Augsburg and were admitted to a hospital in the respective state of Saxony or Bavaria. Linkage was based on the hospital's state and the patient's official residency codes. Due to German data protection regulations, information on the hospital location is only available at the state rather than at the city levels. We assumed that people living in one city are also likely to be hospitalized in the same city/region, especially since we included only ordinary (no outpatient cases) and acute (no planned cases) hospital admissions. As a result, the final case numbers of each city represent the people living in one city that were hospitalized in the same city/region. We excluded cases hospitalized before the study period or with coded hospital admissions for which the underlying cause was unknown. In addition, the final data set also comprised information on biological sex (female, male) and age (six age categories: 0–17 years, 18–44 years, 45–64 years, 65–74 years, 75–84 years, and 85+ years). Finally, we retrieved population data for the three cities from official statistical yearbooks.

2.2. Environmental data

We obtained data from six fixed monitoring stations located in Augsburg, Dresden, and Leipzig: four urban background stations (Augsburg-Hochschule [AFH]; Dresden-Winckelmannstr. [DDW]; Leipzig-West [LWE]; Leipzig-TROPOS [LTR]), and two traffic-related stations (Dresden-Nord [DDN]; Leipzig-Mitte [LMI]). Supplementary Table 1 provides more information on the included measurement stations. We assumed that the exposure concentrations at the background stations represented the respective city populations, whereas the traffic-related stations better captured the effects of peak concentrations. All six locations contributed to the German Ultrafine Aerosol Network (GUAN) (Birmili et al., 2016), which included air pollutants not routinely monitored, such as black carbon (BC) or particle number concentrations in different size ranges (Birmili et al., 2015; Birmili et al., 2016; Sun et al., 2019). Each individual set of station-specific air pollution data was then assigned to the respective hospital admission data for the corresponding city. Using distance metrics or other exposure assignment methods was not possible because the relevant data (e.g., patient address data) were unavailable due to data protection regulations. A map of all GUAN stations, their station type, and further information on the network and the selected stations are provided in the supplement (Supplementary Fig. 1). In brief, monitoring stations met the following three criteria: i) an exposure profile representative for the urban population, ii) a sufficient number of cases in the cities, and iii) high comparability and standardization of the monitoring devices.

Number concentrations of UFP and PNC (10–800 nm) were considered exposures of primary interest. On an exploratory basis, we also analyzed size-fractioned particle number concentrations in the following ranges: 10–20 nm, 20–30 nm, 30–50 nm, 50–70 nm, and 70–100 nm and defined nucleation mode (10–30 nm; NuMP), Aitken mode (30–100 nm; AiMP), and accumulation mode particles (100–800 nm; AcMP). Black carbon (BC), nitrogen dioxide (NO_2), and fine particles ($PM_{2.5}$) were treated as exposures of secondary interest.

The setup of the monitoring devices has been described in detail elsewhere (Birmili et al., 2015; Birmili et al., 2016; Schwarz et al., 2023;

Sun et al., 2019). An overview of device characteristics at the stations can be found in Supplementary Table 2. In brief, particle size distribution (PSD) data was measured by a mobility particle size spectrometer (MPSS, TROPOS-design [manufacturer]) in the size range of 3–800 nm, with different configurations at the monitoring stations. Additional information, such as quality assurance and calibration procedures, has been published elsewhere (Pfeifer et al., 2014; Schladitz et al., 2014; Wiedensohler et al., 2012; Wiedensohler et al., 2018). BC mass concentrations were measured using multiangle absorption photometers (MAAP, Model 5012, Thermo Scientific) for the Saxon stations and an aethalometer (Type 8100, Thermo Fisher Scientific Inc.) for Augsburg. Further information on BC measurements can be found elsewhere (Birmili et al., 2015; Birmili et al., 2016) and in Supplementary Table 2. High-volume samplers (HVS, model DHA-80, DIGITEL Elektronik AG) measured $PM_{2.5}$ mass concentrations at the Saxon stations, and tapered element oscillating microbalances (TEOM, model 1400a incl. FDMS 8500, Rupprecht & Patashnick Co., and TEOM model 1405, Thermo Fisher Scientific Inc.) were used at the Augsburg site. In Augsburg, both TEOMs were equipped with a Filter Dynamics Measurement System (FDMS model 8500b, Thermo Fisher Scientific Inc.) to correct for losses of some volatile fractions of PM. Additional information on $PM_{2.5}$ and NO_2 measurements is available online at the German Environmental Agency website (https://www.env-it.de/stationen/public/open.do).

When applicable, hourly and daily averages were calculated for all air pollutants and measured meteorological variables (e.g., temperature, relative humidity, and barometric pressure) at each station if 75% of the data was available. In the main analysis, the imputation of missing data was not performed. Based on the daily averages, we calculated lagged exposure concentrations for the same day of the event (lag 0) and up to seven days before the event (lag 7). In addition, multi-day averages were calculated representing immediate (lag 0–1), delayed (lag 2–4, lag 5–7), and cumulative effects (lag 0–7). At the LTR station, only PSD and BC were available; consequently, this station was excluded from the NO_2 and $PM_{2.5}$ analyses. In addition, data on meteorology were extracted from another urban background station, LWE, showing high correlations between the two stations. NO_2 was not measured at the Augsburg station (AFH). Therefore, we selected NO_2 data from another urban background station (A-LfU: Augsburg - Bavarian State Office for the Environment) with comparable station characteristics and high correlations.

2.3. Statistical analysis

We calculated descriptive statistics for air pollutants and meteorological variables and counts of hospital admissions. Spearman correlation coefficients were used to assess temporal variations, with values $\geq$0.7 considered high correlations.

We used a two-stage modeling approach of site-specific risk estimates in the first stage and pooled estimates in the second stage to examine the association between air pollutants and cause-specific hospital admissions.

In the first stage, we calculated confounder-adjusted Poisson regression models that allow for overdispersion. A priori, we set up a general confounder model and included a log offset for annual population numbers for each station. Based on the previous UFIREG project (UFIREG Project 2014) and current literature, we included the following confounders in each site-specific model: time trend, day of the week, public holidays, vacation periods, relative humidity, and air temperature. For air temperature, we adjusted for high and low temperatures separately, according to Stafoggia et al. (2013). Briefly, this method allows for modeling different lag structures of heat and cold (Stafoggia et al., 2013). We used cubic regression splines with four degrees of freedom (DF) per year for the time trend and three DF for meteorological variables to account for non-linear confounding and temporal/seasonal variations. We focused primarily on immediate (lag 0–1), delayed (lag 2–4, lag 5–7), and cumulative (lag 0–7) effects and investigated single-lag models secondarily. We decided to use this modeling approach over distributed lag models (DLM), as multiple missing exposure data and low hospital admission counts could influence the statistical power.

In the second stage, we pooled the site-specific estimates using a novel random-effects meta-analytical method for environmental research (Sera et al., 2019; Sera and Gasparrini, 2022). This method accounted for different nested hierarchical structures of the data (e.g., geographical variation between cities and stations within a city). We included a random term for city and station and used restricted maximum likelihood (REML) estimation. Furthermore, we included the same analysis with fixed-effects models as an additional analysis. We examined potential heterogeneity among the station-specific estimates by calculating the I^2 statistic and the corresponding p-value. We considered $I^2 > 50\%$ and p-value <0.05 as substantial heterogeneity.

We performed further exploratory analyses only for the combination of air pollutants, lag structures, and hospital admission endpoints, showing the most adverse effect estimates in the main models. First, we obtained separate results for urban background and traffic-related sites to explore if the underlying exposure profiles showed different patterns. Second, we conducted two-pollutant models if the Spearman correlation coefficient between the two pollutants was less than 0.7. We included the second pollutant also as a linear term in the model and followed the general modeling strategy. Third, we examined possible effect modifications by age, sex, and season. Therefore, age- (0–17 years, 18–64 years, 65+ years) and sex-stratified (female, male) data was analyzed according to the main model. We included an interaction term to analyze the differences between warm (April-September) and cold periods (October-March). Finally, based on the literature, we used a fixed increment in air pollution concentration. This alternative standardization method facilitates comparison with the results of other epidemiological studies. We used 10,000 particles/cm^3 for all particle number concentrations (e.g., UFP or AiMP), 10 $\mu g/m^3$ for $PM_{2.5}$ and NO_2, and 1 $\mu g/m^3$ for BC mass concentrations.

2.4. Sensitivity analyses

We performed several sensitivity analyses to test the robustness of our main models.

I. We used 3 or 6 DF per year for time trend instead of 4 DF per year.
II. We increased the DF for air temperature and relative humidity terms to 5 DF (instead of 3 DF).
III. We replaced air temperature and relative humidity by apparent temperature (O'Neill et al., 2003; Wolf et al., 2009).
IV. We included barometric pressure as an additional variable in the main model.
V. We considered potential changes in hospital admissions due to influenza epidemics by including an influenza variable as an additional linear term for each city in the main model. In Germany, data on influenza epidemics data are publicly available at the Robert Koch Institute's database "SurvStat@RKI 2.0" (https://survstat.rki.de/default.aspx).
VI. For respiratory diseases (J00-J99), we excluded the following three ICD-10 codes because it could be assumed that these diagnoses involved planned hospital admissions:
    a. J32: Chronic sinusitis
    b. J34: Other diseases of the nose and paranasal sinuses
    c. J35: Chronic diseases of the palatine tonsils and pharyngeal tonsil
VII. We excluded the lower size fraction of 10–20 nm and created an alternate definition for UFP (20–100 nm) and PNC (20–800 nm). This was driven by potential measurement uncertainty in the lower range of PSD published by Wiedensohler et al. (2012).
VIII. We calculated city-specific exposure averages according to an adapted APHEA approach published by Berglind et al. (Berglind et al., 2009). Briefly, this method also included the imputation of missing values following a standardized procedure.

IX. Finally, we checked the exposure–response functions to investigate any deviations from linearity. Therefore, we replaced the linear term for the pollutant with a cubic regression spline with three DF, visually assessed the different slopes and compared the model output with a likelihood-ratio test.

To better compare the relative health effects of different air pollutants, we presented the results as percent change per interquartile range (IQR) increase in the respective pollutant along with the corresponding 95% confidence interval (CI). We provide a detailed description in the supplement together with fixed increment standardized main results. Results with a p-value less than 0.05 were considered statistically significant. All analyses and data management were performed using RStudio version 1.3.1335/1.4.1106 with R version 3.6.1/4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) and the R packages *mgcv* and *ggplot2*. The R package *mixmeta* was used for the second-stage analysis.

3. Results

3.1. Description of hospital admission data and air pollutants

The description of cause-specific hospital admissions and population numbers per city is presented in Table 1. Average daily cases ranged from 40.5 cases per day for cardiovascular hospital admissions for Leipzig to 3.2 cases per day for cerebrovascular hospital admissions for Augsburg. Table 2 describes the 24-hour-mean concentrations of air pollutants and meteorological variables; an extended version can be found in the supplement (Supplementary Table 3). The highest median UFP concentrations were measured at the traffic-related stations LMI and DDN with 10,123 particles/cm^3 and 8,637 particles/cm^3, respectively. The concentrations at the urban background stations ranged from 4,520 particles/cm^3 for LWE to 5,655 particles/cm^3 at AFH (Table 2). A similar pattern, but with higher concentrations, was observed for PNC.

Table 1
Description of the population living in one city that was hospitalized in the same city/area. N = 2922 days.

Variable	Leipzig	Dresden	Augsburg
Mean population 2010–2017	542,918	534,382	279,159
Total counts of cardiovascular disease HA.	118,265	97,508	59,230
Total counts of heart disease HA.	81,323	68,711	40,582
Total counts of cerebrovascular disease HA.	14,955	14,121	9,434
Total counts of respiratory disease HA.	51,383	45,271	38,396
Total counts of LRTI HA.	17,801	14,489	13,467
Mean daily cardiovascular disease HA. (SD)	40.5 (16.7)	33.4 (12.4)	20.3 (8.7)
Mean daily heart disease HA. (SD)	27.8 (11.2)	23.5 (8.9)	13.9 (6.3)
Mean daily cerebrovascular disease HA. (SD)	5.1 (2.6)	4.8 (2.4)	3.2 (2.0)
Mean daily respiratory disease HA. (SD)	17.6 (7.8)	15.5 (6.6)	13.1 (7.0)
Mean daily LRTI HA. (SD)	6.1 (3.4)	5.0 (3.0)	4.6 (2.9)

N: Number of days with valid data; HA: Hospital admission; SD: Standard deviation; LRTI: Lower respiratory tract infections; Population data based on official statistical yearbook of the cities, own calculations; Cardiovascular disease: ICD-10: I00-I99; Heart disease: ICD-10: I00-I52; Cerebrovascular disease: ICD-10: I60-J69; Respiratory disease: ICD-10: J00-J99; LRTI disease: ICD-10: J12-J18 & J20-J22; Source: Research Data Centre of the Federal Statistical Office and Statistical Offices of the Federal States ([Hospital Statistics (EVAS 23131)], survey years [2010–2017], DOI: 10.21242/23131.2010.00.02.1.1.0 to 10.21242/23131.2017.00.02.1.1.0, own claculations).

Compared to the routinely monitored air pollutants NO_2 and $PM_{2.5}$, the particle number concentrations and BC exhibited a higher percentage of missing values.

UFP and PNC were highly correlated (correlation coefficients between 0.96 and 0.98) but showed mostly weak to moderate correlations with the other pollutants and meteorological variables (Supplementary Table 4). In addition, UFP and PNC were moderately correlated between stations, with a clear pattern observed indicating higher correlations between stations for larger particle size fractions and $PM_{2.5}$ (Supplementary Table 5). Compared to UFP, higher correlations between PNC and BC, NO_2, and $PM_{2.5}$ were observed.

3.2. Air pollution and cause-specific hospital admissions

Fig. 1 (and Supplementary Table 6) displays the results of the pooled main models. UFP or PNC did not show a clear pattern across different exposure windows and hospital admission endpoints. However, results suggested a slight increase in cardiovascular hospital admissions and hospital admissions for heart diseases on the same day or one day after UFP exposure (lag 0–1). An interquartile range increase of 3,420 particles/cm^3 in UFP concentration resulted in a 0.43% [95% CI: −0.25%; 1.12%] higher risk of cardiovascular hospital admissions (I^2 = 30.60%, p = 0.206). The effects of UFP on respiratory hospital admissions showed a delayed pattern with a 0.69% [95% CI: −0.28%; 1.67%] increased risk per 3,220 particles/cm^3 2 to 4 days after exposure (I^2 = 25.10%, p = 0.246). Comparable results were observed for PNC. For cerebrovascular hospital admissions and LRTI hospital admissions, mostly null results were seen.

We observed clearer association patterns for size-fractioned exposures (Fig. 2 and Supplementary Table 7). Results indicated increases in cardiovascular hospital admissions, hospital admissions for heart diseases, and respiratory hospital admissions in association with delayed and cumulative exposures to particles in the Aitken mode size ranges (NC 50–70 nm and NC 70–100 nm). In addition, we observed immediate, delayed, and cumulative pattern effects of particles in the accumulation mode (e.g., lag 0–7: cardiovascular hospital admissions: 1.20% [95% CI: 0.66%; 1.73%]; hospital admissions for heart diseases: 1.13% [95% CI: 0.54%; 1.72%]). For respiratory hospital admissions, an increase in risk was observed for larger size fractions 2 to 4 days after exposure (e.g., AcMP 1.55% [95% CI: 0.86%; 2.25%]), but size fractions in the ultrafine range also indicated higher risks (e.g., NC 70–100 nm 1.37% [95% CI: −0.24%; 3.00%]). For cerebrovascular hospital admissions, results indicated immediate and cumulative patterns for accumulation mode particles, whereas for LRTI hospital admissions, mostly null results were seen.

When we used fixed-effects instead of random-effects models, the direction and effect sizes did not change substantially (see Supplementary Figs. 2 and 3 and Supplementary Tables 8 and 9). However, considerably more associations reached statistical significance indicating that our main analysis using random-effects models can be considered rather conservative in terms of model interpretation and that accounting for hierarchical structures in the data by random structures (differences within and between cities) may be useful when pooling the station-specific effects of UFPs. It is important to note that substantial heterogeneity was observed mainly for cerebrovascular hospital admissions, cardiovascular hospital admissions and particles in the nucleation mode, or respiratory hospital admissions and particle size fractions in the Aitken mode (Supplementary Tables 8 and 9).

Single-lag and station-specific results for respiratory and cardiovascular hospital admissions can be found in Supplementary Fig. 4 and Supplementary Table 10. The results generally showed higher risks at lag 2 or lag 3 for respiratory hospital admissions. For cardiovascular hospital admissions, patterns can be seen for smaller particle sizes at immediate lags (e.g., lag 0), but also for delayed lags (e.g., lag 2 or lag 6) and larger size fractions (Supplementary Fig. 4). In addition, the results were mainly influenced by the Leipzig stations (Supplementary

Table 2
Basic descriptive statistics of air pollution and environmental data per measurement station.

Variable	N_{days}	Min.	Max.	Mean	SD	Median	IQR
UFP (10–100 nm, n/cm^3)							
LMI	2,279	2,212	35,987	10,747	4,172	10,123	5,156
LWE	1,787	931	21,681	5,126	2,619	4,520	3,003
LTR	2,668	798	32,917	5,469	2,881	4,839	3,154
DDN	2,287	2,100	24,781	9,128	3,436	8,637	4,366
DDW	2,211	705	22,526	5,341	2,754	4,791	3,156
AFH	2,392	953	49,075	6,366	3,621	5,655	3,514
PNC (10–800 nm, n/cm^3)							
LMI	2,279	2,632	38,180	12,590	4,692	11,922	5,866
LWE	1,787	1,288	23,362	6,265	2,886	5,748	3,482
LTR	2,668	1,054	34,927	6,703	3,231	6,054	3,686
DDN	2,287	2,450	30,684	10,912	3,924	10,292	4,975
DDW	2,211	941	24,714	6,714	3,184	6,186	3,902
AFH	2,392	1,214	51,597	7,668	4,113	6,909	4,017
BC (μg/m^3)							
LMI	2,499	0.4	10.9	2.3	1.2	2.0	1.3
LWE	2,067	0.1	10.1	1.0	0.9	0.8	0.8
LTR	2,807	0.0	12.6	1.0	1.0	0.7	0.8
DDN	2,693	0.3	11.5	1.8	1.0	1.5	1.1
DDW	2,057	0.1	7.4	0.9	0.7	0.7	0.8
AFH	2,644	0.5	10.5	1.7	1.0	1.4	1.0
NO_2 (μg/m^3)							
LMI	2,886	11.0	100.0	44.0	12.7	43.0	17.0
LWE	2,896	3.0	66.0	17.6	8.9	16.0	11.0
LTR*	0	–	–	–		–	
DDN	2,874	9.0	77.0	34.2	10.4	33.0	14.0
DDW	2,890	3.0	72.0	20.2	9.5	18.0	12.0
AFH	2,212	2.5	84.0	19.8	10.2	17.7	12.3
$PM_{2.5}$ (μg/m^3)							
LMI	2,891	2.2	120.8	17.5	13.0	13.6	12.2
LWE	2,885	1.0	111.2	13.5	12.0	9.6	10.5
LTR*	0	–	–	–		–	
DDN	2,900	1.9	137.8	16.2	12.6	12.3	11.6
DDW	2,892	0.5	136.4	15.1	12.9	10.9	12.3
AFH	2,922	1.1	98.7	13.0	10.3	10.2	10.3
Air temperature (°C)							
LMI	2,911	−14.0	32.1	11.7	8.0	11.4	12.1
LWE	2,919	−15.0	29.2	9.9	7.7	9.7	11.7
LTR*	0	–	–	–		–	
DDN	2,915	−14.2	31.8	11.4	8.1	11.3	12.5
DDW	2,922	−13.4	31.0	11.6	8.0	11.6	12.4
AFH	2,803	−13.4	28.9	9.9	7.9	9.9	12.3
Relative humidity (%)							
LMI	2,909	34.5	98.5	70.9	12.6	71.8	19.6
LWE	2,905	37.5	100.0	74.2	12.2	75.3	18.6
LTR*	0	–	–	–	–	–	
DDN	2,915	37.5	100.0	70.6	11.4	70.9	16.8
DDW	2,922	36.0	97.2	70.8	11.4	71.8	17.3
AFH	2,803	39.6	100.0	77.8	12.7	79.2	20.3
Barometric pressure (hPa)							
LMI	2911	975.0	1040.0	1015.8	8.1	1016.0	10.0
LWE	2919	975.0	1041.0	1016.1	8.3	1016.0	10.0
LTR*	0	–	–	–	–	–	–
DDN	2915	976.0	1042.0	1016.2	8.2	1016.0	10.0
DDW	2922	976.0	1041.0	1016.0	8.0	1016.0	10.0
AFH	2803	923.9	984.5	961.0	7.4	961.4	9.0

N_{days}: Number of days with valid data; Min.: Minimum; Max.: Maximum; SD: Standard deviation; IQR: Interquartile range; UFP: Particle number concentration of particles in the ultrafine range (10–100 nm); LMI: Leipzig-Mitte; LWE: Leipzig-West; LTR: Leipzig-TROPOS; DDN: Dresden-Nord; DDW: Dresden-Winckelmannstr.; AFH: Augsburg-Hochschule; PNC: Total particle number concentration (10–800 nm); BC: Black carbon; NO_2: Nitrogen dioxide; $PM_{2.5}$: Particulate matter with an aerodynamic diameter $\leq$ 2.5 μm; °C: Degree Celsius; hPa: hectopascal. *: No data available.

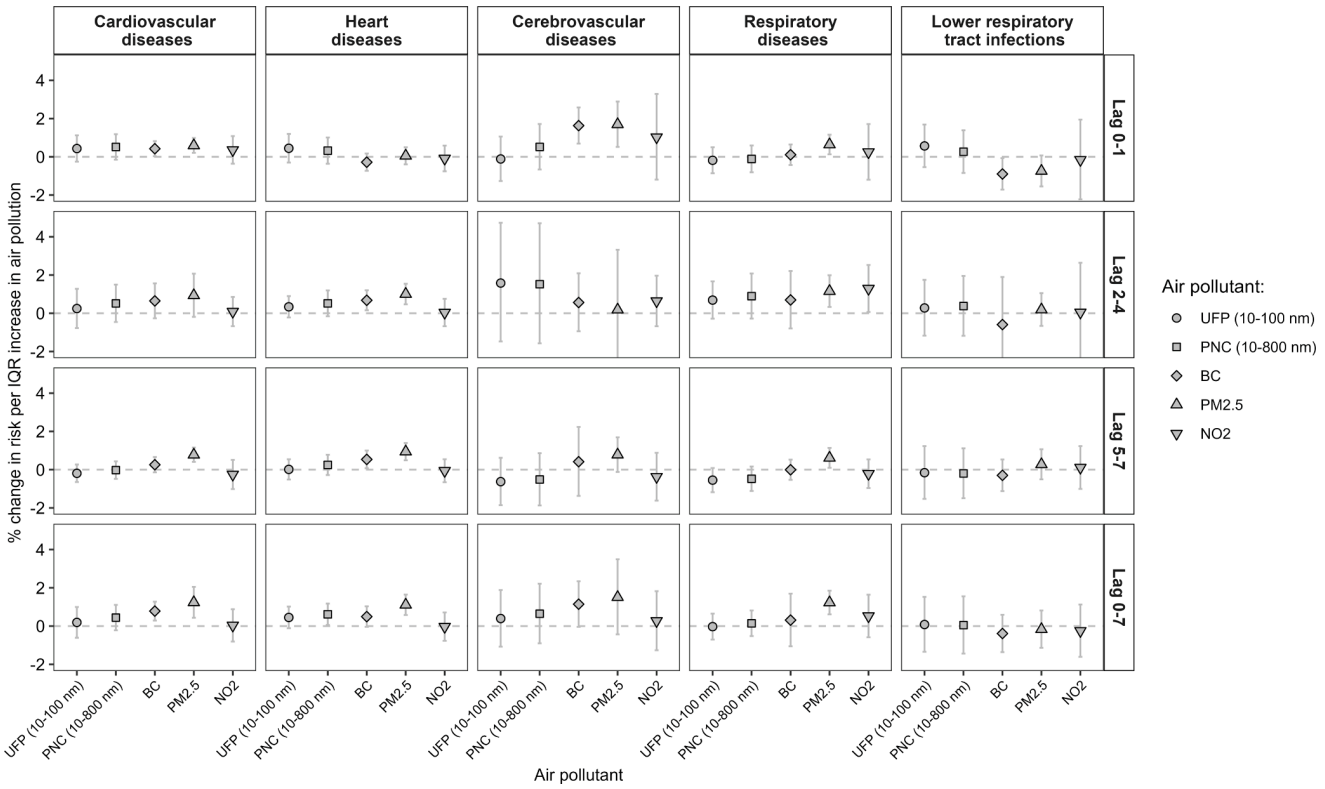

Fig. 1. Percent changes in the relative risk and 95% confidence interval per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increases in air pollutants for cardiovascular disease- (left), heart disease- (second from left), cerebrovascular disease- (middle), respiratory disease- (second from right), and lower respiratory tract infection hospital admission (right). Standardization by IQR facilitates comparison between different pollutants. The x-axis and the shape show the type of pollutant. The y-axis represents the percent change of risk per interquartile range increase in air pollution concentration (left side) per average lag concentration of air pollutants (right side). All estimates represent the pooled analysis of the measurement stations using multi-level random-effects models, adjusted for main model covariates.

Table 10). Furthermore, an exploratory comparison of risks between urban background and traffic-related stations indicated comparable results, although the results indicated slightly higher associations at the traffic-related stations (Supplementary Figure 5 and Supplementary Table 11).

For both BC and $PM_{2.5}$, we found the most consistent associations with cause-specific hospital admissions for cardiovascular and cerebrovascular hospital admissions in association with immediate (lag 0–1) exposures, and for cardiovascular hospital admissions and hospital admissions for heart diseases for delayed (lag 5–7) and cumulative (lag 0–7) exposures. For example, an increase of 0.77 μg/m^3 in BC (lag 0–7) was associated with a 0.78% [95% CI: 0.29%; 1.27%] higher risk of cardiovascular hospital admissions (Fig. 1 and Supplementary Table 6). All four $PM_{2.5}$ average lags were associated with respiratory hospital admissions (e.g., lag 2–4: 1.16% [95% CI: 0.33%; 1.99%]), showing consistent results with the association patterns for the larger particle size fractions. NO_2 was not associated with any cause-specific hospital admissions, except for respiratory hospital admissions at lag 2–4, where an increase of 11.00 μg/m^3 was associated with a 1.29% [95% CI: 0.07%; 2.52%] higher risk (Fig. 1 and Supplementary Table 6).

3.3. Two-pollutant models and effect modification

We examined two-pollutant models and effect modification analyses for the combination of UFP exposure, average lag concentration, and hospital admission endpoint, for which the most consistent and strongest results were found in the main analysis. Fig. 3 and Supplementary Table 12 provide an overview of the results. The UFP effects on respiratory hospital admissions (lag 2–4) remained relatively stable and unchanged after additional adjustments for BC or $PM_{2.5}$. In particular, for $PM_{2.5}$, the smaller confidence intervals suggested independent, although insignificant, results. Further adjustment for NO_2 resulted in lower effect estimates and null effects. However, high correlations between UFP and NO_2 at station Leipzig-Mitte (LMI) restricted us from including this station in the pooled analysis.

There were no substantial differences in risks between women and men. For respiratory hospital admissions, higher risks were indicated for the younger age groups. Although not significant, children and adolescents had the largest point estimates for UFP exposure (age 0–17: 2.54% [95% CI: −0.47%; 5.63%] vs. age 65+: −0.19% [95% CI: −1.11%; 0.75]). An increase in the UFP concentration by 3,220 particles/cm^3 resulted in a 1.47% [95% CI: 0.25%; 2.70%] higher risk for respiratory hospital admissions in the cold season (Oct.-Mar.) (vs. Apr.-Sep.: −0.54% [95% CI: −1.55%; 0.48%]; Fig. 3 and Supplementary Table 12). In general, PNC showed comparable results for the two-pollutant and effect modification analyses. An alternative standardization with fixed-unit increments can be found in Supplementary Table 13 and 14, and Supplementary Figs. 6 and 8.

3.4. Sensitivity analysis

The results of the sensitivity analysis can be found in Fig. 4 and in the supplement and are presented again for the combination of UFP exposure, hospital admission endpoint, and average lag concentration with the most consistent and strongest results in the main analysis. Adjusting the model parameters did not substantially change the results, although setting the degrees of freedom for the long-term trend to three led to higher and significant results (Fig. 4). Similarly, we observed no changes when additionally adjusting for influenza, barometric pressure, or apparent temperature in the main model. The exclusion of three ICD-10

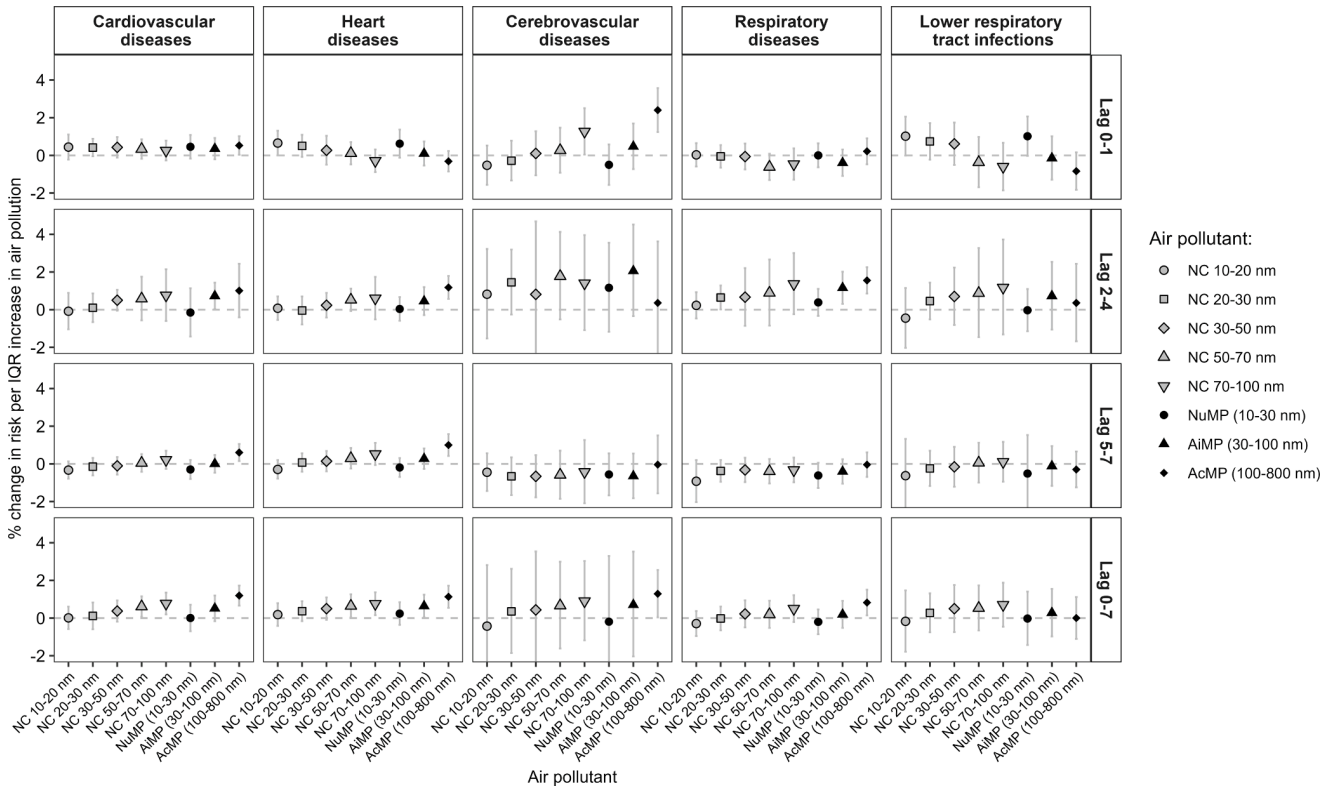

Fig. 2. Percent changes in the relative risk and 95% confidence interval per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increases in air pollutants for cardiovascular disease- (left), heart disease- (second from left), cerebrovascular disease- (middle), respiratory disease- (second from right), and lower respiratory tract infection hospital admission (right). Standardization by IQR facilitates comparison between different pollutants. The x-axis and the shape show the type of pollutant. The y-axis represents the percent change of risk per interquartile range increase in air pollution concentration (left side) per average lag concentration of air pollutants (right side). All estimates represent the pooled analysis of the measurement stations using multi-level random-effects models, adjusted for main model covariates.

codes (potentially representing planned hospital admissions) yielded similar results. When an alternate definition for UFP or PNC was used (setting the lower cut-off values from 10 nm to 20 nm), the results changed only marginally from 0.69% [95% CI: −0.28%; 1.67%] (UFP 10–100 nm) to 0.90% [95% CI: −0.68%, 2.50%] (UFP 20–100 nm; Supplementary Table 15). Nevertheless, there was significant heterogeneity between the stations, particularly for lag 2–4 and respiratory hospital admissions (Supplementary Table 15). City-specific average concentrations generally resulted in smaller effect sizes and wider confidence intervals, although most results were comparable, especially for the larger particle size fractions and $PM_{2.5}$ (Supplementary Figure 9). Visual inspection of the exposure–response function showed no major deviations from linearity, although a likelihood-ratio test indicated significant differences between the linear and nonlinear models for the stations LWE and AFH (Supplementary Figure 10).

4. Discussion

This time-series analysis found no clear association between UFP or PNC and five cause-specific hospital admission endpoints. However, the results suggested delayed patterns for respiratory hospital admissions 2 to 4 days after exposure. Size-fractioned analyses showed more pronounced delayed and cumulative effects of Aitken mode and accumulation mode particles on cardiovascular hospital admissions, hospital admissions for heart disease, and respiratory hospital admissions, and the most consistent results for the larger particles $PM_{2.5}$. At the same time, more immediate patterns were found for smaller fractions. The results indicated higher risks for children and adolescents compared to the elderly, and higher risks in the cold season compared to the warm season, whereas the risk was comparable for men and women. Further adjustment for $PM_{2.5}$ and BC did not change the results for respiratory hospital admissions; adjustment for NO_2 led to null results.

To date, there is still limited evidence on UFP or PNC effects on hospital admissions, and only two multi-center studies have investigated this research question. A study conducted in five northern and southern European cities (Samoli et al., 2016a) reported no clear association between UFP exposure and respiratory hospital admissions. However, higher delayed risks were found for pooled single lags 3, 5, and 6, although significant heterogeneity was observed (e.g., lag 3 and respiratory HA: 0.43% [95% CI: −0.94%; 1.83%]) (Samoli et al., 2016a). In addition, point estimates increased when cities with no measured accumulation mode particles were excluded, although they remained insignificant (Samoli et al., 2016a). This observation is consistent with our findings of stronger effects for larger particle size fractions, especially for accumulation mode particles. Despite some methodological differences between our study and the study by Samoli and colleagues (e.g., different statistical methods, lag periods, or study area), we found comparable results that overall suggest patterns of delayed UFP effects on respiratory hospital admissions. In addition, both analyses suggest that the strongest effects are seen in children. Another multi-city study in five central and eastern European countries (Lanzinger et al., 2016) found a higher risk of respiratory hospital admissions, most strongly for a 6-day average UFP exposure. An increase of 2,750 particles/cm^3 was associated with a 3.40% [95% CI: −1.70%; 8.80%] increase in the risk of respiratory hospital admissions. Effects were generally higher for PNC, and no clear association was observed for cardiovascular hospital admissions (Lanzinger et al., 2016). Two stations of the study by Lanzinger et al. were also part of our study (AFH and DDW). We saw comparable results, although with smaller effect sizes but higher precision (narrower confidence intervals), probably due to the longer time series. However,

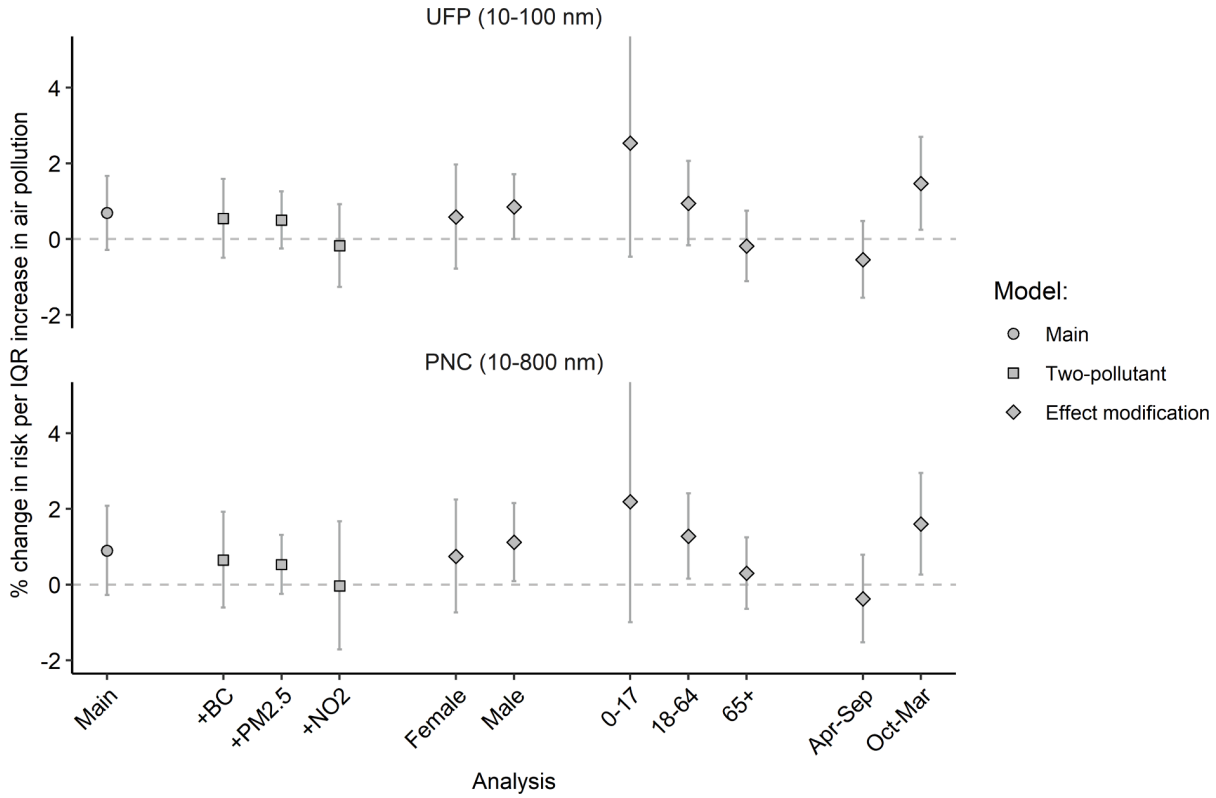

Fig. 3. Percent changes in the relative risk of respiratory hospital admission and 95% confidence intervals per interquartile range increases in ultrafine particles (10–100 nm; UFP; top panel) and total particle number concentrations (10–800 nm; PNC; bottom panel) (Lag 2–4). The x-axis shows the results for the main (displayed as dot), two-pollutant (displayed as rectangle), and effect modification analysis (displayed as diamond). The y-axis represents the percent change of risk per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollution concentration. Standardization by IQR facilitates comparison between different pollutants. All estimates represent the pooled analysis of the measurement stations using multi-level random-effects models, adjusted for main model covariates. It should be noted that for the two-pollutant models $PM_{2.5}$ and NO_2, the station Leipzig-TROPOS was not included in the model (no air pollution data). Additionally, the station Leipzig-Mitte was not included in the NO_2 model because Spearman correlation coefficients were above 0.7.

compared to our analysis, this study used 20 nm as lower cut-off value for defining UFP exposure, different exposure lags, and stations. We cannot exclude that the particle chemical composition changed maybe being partially responsible for the differences in effect estimates.

Other studies have investigated the effects of UFP in single cities. Branis and colleagues reported for Prague, Czech Republic, increasing risks of cardiovascular and respiratory hospital admissions for several particle sizes fractions (Braniš et al., 2010). The highest risks were observed for an eight-day average of particles in the accumulation mode. An increase of 1,000 particles/cm^3 was associated with a RR of 1.33 [95% CI: 1.13; 1.58] and 1.16 [95% CI: 1.05; 1.29], for respiratory and cardiovascular hospital admissions, respectively. In addition, effects were also present at more immediate lags (lag 0, 1), particularly for cardiovascular hospital admissions or Aitken mode particles (Braniš et al., 2010). However, a different exposure assessment, a shorter time series of less than one year, and a different region must be considered when comparing the results of Branis and colleagues with our results. A study conducted in London, UK, found higher but insignificant results for PNC, indicating stronger effects on pediatric respiratory hospital admissions (Samoli et al., 2016b). For respiratory hospital admissions, the authors reported a percent change in RR of 1.86% [95% CI: −0.28%; 4.05%] per IQR increase of PNC. Cardiovascular hospital admissions also showed positive but insignificant results (Samoli et al., 2016b). However, the time series included only the years 2011–2012, and different methods make it difficult to compare the results consistently to our study.

Our analysis observed different risk patterns for different particle size fractions. Generally, larger particle size fractions showed stronger delayed risks, highest for Aitken mode and accumulation mode particles (Fig. 2). These results are supported by the consistent results for $PM_{2.5}$. $PM_{2.5}$ represents the largest particles in our analysis, and although they are measured differently (mass concentration, not particle number concentration), we were able to validate our results showing the larger effects on hospital admissions for the larger particles. In contrast, for cardiovascular hospital admissions and hospital admissions for heart disease, we also found indications of immediate effects, but for smaller particle size fractions. Two studies using size-resolved particle metrics in Beijing, China, and Prague, Czech Republic, also found higher risks for larger particle size fractions with the strongest associations for accumulation mode particles (Braniš et al., 2010; Leitte et al., 2011). However, Branis and colleagues also reported associations between nucleation mode particles and respiratory hospital admissions (Braniš et al., 2010), which we did not observe in our study. Nevertheless, different size classifications (e.g., NuMP: 14.6–48.7 nm vs. 10–30 nm) make it difficult to compare the results consistently, because even small changes in cut-off values can have large effects on particle number (especially in the lower size range). A short-term study from Beijing, China, found significantly higher risks of cardiovascular emergency room visits in association with an 11-day moving average for the size fraction of 10–30 nm and 30–50 nm but no significant effects for shorter exposure lags or larger particle size fractions (Liu et al., 2013). Interestingly, we found significant heterogeneity in the smaller size fractions (e.g., cardiovascular hospital admissions and the size fraction of 10–30 nm; respiratory hospital admissions and the fraction 50–70 nm, Supplementary Table 7), triggered by the Augsburg results (data not shown). Using fixed-effects models (that consider less the heterogeneity

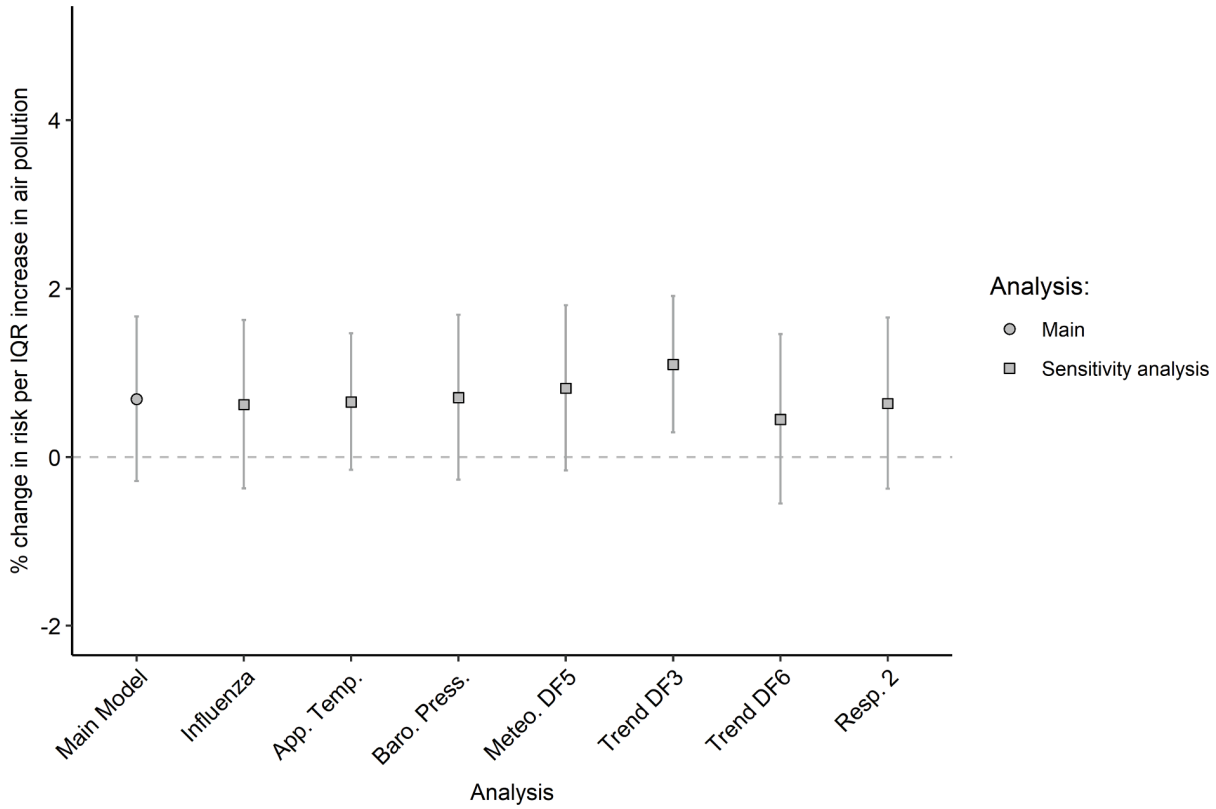

Fig. 4. Percent changes in the relative risk of respiratory hospital admissions and 95% confidence interval per interquartile range increases in ultrafine particles (10–100 nm; UFP) (Lag 2–4). The x-axis shows the results of the main model (displayed as dot) and different sensitivity analysis (displayed as rectangle). The y-axis represents the percent changes of risk per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollution concentration. Standardization by IQR facilitates comparison between different pollutants. All estimates represent the pooled analysis of the measurement stations using multi-level random-effects models, adjusted for main model covariates.

between the stations) also showed associations for particles in the Aitken mode size range (Supplementary Fig. 3 and Supplementary Table 9). Unfortunately, we could not validate this issue with data from another region and therefore highlight the suggestive character of our findings. We can only hypothesize that different prevailing exposure sources could cause these differences. This would fit with the wider range of UFP particles, and the higher median concentrations observed in Augsburg, possibly indicating different sources (Table 2). In the study by Samoli and colleagues, source apportionment (via Positive Matrix Factorization) was used to identify four best-fit profiles of PSD origin (Samoli et al., 2016b). However, no significant associations were found for age-segregated cardiovascular or respiratory hospital admissions (Samoli et al., 2016b). Nevertheless, a higher risk was reported for traffic-related sources and cardiovascular hospital admissions (Lag 1; age 15–64 years) and for nucleation or urban background sources (Lag 2; age 0–14 years) and respiratory hospital admissions. Traffic-related sources had a distribution mode of around 30 nm, whereas regional nucleation and urban background sources showed modes around 20 nm and 70 nm, respectively (Samoli et al., 2016b). However, our study could only hypothesize different sources according to particle size because no source apportionment was conducted.

Only a few studies reported potential effect modification, primarily investigating differences between age categories. Three short-term studies (Belleudi et al., 2010; Samoli et al., 2016a; Samoli et al., 2016b) and two systematic reviews (Ohlwein et al., 2019; Samoli et al., 2020) reported higher respiratory hospital admissions of different causes for younger people, especially children. Our results are consistent with those findings, indicating the highest risk in the age category 0–17 years. Children spend more time active and outdoors and are therefore more exposed to air pollution (Bateson and Schwartz, 2007). Moreover, early-life developmental differences such as an immature immune system or different breathing patterns may make children more vulnerable than older people (Bateson and Schwartz, 2007). In contrast, Lanzinger and colleagues reported a higher risk for older people (Lanzinger et al., 2016). Higher risks of cause-specific hospital admissions have been reported for the warmer season (Ohlwein et al., 2019; Samoli et al., 2016a; Samoli et al., 2020). Our results showed no significant effect modification by temperature, although the cold season indicated stronger effects. A similar finding was observed by Lanzinger and colleagues (Lanzinger et al., 2016). A possible explanation could be differences in the exposure mix, a more substantial influence of lower temperatures, or less dilution of the air in the atmosphere. In particular, meteorological variables seem to play a role in particle formation processes for traffic-generated particles, and concentrations might be higher in the cold season (Vu et al., 2015). Finally, we did not find differences between men and women. Only one multi-city study investigated modifying effects of sex, observing comparable results between men and women (Lanzinger et al., 2016), similar to our findings.

Until today, it remains controversial whether the adverse health effects of ultrafine particles occur independently of those of fine particles. Although UFP/PNC represents a subfraction of $PM_{2.5}$, sources and temporal-spatial patterns may differ. As a result, high UFP/PNC concentrations do not mean high $PM_{2.5}$ concentrations (and vice versa), leading to limited representativeness and almost no relationship between the two quantities (de Jesus et al., 2019). Our results suggest independent UFP effects of other particulate air pollutants (e.g., $PM_{2.5}$ and BC) because the effects did not change substantially, and the confidence interval for $PM_{2.5}$ narrowed slightly. However, the interpretation of results from two-pollutant models is not intuitive and straightforward, especially when air pollutants share similar primary

sources and therefore could reflect more general effects of, e.g., combustion-related exposure mixtures. However, we did not see high correlations between the pollutants that would affect the correct attribution of the observed effects. In addition, although some pollutants have similar sources, they could differ in terms of characteristics, such as chemical composition. Nevertheless, without further investigation and characterization of UFP, we cannot exclude the possibility that our findings for UFP are influenced by other factors of air pollution or residual confounding. Further adjustment for NO_2 resulted in null results and thus increased uncertainty. This observation would support the assumption that UFP may be more closely linked to traffic-related exposures such as NO_x or CO (Cassee et al., 2019) and highlights the potential importance of considering traffic-related factors when examining the health effects of UFP in populations. Recently, a review concluded that NO_2 adjustment had the most pronounced effect on UFP effects when adjusting for other co-pollutants (Ohlwein et al., 2019). High correlations and similar distribution patterns of UFP with other pollutants from the same source may lead to more unstable models and more biased effect estimates (e.g., multicollinearity or methodological issues) (Ohlwein et al., 2019). In addition, effect transfer could be present in multi-pollutant models when measurement error is present, leading to a higher attenuation of effects estimates for the pollutant with the higher error (Evangelopoulos et al., 2021). Future research could address this issue by implementing chemical composition or source-specific analyses in large epidemiological contexts with multiple monitoring stations per city. In addition, spatiotemporal modeling of UFP could contribute to more comprehensive and personalized exposure assessment. However, the high spatial variability of UFP and the simultaneous presence of multiple pollutants remains a challenge and a target for future research. For example, a recent study in the New York State, USA, reported delayed adverse effects of modeled UFP concentrations on cardiovascular hospital admissions, although concerns on the model resolution accuracy remains (Lin et al., 2022).

In the analysis by Samoli and colleagues, different effects on pediatric respiratory hospital admissions were observed for urban background particles (0.51% [95% CI: −1.39%; 2.45%]) compared with traffic sources (-0.20% [95% CI: −2.38%; 2.03%]) (Samoli et al., 2016b). On an exploratory basis, our analysis compared risks for two different underlying exposure patterns (urban background vs. traffic-related). In general, we found mostly comparable results between station types, although the analyses with traffic-related stations yielded slightly higher risk estimates. However, concentrations at urban background stations are assumed to better represent a city's population. In addition, to account for peak concentrations in pollutant levels more accurately, we included LMI and DDN as two traffic-related stations. However, a different local exposure composition could influence the estimates between, but also within, a city. For example, nucleation events or the formation of new particles can occur in locations with high solar irradiation, contributing notably to the PSD. For future research, this differentiation between station types may provide additional insights in situations where source apportionment is not possible, but the results need to be interpreted cautiously. To date, measurement of PSD has usually been conducted at sites where measurement infrastructure is already in place (e.g., routine monitoring of $PM_{2.5}$ or NO_2). However, it is unclear whether these locations are also adequate to represent the risk of spatially variable exposures such as UFP to the population. If future research consolidates evidence of adverse UFP effects independent of fine PM, current regulatory air quality monitoring standards would no longer be adequate. These inherently assume a good representation of UFP health effects by monitoring mass concentrations of the larger PM fraction (e.g., $PM_{2.5}$ and PM_{10}).

Three main potential pathways are hypothesized that, in combination, could promote adverse health effects of particulate air pollution (Rückerl et al., 2011). First, changes in cardiac autonomic tone are generally the first and most immediate response to the inhalation of air pollution and involve multiple reflex arcs (Perez et al., 2015). These alterations are directly triggered by stimulated neuronal reflexes that lead to changes in cardiac autonomic regulation (Rückerl et al., 2011). Second, after inhalation, UFP can enter the interstitium by transcytosis across epithelial cells of the alveoli and eventually enter the circulation, where they translocate from the lung throughout the body to distant non-pulmonary regions (Oberdörster et al., 2005; Rückerl et al., 2011). UFP can absorb toxic chemical compounds more easily because of their large surface area per unit mass and surface reactivity (Kwon et al., 2020). These substances can be transported throughout the body, leading to further damage. Third, subclinical systemic responses such as the release of pro-oxidative and pro-inflammatory mediators can be induced, leading to several inflammatory processes throughout the body, promoting endothelial dysfunction, a pro-coagulation state, and triggering pro-thrombotic effects (Brook et al., 2010; Rückerl et al., 2011).

In general, the epidemiological evidence can only provide rather suggestive evidence for cause-specific hospital admissions (except for the more consistent findings for children and larger particles such as $PM_{2.5}$). However, clinical relevance is given, as adverse health effects may already occur at a subclinical state (e.g., heart rate variability or systemic inflammation) and studies have already shown associations with UFP (Ohlwein et al., 2019).

5. Strengths and limitations

This study represents one of the so far few carefully designed multi-city studies implementing a harmonized exposure design over eight consecutive years. The GUAN and its operators ensured a high degree of standardization to measure PSD data with routine calibration and maintenance procedures of all devices. To our knowledge, for the first time in a multi-city epidemiological context, we included and compared monitoring stations with different exposure settings to better capture peak concentrations and thus more adequately represent the exposure situation in the cities. We thoroughly adjusted for confounders to rule out influences from time trends or meteorological variables, e.g., using apparent temperature as an alternative measure of the thermal environment does not lead to different results. A large number of sensitivity analyses demonstrated the robustness and conservativeness of our main results with respect to changes in the model. Several limitations must be acknowledged. First, as we performed multiple analyses, we cannot rule out that some of our results may have been caused by chance. As seen for additional NO_2 adjustment or adjustment for time trend with fewer degrees of freedom, residual confounding could be present, especially when originating from similar sources, as real-world air pollution is a complex mixture of different particles and gases. In general, the possibility of residual confounding cannot be ruled out because of the complex nature of UFP and the observational study design itself. Second, we did not have source-specific information on different air pollutants and could only assume their origin using particle size fractions, different particle size modes, or station types. In addition, local exposure compositions or influences (e.g., nucleation events or prevailing exposures in warm or cold period) may play an important role that will only be accurately characterized with further source or composition analyses. Therefore, it remains an open question whether the observed health effects are due to the particle number concentration per se, and a more detailed characterization of the PSD is needed to further investigate this issue. Schmid and Stoeger highlighted that surface area might play an important biological role, as it represents the area where other molecules can interact with tissues or fluids (Schmid and Stoeger, 2016). However, to optimally display the related aerosol exposure risk, multiple dose metrics should be included in analyses (Schmid and Stoeger, 2016). Third, unlike $PM_{2.5}$, UFP exhibits a higher spatial and temporal variation, which can lead to measurement error or exposure misclassification and limit the statistical strength of the association, especially when monitoring campaigns are adapted from those of larger and, therefore, more spatially homogeneous particles (HEI Review Panel on

Ultrafine Particles, 2013). This would be even more prominent if only one station were used to assess the exposure risk for an entire city. However, a study by Cyrys and colleagues (Cyrys et al., 2008) showed for Augsburg, Germany, that one carefully selected urban background station can adequately characterize the temporal variation in a city. However, we included only six stations, which may result in a lack of statistical power, e.g., the number of cities may not be sufficient to detect health effects for the smallest particles, and we did not statistically correct for measurement error and its potential impact on the results (van Smeden et al., 2019). In addition, a more in-depth consideration of potential measurement error, especially in multi-pollutant models, can help to quantify the health effects and interdependency of different air pollutants more correctly since effect transfer could occur leading to an underestimation of the true independent health effect for the pollutant with the higher measurement error (Evangelopoulos et al., 2021). Fourth, the number of cases in the population for some cause-specific endpoints were rather low (e.g., cerebrovascular hospital admissions), although no large uncertainty was seen in the confidence intervals. In addition, due to data protection regulations, the exact location of each hospital admission was not available. We therefore had to assume that individuals living in a city were likely to be hospitalized in the same city/region, leading to only a small degree of uncertainty. Last, only German locations were included, which should be considered when comparing the results with other studies. For example, meteorological or climatic conditions could have an influence on ambient UFP concentrations (e.g., wind speed or precipitation), calling for further multi-country or multi-city studies.

6. Conclusion

In summary, this time series analysis found no clear pattern of associations for UFP or PNC with cause-specific hospital admissions. However, we found clear associations for $PM_{2.5}$ and suggestive delayed effects were seen for respiratory hospital admissions and multi-day averages of 2 to 4 days. In addition, the effects of different particle size fractions seemed to be larger for Aitken mode particles and strongest for accumulation mode particles, which is in line with the findings for $PM_{2.5}$. Furthermore, children showed the highest risk with respect to UFP exposure and higher effects were seen in the cold season. Different methodological approaches for exposure and statistical assessment (e.g., measurement routines, devices, lag structures, and classification of particles) and the overall still scarce evidence contribute to difficulties in assessing the overall evidence. Future research would greatly benefit from further standardization of methods; first, initial recommendations were published by the World Health Organization in 2021 (see “Good practice statement – UFP” (World Health Organization, 2021)).

Funding:

This work was supported by grants from the Saxon State Office for Environment, Agriculture and Geology (LfULG), Dresden, Germany.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Acknowledgements

Source for hospital admission data: RDC of the Federal Statistical Office and Statistical Offices of the Federal States, Hospital Statistics [EVAS 23131], survey years [2010-2017], DOI: 10.21242/23131.2010.00.02.1.1.0 to 10.21242/23131.2017.00.02.1.1.0, own calculations.

The authors thank Karen Meyer (Research Data Centre of the Federal Statistical Office and Statistical Offices of the Federal States (FDZ), Fürth, Germany) for support with the hospital admission data. We thank Maik Merkel (Leibniz Institute for Tropospheric Research (TROPOS), Leipzig, Germany) for providing data of Leipzig-TROPOS, and Andrea Hausmann and Gunter Löschau for advice with the study concept. Finally, we thank the editors and unknown reviewers for their thoughtful comments and suggestions on the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108032.

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Impact of ultrafine particles and total particle number concentration on five cause-specific hospital admission endpoints in three German cities

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ONLINE DATA SUPPLEMENT

SUPPLEMENTARY METHODS:

The German Ultrafine Aerosol Network (GUAN):

The GUAN project targeted the scientific investigation of atmospheric aerosol effects and covered a large number of pollutants and exceeded the legally regulated air quality measurements (e.g., measurement of soot particles and particle counts in the ultrafine size range) (Birmili et al. 2016). For stations of the urban background (LWE: Leipzig-West; LTR: Leipzig-TROPOS; DDW: Dresden-Winckelmannstr.; AFH: Augsburg Hochschule) and two traffic-related stations (LMI: Leipzig-Mitte; DDN: Dresden-Nord) were included into the analysis. Pronounced diurnal cycles and the highest numbers of traffic-related pollutants were reported at these stations (Birmili et al. 2016). The monitoring station in Augsburg was operated by Helmholtz Munich in cooperation with the University of Augsburg/WZU and the stations in Saxony by the BfUL (Betriebsgesellschaft für Umwelt und Landwirtschaft Saxony, in cooperation with TROPOS (for particle size distributions (PSD) measurements)). Further information on the GUAN project (e.g., the general concept in more detail, other monitoring stations and equipment) has been published previously and can be found elsewhere (Birmili et al. 2015; Birmili et al. 2016; Sun et al. 2019). Information can be accessed online via the GUAN project website (http://wiki.tropos.de/index.php/GUAN)

Measurement stations included in the analysis:

1. First, stations met the criteria of urban background and traffic-related settings. This was done to obtain a representative exposure assignment, since most people in Germany live in comparable urban environments. (→ Exclusion of stations in rural or mountain/alpine settings)
2. Second, we excluded stations if the underlying case number was insufficient for epidemiological analyses (low N for cause-specific hospital admission endpoints). (→ Exclusion of the cities “Annaberg” and “Langen”)
3. Third, we excluded cities in which the measurement devices were not well comparable (→ Exclusion of station “Mülheim-Styrum”) or which have a different underlying exposure setting (e.g., street canyons; → Exclusion of station “Leipzig-Eisenbahnstraße”)

Sensitivity Analyses:

Apparent temperature was calculated: *at = -2.653 + (0.994 * temp) + (0.0153 * (dp*dp))* with *at* = apparent temperature, *temp* = air temperature, and *dp* = dew point. Dew point temperature (*dp*) was calculated as:

$$\frac{1}{\frac{1}{temp + 241.413} - \frac{log_{10}(\frac{rh}{100})}{1{,}838.675}} - 241.413$$

with *temp* = air temperature and *rh* = relative humidity

The IQR corresponds to the dispersion of the middle 50% of a variable, calculate by the difference between the 75th and 25th percentile. By accounting for the spread, comparisons of relative health effects across different pollutants can be obtained. We have chosen this approach over standardization with fixed increments because the question of whether different particle sizes have different health effects has not yet been resolved. However, standardization for fixed increments is provided in the supplement.

SUPPLEMENTARY RESULTS:

Supplementary tables:

Supplementary Table 1: Description of station characteristics.

City	Station name	Measured since	Abbr.	Type	Operator	Station characteristics
Leipzig	L-Mitte	2010	LMI	Traffic-related	LfULG/BfUL	Distance to road: ~5 m, DTV: ~45,000, intersection
Leipzig	L-West	2010	LWE	Urban background	LfULG/BfUL	Park area with trees
Leipzig	L-TROPOS	1997	LTR	Urban background	TROPOS	On the roof of a three-story building, park
Dresden	DD-Nord	2002	DDN	Traffic-related	LfULG/BfUL	Distance to road: ~9 m, DTV: ~19,400, train station square
Dresden	DD-Winckelmannstr.	2010	DDW	Urban background	LfULG/BfUL	Backyard with park and parking lot
Augsburg	A-Hochschule	2004	AFH	Urban background	HMGU/University Augsburg	On the premises of the AFH, major road: ~100 m

Information based on Pausch, A. & Mühlner, M. 2020; Löschau et al. 2017; Cyrys et al. 2008 (Cyrys et al. 2008; Löschau et al. 2017; Pausch and Mühlner 2020); Abbr.: abbreviation; L: Leipzig; TROPOS: Leibniz Institute for Tropospheric Research; DD: Dresden; A: Augsburg; LfULG: Saxon State Office for Environment, Agriculture and Geology; BfUL: Betriebsgesellschaft für Umwelt und Landwirtschaft Saxony (in cooperation with TROPOS for particle number size distributions); HMGU: Helmholtz Zentrum Munich; DTV: daily traffic volume; AFH: University of Applied Sciences Augsburg.

Supplementary Table 2: Description of measurement devices per station.

Station	Type	Height of inlet above ground	Mobility particle size spectrometer	Size range	Thermo-denuder	BC instrument	BC cut-off
LMI	Portable cabin	4m	TDMPSS – TROPOS design	5-800nm	no	MAAP	PM_{10}
LWE	Portable cabin	4m	TDMPSS – TROPOS design	10-800nm	no	MAAP	PM_{10}
LTR	Portable cabin	~16m	TDMPSS – TROPOS design	5-800nm	yes	MAAP	PM_{10}
DDN	Portable cabin	4m	TMPSS – TROPOS design	5-800nm	no	MAAP	PM_1*
DDW	Portable cabin	4m	MPSS – TROPOS design	10-800nm	no	MAAP	PM_1
AFH	Portable cabin	4m	TDMPSS – TROPOS design	5-800nm	yes	Aethalometer	$PM_{2.5}$

Table adapted from Birmili et al. (Birmili et al. 2016); Further information on the type of mobility particle size spectrometer can be found by (Sun et al. 2019); BC: black carbon; LMI: Leipzig-Mitte; LWE: Leipzig-West; LTR: Leipzig-TROPOS; DDN: Dresden-Nord; DDW: Dresden-West; AFH: Augsburg-Hochschule; TDMPSS: Thermodenuder Mobility Particle Size Spectrometer; TROPOS: Leibniz Institute for Tropospheric Research; TMPSS: Tandem Mobility Particle Size Spectrometer; MPSS: Mobility Particle Size Spectrometer; MAAP: Multiangle Absorption Photometer; PM_{10}: Particulate matter with an aerodynamic diameter $\leq$ 10µm; $PM_{2.5}$: Particulate matter with an aerodynamic diameter $\leq$ 2.5µm; PM_1: Particulate matter with an aerodynamic diameter $\geq$ 1µm.

*: Station DDN: PM_{10} inlet until Feb. 12, 2012, afterwards PM_1 inlet.

Supplementary Table 3: Basic descriptive statistics of air pollutants and meteorological variables per measurement station.

Variable	Ndays	Miss%	Min	Max	Mean	SD	Median	IQR
UFP (10-100nm, n/cm^3)								
LMI	2,279	22.0	2,212	35,987	10,747	4,172	10,123	5,156
LWE	1,787	38.8	931	21,681	5,126	2,619	4,520	3,003
LTR	2,668	8.7	798	32,917	5,469	2,881	4,839	3,154
DDN	2,287	21.7	2,100	24,781	9,128	3,436	8,637	4,366
DDW	2,211	24.3	705	22,526	5,341	2,754	4,791	3,156
AFH	2,392	18.1	953	49,075	6,366	3,621	5,655	3,514
PNC (10-800nm, n/cm^3)								
LMI	2,279	22.0	2,632	38,180	12,590	4,692	11,922	5,866
LWE	1,787	38.8	1,288	23,362	6,265	2,886	5,748	3,482
LTR	2,668	8.7	1,054	34,927	6,703	3,231	6,054	3,686
DDN	2,287	21.7	2,450	30,684	10,912	3,924	10,292	4,975
DDW	2,211	24.3	941	24,714	6,714	3,184	6,186	3,902
AFH	2,392	18.1	1,214	51,597	7,668	4,113	6,909	4,017
NuMP (10-30nm, n/cm^3)								
LMI	2,279	22.0	963	26,652	6,016	2,592	5,658	3,254
LWE	1,787	38.8	287	15,255	2,695	1,715	2,262	1,643
LTR	2,668	8.7	182	23,763	2,851	1,892	2,404	1,776
DDN	2,287	21.7	937	18,616	4,907	2,155	4,526	2,571
DDW	2,211	24.3	336	13,589	2,545	1,549	2,186	1,583
AFH	2,392	18.1	400	43,130	3,083	2,064	2,704	1,767
AiMP (30-100nm, n/cm^3)								
LMI	2,279	22.0	709	14,691	4,731	1,908	4,449	2,374
LWE	1,787	38.8	309	9,904	2,432	1,212	2,178	1,530
LTR	2,668	8.7	332	11,706	2,618	1,343	2,333	1,598
DDN	2,287	21.7	752	11,813	4,221	1,645	3,979	2,064
DDW	2,211	24.3	286	10,782	2,796	1,518	2,518	1,851
AFH	2,392	18.1	334	26,294	3,283	1,898	2,898	2,048
AcMP (100-800nm, n/cm^3)								
LMI	2,279	22.0	282	6,833	1,842	906	1,673	1,068
LWE	1,787	38.8	137	5,667	1,138	689	1,016	826
LTR	2,668	8.7	132	7,010	1,233	758	1,085	863
DDN	2,287	21.7	266	9,299	1,784	900	1,614	1,037
DDW	2,211	24.3	122	5,154	1,372	822	1,217	1,064
AFH	2,392	18.1	147	7,077	1,302	763	1,171	819
NC 10-20nm (n/cm^3)								
LMI	2,279	22.0	564	20,416	3,803	1,737	3,538	2,159
LWE	1,787	38.8	158	12,401	1,700	1,213	1,382	1,094
LTR	2,668	8.7	109	15,155	1,824	1,361	1,492	1,190
DDN	2,287	21.7	576	13,112	3,079	1,416	2,814	1,676
DDW	2,211	24.3	202	9,179	1,562	1,050	1,298	1,033
AFH	2,392	18.1	225	30,162	1,761	1,168	1,542	1,036

NC 20-30nm (n/cm^3)								
LMI	2,279	22.0	373	10,065	2,213	961	2,054	1,173
LWE	1,787	38.8	118	5,907	995	591	848	598
LTR	2,668	8.7	73	8,608	1,028	633	891	611
DDN	2,287	21.7	260	5,930	1,823	791	1,680	948
DDW	2,211	24.3	123	5,504	983	575	843	615
AFH	2,392	18.1	175	30,432	1,322	1,063	1,142	781
NC 30-50nm (n/cm^3)								
LMI	2,279	22.0	356	7,331	2,360	978	2,203	1,181
LWE	1,787	38.8	185	5,165	1,178	628	1,041	695
LTR	2,668	8.7	148	7,903	1,232	676	1,091	731
DDN	2,287	21.7	388	6,715	2,021	812	1,890	1,000
DDW	2,211	24.3	139	5,872	1,270	725	1,115	809
AFH	2,392	18.1	197	11,851	1,619	961	1,408	977
NC 50-70nm (n/cm^3)								
LMI	2,279	22.0	213	3,989	1,274	534	1,192	664
LWE	1,787	38.8	62	3,066	667	349	596	436
LTR	2,668	8.7	88	3,243	730	389	647	468
DDN	2,287	21.7	191	3,557	1,176	482	1,098	615
DDW	2,211	24.3	73	3,285	796	454	705	540
AFH	2,392	18.1	70	10,936	902	573	789	579
NC 70-100nm (n/cm^3)								
LMI	2,279	22.0	140	3,519	1,097	476	1,022	613
LWE	1,787	38.8	58	2,465	587	328	532	411
LTR	2,668	8.7	80	3,385	656	376	581	477
DDN	2,287	21.7	173	3,547	1,041	450	978	575
DDW	2,211	24.3	63	3,005	730	428	665	572
AFH	2,392	18.1	67	3,832	762	457	672	521
BC ($\mu g/m^3$)								
LMI	2.499	14.5	0.4	10.9	2.3	1.2	2.0	1.3
LWE	2.067	29.3	0.1	10.1	1.0	0.9	0.8	0.8
LTR	2.807	3.9	0.0	12.6	1.0	1.0	0.7	0.8
DDN	2.693	7.8	0.3	11.5	1.8	1.0	1.5	1.1
DDW	2.057	29.6	0.1	7.4	0.9	0.7	0.7	0.8
AFH	2.644	9.5	0.5	10.5	1.7	1.0	1.4	1.0
NO_2 ($\mu g/m^3$)								
LMI	2,886	1.2	11.0	100.0	44.0	12.7	43.0	17.0
LWE	2,896	0.9	3.0	66.0	17.6	8.9	16.0	11.0
LTR*	0	-	-	-	-		-	
DDN	2,874	1.6	9.0	77.0	34.2	10.4	33.0	14.0
DDW	2,890	1.1	3.0	72.0	20.2	9.5	18.0	12.0
AFH	2,212	24.3	2.5	84.0	19.8	10.2	17.7	12.3
$PM_{2.5}$ ($\mu g/m^3$)								
LMI	2,891	1.1	2.2	120.8	17.5	13.0	13.6	12.2
LWE	2,885	1.3	1.0	111.2	13.5	12.0	9.6	10.5
LTR*	0	-	-	-	-		-	
DDN	2,900	0.8	1.9	137.8	16.2	12.6	12.3	11.6

DDW	2,892	1.0	0.5	136.4	15.1	12.9	10.9	12.3
AFH	2,922	0.0	1.1	98.7	13.0	10.3	10.2	10.3
Air temperature (°C)								
LMI	2,911	0.4	-14.0	32.1	11.7	8.0	11.4	12.1
LWE	2,919	0.1	-15.0	29.2	9.9	7.7	9.7	11.7
LTR*	0	-	-	-	-		-	
DDN	2,915	0.2	-14.2	31.8	11.4	8.1	11.3	12.5
DDW	2,922	0.0	-13.4	31.0	11.6	8.0	11.6	12.4
AFH	2,803	4.1	-13.4	28.9	9.9	7.9	9.9	12.3
Relative humidity (%)								
LMI	2,909	0.4	34.5	98.5	70.9	12.6	71.8	19.6
LWE	2,905	0.6	37.5	100.0	74.2	12.2	75.3	18.6
LTR*	0	-	-	-	-		-	
DDN	2,915	0.2	37.5	100.0	70.6	11.4	70.9	16.8
DDW	2,922	0.0	36.0	97.2	70.8	11.4	71.8	17.3
AFH	2,803	4.1	39.6	100.0	77.8	12.7	79.2	20.3
Barometric pressure (hPa)								
LMI	2,911	0.4	975.0	1,040.0	1,015.8	8.1	1,016.0	10.0
LWE	2,919	0.1	975.0	1,041.0	1,016.1	8.3	1,016.0	10.0
LTR*	0	-	-	-	-	-	-	-
DDN	2,915	0.2	976.0	1,042.0	1,016.2	8.2	1,016.0	10.0
DDW	2,922	0	976.0	1,041.0	1,016.0	8.0	1,016.0	10.0
AFH	2,803	4.1	923.9	984.5	961.0	7.4	961.4	9.0

N_{days}: Number of days with valid data; Min.: Minimum; Max.: Maximum; SD: Standard deviation; IQR: Interquartile range; UFP: Particle number concentration of particles in the ultrafine range (10-100nm); LMI: Leipzig-Mitte; LWE: Leipzig-West; LTR: Leipzig-TROPOS; DDN: Dresden-Nord; DDW: Dresden-Winckelmannstr.; AFH: Augsburg-Hochschule; PNC: Total particle number concentration (10-800nm); BC: Black carbon; NO_2: Nitrogen dioxide; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≤ 2.5µm; °C: Degree Celsius; hPa: hectopascal.

*: No data available

Supplementary Table 4: Station-specific Spearman correlation coefficients of air pollutants and meteorological variables.

Variable	UFP (10-100nm, n/cm^3)	PNC (10-800nm, n/cm^3)	BC (µg/m^3)	NO_2 (µg/m^3)*	$PM_{2.5}$ (µg/m^3)	Temp. (°C)	Rel hum. (%)
Leipzig-Mitte							
PNC (10-800nm, n/cm^3)	**0.98**						
BC (µg/m^3)	0.59	0.69					
NO_2 (µg/m^3)	**0.73**	**0.77**	**0.73**				
$PM_{2.5}$ (µg/m^3)	0.28	0.40	0.72	0.50			
Temperature (°C)	0.09	0.08	-0.11	-0.08	-0.30		
Relative humidity (%)	-0.13	-0.14	0.18	-0.05	0.14	-0.62	
Barometric pressure (hPa)	0.18	0.20	0.16	0.15	0.25	-0.10	-0.02
Leipzig-West							
PNC (10-800nm, n/cm^3)	**0.96**						
BC (µg/m^3)	0.22	0.40					
NO_2 (µg/m^3)	0.18	0.30	**0.78**				
$PM_{2.5}$ (µg/m^3)	0.09	0.30	**0.86**	0.67			
Temperature (°C)	0.42	0.36	-0.26	-0.46	-0.32		
Relative humidity (%)	-0.47	-0.42	0.24	0.31	0.19	-0.55	
Barometric pressure (hPa)	0.12	0.16	0.19	0.21	0.25	-0.08	-0.03
Leipzig-TROPOS							
PNC (10-800nm, n/cm^3)	**0.96**						
BC (µg/m^3)	0.31	0.49					
NO_2 (µg/m^3)	-†	-†	-†				
$PM_{2.5}$ (µg/m^3)	-†	-†	-†	-†			
Temperature (°C)	-†	-†	-†	-†	-†		
Relative humidity (%)	-†	-†	-†	-†	-†	-†	
Barometric pressure (hPa)	-†	-†	-†	-†	-†	-†	-†
Dresden-Nord							
PNC (10-800nm, n/cm^3)	**0.98**						
BC (µg/m^3)	0.53	0.65					
NO_2 (µg/m^3)	0.63	0.64	0.68				
$PM_{2.5}$ (µg/m^3)	0.14	0.30	0.66	0.32			
Temperature (°C)	0.07	0.04	-0.24	-0.25	-0.34		
Relative humidity (%)	-0.20	-0.19	0.17	0.15	0.19	-0.58	
Barometric pressure (hPa)	0.20	0.21	0.06	0.04	0.20	-0.08	-0.01
Dresden-Winckelmannstr.							
PNC (10-800nm, n/cm^3)	**0.96**						
BC (µg/m^3)	0.33	0.50					
NO_2 (µg/m^3)	0.28	0.39	**0.79**				
$PM_{2.5}$ (µg/m^3)	0.21	0.41	**0.87**	0.66			
Temperature (°C)	0.35	0.27	-0.33	-0.43	-0.35		
Relative humidity (%)	-0.40	-0.35	0.28	0.33	0.16	-0.53	

Barometric pressure (hPa)	0.19	0.22	0.23	0.25	0.25	-0.16	0.01
Augsburg-Hochschule							
PNC (10-800nm, n/cm^3)	**0.98**						
BC (µg/m^3)	0.57	0.67					
NO_2 (µg/m^3)*	0.37	0.48	**0.78**				
$PM_{2.5}$ (µg/m^3)	0.57	0.62	**0.80**	0.66			
Temperature (°C)	0.09	0.06	-0.21	-0.29	-0.47		
Relative humidity (%)	-0.28	-0.26	0.17	0.09	0.19	-0.57	
Barometric pressure (hPa)	0.20	0.22	0.16	0.19	0.13	-0.01	-0.11

UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); NC: Number count; BC: Black carbon; NO_2: Nitrogen dioxide; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≤ 2.5µm. Temp.: Temperature; °C: Degree Celsius; Rel. hum.: relative humidity; hPa: hectopascal. Number printed in bold indicate high correlation (≥ ± 0.7)

*: NO_2 data for Augsburg measured at station A-LfU instead of AFH.
†: No data at this station available.

Supplementary Table 5: Between-station Spearman correlation coefficients of different particle number concentrations and $PM_{2.5}$.

Variable	Leipzig-Mitte	Leipzig-West	Leipzig-TROPOS	Dresden-Nord	Dresden-Winckelmann-str.
UFP (10-100nm, n/cm^3)					
Leipzig-West	0.62				
Leipzig-TROPOS	**0.70**	**0.85**			
Dresden-Nord	0.56	0.47	0.57		
Dresden-Winckelmannstr.	0.51	0.67	0.68	0.66	
Augsburg-Hochschule	0.44	0.30	0.43	0.38	0.39
PNC (10-800nm, n/cm^3)					
Leipzig-West	0.65				
Leipzig-TROPOS	**0.72**	**0.88**			
Dresden-Nord	0.60	0.50	0.60		
Dresden-Winckelmannstr.	0.56	**0.71**	**0.73**	**0.70**	
Augsburg-Hochschule	0.47	0.35	0.46	0.42	0.45
NC (10-20nm, n/cm^3)					
Leipzig-West	0.49				
Leipzig-TROPOS	0.58	0.60			
Dresden-Nord	0.41	0.25	0.40		
Dresden-Winckelmannstr.	0.35	0.48	0.40	0.50	
Augsburg-Hochschule	0.31	0.13	0.33	0.29	0.19
NC (20-30nm, n/cm^3)					
Leipzig-West	0.56				
Leipzig-TROPOS	0.68	**0.82**			

Dresden-Nord	0.52	0.41	0.52		
Dresden-Winckelmannstr.	0.48	0.62	0.65	0.66	
Augsburg-Hochschule	0.43	0.29	0.39	0.36	0.36
NC (30-50nm, n/cm^3)					
Leipzig-West	0.65				
Leipzig-TROPOS	**0.76**	**0.88**			
Dresden-Nord	0.64	0.56	0.63		
Dresden-Winckelmannstr.	0.59	**0.70**	**0.74**	**0.77**	
Augsburg-Hochschule	0.49	0.36	0.41	0.41	0.43
NC (50-70nm, n/cm^3)					
Leipzig-West	**0.75**				
Leipzig-TROPOS	**0.80**	**0.94**			
Dresden-Nord	**0.71**	0.67	**0.72**		
Dresden-Winckelmannstr.	**0.70**	**0.78**	**0.81**	**0.85**	
Augsburg-Hochschule	0.49	0.44	0.46	0.45	0.49
NC (70-100nm, n/cm^3)					
Leipzig-West	**0.82**				
Leipzig-TROPOS	**0.85**	**0.95**			
Dresden-Nord	**0.79**	**0.75**	**0.78**		
Dresden-Winckelmannstr.	**0.78**	**0.83**	**0.86**	**0.90**	
Augsburg-Hochschule	0.52	0.53	0.53	0.51	0.56
NC (10-30nm, n/cm^3)					
Leipzig-West	0.53				
Leipzig-TROPOS	0.63	**0.71**			
Dresden-Nord	0.46	0.32	0.46		
Dresden-Winckelmannstr.	0.40	0.55	0.51	0.56	
Augsburg-Hochschule	0.36	0.19	0.37	0.32	0.27
NC (30-100nm, n/cm^3)					
Leipzig-West	**0.72**				
Leipzig-TROPOS	**0.79**	**0.92**			
Dresden-Nord	**0.70**	0.64	0.69		
Dresden-Winckelmannstr.	0.67	**0.76**	**0.80**	**0.82**	
Augsburg-Hochschule	0.50	0.42	0.46	0.45	0.49
NC (100-800nm, n/cm^3)					
Leipzig-West	**0.91**				
Leipzig-TROPOS	**0.92**	**0.97**			
Dresden-Nord	**0.87**	**0.81**	**0.85**		
Dresden-Winckelmannstr.	**0.87**	**0.87**	**0.90**	**0.94**	
Augsburg-Hochschule	0.59	0.61	0.60	0.57	0.61
$PM_{2.5}$ (µg/m^3)					
Leipzig-West	**0.95**				
Leipzig-TROPOS	-*	-*			
Dresden-Nord	**0.91**	**0.92**	-*		

Dresden-Winckelmannstr.	**0.89**	**0.93**	-*	**0.98**	
Augsburg-Hochschule	**0.70**	**0.72**	-*	**0.70**	**0.71**

UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); NC: Number concentration; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≤ 2.5µm; Number printed in bold indicate high correlation (≥ ± 0.7).

*: No data at this station available.

Supplementary Table 6: Percent changes in the pooled relative risk of cause-specific hospital admissions [and 95% confidence intervals] per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollutants. Standardization by IQR facilitates comparison between different pollutants. Pooled estimates, by air pollutant, average lag, and hospital admission endpoint, based on multilevel random-effects models adjusting for main model covariates.

Variable	IQR	Cardio. HA [95% CI]	Heart. HA [95% CI]	Cerebr. HA [95% CI]	Resp. HA [95% CI]	LRTI HA [95% CI]
UFP						
Lag 0-1	3,420	0.43% [95% CI: -0.25%; 1.12%]	0.44% [95% CI: -0.30%; 1.20%]	-0.11% [95% CI: -1.27%; 1.06%]	-0.18% [95% CI: -0.86%; 0.50%]	0.57% [95% CI: -0.54%; 1.69%]
Lag 2-4	3,220	0.25% [95% CI: -0.77%; 1.28%]*	0.34% [95% CI: -0.22%; 0.90%]	1.58% [95% CI: -1.47%; 4.73%]*	0.69% [95% CI: -0.28%; 1.67%]	0.28% [95% CI: -1.17%; 1.74%]
Lag 5-7	3,223	-0.19% [95% CI: -0.65%; 0.27%]	0.01% [95% CI: -0.51%; 0.54%]	-0.63% [95% CI: -1.86%; 0.62%]	-0.55% [95% CI: -1.18%; 0.09%]	-0.16% [95% CI: -1.53%; 1.23%]
Lag 0-7	2,804	0.19% [95% CI: -0.61%; 1.00%]	0.45% [95% CI: -0.11%; 1.01%]	0.39% [95% CI: -1.08%; 1.89%]*	-0.03% [95% CI: -0.70%; 0.65%]	0.08% [95% CI: -1.34%; 1.52%]
PNC						
Lag 0-1	3,978	0.51% [95% CI: -0.15%; 1.18%]	0.32% [95% CI: -0.36%; 1.01%]	0.52% [95% CI: -0.67%; 1.71%]	-0.11% [95% CI: -0.81%; 0.59%]	0.26% [95% CI: -0.84%; 1.39%]
Lag 2-4	3,744	0.52% [95% CI: -0.46%; 1.50%]*	0.52% [95% CI: -0.16%; 1.19%]	1.52% [95% CI: -1.57%; 4.70%]*	0.90% [95% CI: -0.28%; 2.08%]	0.38% [95% CI: -1.18%; 1.95%]
Lag 5-7	3,747	-0.02% [95% CI: -0.48%; 0.44%]	0.25% [95% CI: -0.28%; 0.78%]	-0.52% [95% CI: -1.87%; 0.86%]	-0.48% [95% CI: -1.11%; 0.16%]	-0.20% [95% CI: -1.50%; 1.12%]
Lag 0-7	3,221	0.44% [95% CI: -0.22%; 1.11%]	**0.61% [95% CI: 0.06%; 1.17%]**	0.64% [95% CI: -0.90%; 2.21%]*	0.14% [95% CI: -0.53%; 0.81%]	0.05% [95% CI: -1.44%; 1.55%]
BC						
Lag 0-1	0.90	**0.42% [95% CI: 0.03%; 0.82%]**	-0.28% [95% CI: -0.73%; 0.17%]	**1.63% [95% CI: 0.69%; 2.58%]**	0.10% [95% CI: -0.43%; 0.64%]	-0.90% [95% CI: -1.72%; -0.07%]
Lag 2-4	0.88	0.65% [95% CI: -0.26%; 1.56%]	**0.68% [95% CI: 0.16%; 1.20%]**	0.56% [95% CI: -0.94%; 2.09%]	0.70% [95% CI: -0.79%; 2.21%]	-0.59% [95% CI: -3.02%; 1.90%]*
Lag 5-7	0.88	0.26% [95% CI: -0.14%; 0.66%]	**0.54% [95% CI: 0.08%; 1.00%]**	0.42% [95% CI: -1.37%; 2.23%]	0.00% [95% CI: -0.53%; 0.52%]	-0.30% [95% CI: -1.12%; 0.53%]
Lag 0-7	0.77	**0.78% [95% CI: 0.29%; 1.27%]**	0.49% [95% CI: -0.04%; 1.03%]	1.14% [95% CI: -0.04%; 2.34%]	0.31% [95% CI: -1.06%; 1.70%]	-0.39% [95% CI: -1.36%; 0.59%]
$PM_{2.5}$†						
Lag 0-1	10.78	**0.59% [95% CI: 0.21%; 0.98%]**	0.05% [95% CI: -0.39%; 0.50%]	**1.70% [95% CI: 0.52%; 2.89%]**	**0.64% [95% CI: 0.13%; 1.16%]**	-0.74% [95% CI: -1.55%; 0.07%]
Lag 2-4	10.32	0.94% [95% CI: -0.19%; 2.07%]*	**1.00% [95% CI: 0.47%; 1.54%]**	0.19% [95% CI: -2.85%; 3.32%]*	**1.16% [95% CI: 0.33%; 1.99%]**	0.19% [95% CI: -0.66%; 1.05%]
Lag 5-7	10.32	**0.78% [95% CI: 0.41%; 1.15%]**	**0.94% [95% CI: 0.49%; 1.39%]**	0.78% [95% CI: -0.12%; 1.69%]	**0.62% [95% CI: 0.10%; 1.14%]**	0.28% [95% CI: -0.51%; 1.06%]
Lag 0-7	9.10	**1.24% [95% CI: 0.43%; 2.05%]**	**1.11% [95% CI: 0.58%; 1.65%]**	1.51% [95% CI: -0.44%; 3.49%]	**1.23% [95% CI: 0.61%; 1.85%]**	-0.17% [95% CI: -1.14%; 0.81%]
NO_2†‡						
Lag 0-1	11.80	0.36% [95% CI: -0.36%; 1.08%]	-0.09% [95% CI: -0.76%; 0.58%]	1.02% [95% CI: -1.19%; 3.29%]	0.25% [95% CI: -1.20%; 1.71%]	-0.16% [95% CI: -2.23%; 1.95%]
Lag 2-4	11.00	0.09% [95% CI: -0.67%; 0.85%]	0.04% [95% CI: -0.68%; 0.76%]	0.64% [95% CI: -0.68%; 1.97%]	**1.29% [95% CI: 0.07%; 2.52%]**	0.04% [95% CI: -2.48%; 2.64%]

Lag 5-7	11.00	-0.25% [95% CI: -1.01%; 0.51%]	-0.06% [95% CI: -0.66%; 0.54%]	-0.37% [95% CI: -1.62%; 0.88%]	-0.21% [95% CI: -0.96%; 0.54%]	0.11% [95% CI: -1.01%; 1.23%]
Lag 0-7	9.16	0.03% [95% CI: -0.81%; 0.88%]	-0.03% [95% CI: -0.77%; 0.71%]	0.27% [95% CI: -1.27%; 1.82%]	0.52% [95% CI: -0.59%; 1.64%]	-0.25% [95% CI: -1.61%; 1.12%]

IQR: Interquartile range; Cardio. HA: cardiovascular disease hospital admission (ICD-10 code: I00-I99); CI: Confidence interval; Heart. HA: Heart disease hospital admission (ICD-10 code: I00-I52); Cerebr. HA: Cerebrovascular disease hospital admission (ICD-10 code: I60-I69); Resp. HA: Respiratory disease hospital admission (ICD-10 code: J00-J99); LRTI HA: Lower Respiratory Tract Infections hospital admission (ICD-10 code: J12-J18 & J20-J22); UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); BC: Black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≤ 2.5µm; NO_2: Nitrogen dioxide. Numbers printed in bold indicate statistical significance ($p < 0.05$).

*: $I^2 > 50\%$ & $p < 0.05$.

†: Pooled analysis for this air pollution without station LTR (no data at this station available).

‡: NO_2 data for Augsburg measured at station A-LfU instead of AFH.

Supplementary Table 7: Percent changes in the pooled relative risk of cause-specific hospital admissions [and 95% confidence intervals] per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in particle metrics. Standardization by IQR facilitates comparison between different pollutants. Pooled estimates, by air pollutant, average lag, and hospital admission endpoint, based on multilevel random-effects models adjusting for main model covariates.

Variable	IQR	Cardio. HA [95% CI]	Heart. HA [95% CI]	Cerebr. HA [95% CI]	Resp. HA [95% CI]	LRTI HA [95% CI]
NC 10-20nm						
Lag 0-1	1,245	0.44% [95% CI: -0.22%; 1.11%]	0.65% [95% CI: 0.00%; 1.31%]	-0.53% [95% CI: -1.56%; 0.52%]	0.03% [95% CI: -0.59%; 0.65%]	1.02% [95% CI: -0.01%; 2.06%]
Lag 2-4	1,150	-0.08% [95% CI: -1.04%; 0.89%]*	0.08% [95% CI: -0.54%; 0.70%]	0.82% [95% CI: -1.53%; 3.22%]*	0.23% [95% CI: -0.46%; 0.93%]	-0.45% [95% CI: -2.02%; 1.15%]
Lag 5-7	1,151	-0.33% [95% CI: -0.79%; 0.13%]	-0.30% [95% CI: -0.78%; 0.20%]	-0.44% [95% CI: -1.44%; 0.56%]	-0.92% [95% CI: -2.03%; 0.20%]	-0.63% [95% CI: -2.54%; 1.33%]*
Lag 0-7	1,042	0.01% [95% CI: -0.58%; 0.61%]	0.18% [95% CI: -0.42%; 0.79%]	-0.43% [95% CI: -3.56%; 2.81%]*	-0.29% [95% CI: -0.95%; 0.37%]	-0.17% [95% CI: -1.79%; 1.47%]
NC 20-30nm						
Lag 0-1	716	0.41% [95% CI: -0.05%; 0.88%]	0.50% [95% CI: -0.08%; 1.09%]	-0.28% [95% CI: -1.33%; 0.78%]	-0.05% [95% CI: -0.65%; 0.55%]	0.74% [95% CI: -0.23%; 1.71%]
Lag 2-4	653	0.10% [95% CI: -0.66%; 0.86%]*	-0.04% [95% CI: -0.79%; 0.70%]	1.45% [95% CI: -0.26%; 3.19%]*	**0.64% [95% CI: 0.01%; 1.28%]**	0.46% [95% CI: -0.52%; 1.44%]
Lag 5-7	654	-0.15% [95% CI: -0.61%; 0.32%]	0.07% [95% CI: -0.42%; 0.56%]	-0.66% [95% CI: -1.66%; 0.34%]	-0.37% [95% CI: -0.95%; 0.20%]	-0.24% [95% CI: -1.17%; 0.70%]
Lag 0-7	568	0.12% [95% CI: -0.59%; 0.83%]	0.36% [95% CI: -0.16%; 0.89%]	0.35% [95% CI: -1.85%; 2.61%]*	-0.02% [95% CI: -0.65%; 0.61%]	0.27% [95% CI: -0.75%; 1.31%]
NC 30-50nm						
Lag 0-1	825	0.43% [95% CI: -0.12%; 0.97%]	0.27% [95% CI: -0.49%; 1.04%]	0.10% [95% CI: -1.06%; 1.28%]	-0.06% [95% CI: -0.75%; 0.62%]	0.61% [95% CI: -0.50%; 1.74%]
Lag 2-4	782	0.50% [95% CI: -0.05%; 1.06%]	0.23% [95% CI: -0.42%; 0.89%]	0.81% [95% CI: -2.91%; 4.68%]*	0.66% [95% CI: -0.85%; 2.21%]	0.70% [95% CI: -0.81%; 2.23%]
Lag 5-7	783	-0.10% [95% CI: -0.57%; 0.36%]	0.14% [95% CI: -0.40%; 0.68%]	-0.66% [95% CI: -1.78%; 0.47%]	-0.32% [95% CI: -0.97%; 0.32%]	-0.16% [95% CI: -1.21%; 0.90%]
Lag 0-7	682	0.37% [95% CI: -0.19%; 0.93%]	0.50% [95% CI: -0.09%; 1.09%]	0.43% [95% CI: -2.58%; 3.54%]*	0.22% [95% CI: -0.49%; 0.94%]	0.50% [95% CI: -0.74%; 1.75%]
NC 50-70nm						
Lag 0-1	503	0.34% [95% CI: -0.18%; 0.85%]	0.11% [95% CI: -0.47%; 0.70%]	0.27% [95% CI: -0.92%; 1.47%]	-0.61% [95% CI: -1.31%; 0.09%]	-0.37% [95% CI: -1.69%; 0.97%]
Lag 2-4	471	0.58% [95% CI: -0.56%; 1.75%]	0.52% [95% CI: -0.07%; 1.12%]	1.78% [95% CI: -0.52%; 4.12%]*	0.89% [95% CI: -0.85%; 2.66%]*	0.88% [95% CI: -1.46%; 3.27%]
Lag 5-7	471	0.05% [95% CI: -0.42%; 0.52%]	0.30% [95% CI: -0.24%; 0.84%]	-0.58% [95% CI: -1.85%; 0.70%]	-0.39% [95% CI: -1.04%; 0.26%]	0.06% [95% CI: -0.99%; 1.12%]
Lag 0-7	401	**0.61% [95% CI: 0.08%; 1.15%]**	**0.64% [95% CI: 0.03%; 1.26%]**	0.66% [95% CI: -1.61%; 2.99%]	0.20% [95% CI: -0.52%; 0.92%]	0.53% [95% CI: -0.66%; 1.74%]
NC 70-						

100nm						
Lag 0-1	479	0.26% [95% CI: -0.26%; 0.78%]	-0.29% [95% CI: -0.89%; 0.31%]	1.27% [95% CI:0.04%; 2.51%]	-0.46% [95% CI: -1.29%; 0.37%]	-0.60% [95% CI: -1.86%; 0.66%]
Lag 2-4	449	0.76% [95% CI: -0.60%; 2.14%]	0.60% [95% CI: -0.52%; 1.74%]	1.40% [95% CI: -1.09%; 3.96%]*	1.37% [95% CI: -0.24%; 3.00%]	1.18% [95% CI: -1.31%; 3.72%]*
Lag 5-7	448	0.21% [95% CI: -0.26%; 0.69%]	0.52% [95% CI: -0.06%; 1.12%]	-0.43% [95% CI: -2.09%; 1.27%]	-0.33% [95% CI: -0.98%; 0.33%]	0.11% [95% CI: -0.94%; 1.17%]
Lag 0-7	364	**0.77% [95% CI: 0.20%; 1.35%]**	0.76% [95% CI:0.16%; 1.37%]	0.90% [95% CI: -1.18%; 3.02%]	0.50% [95% CI: -0.21%; 1.21%]	0.70% [95% CI: -0.46%; 1.88%]
NuMP						
Lag 0-1	1,921	0.46% [95% CI: -0.17%; 1.08%]	0.62% [95% CI: -0.12%; 1.37%]	-0.50% [95% CI: -1.57%; 0.58%]	0.00% [95% CI: -0.63%; 0.64%]	1.02% [95% CI: -0.02%; 2.07%]
Lag 2-4	1,786	-0.15% [95% CI: -1.42%; 1.13%]*	0.04% [95% CI: -0.59%; 0.67%]	1.16% [95% CI: -1.17%; 3.55%]*	0.38% [95% CI: -0.33%; 1.10%]	-0.03% [95% CI: -1.15%; 1.09%]
Lag 5-7	1,787	-0.30% [95% CI: -0.80%; 0.21%]	-0.19% [95% CI: -0.69%; 0.31%]	-0.56% [95% CI: -1.67%; 0.56%]	-0.62% [95% CI: -1.28%; 0.06%]	-0.52% [95% CI: -2.52%; 1.53%]
Lag 0-7	1,578	0.00% [95% CI: -0.70%; 0.71%]	0.24% [95% CI: -0.36%; 0.84%]	-0.19% [95% CI: -3.56%; 3.30%]*	-0.20% [95% CI: -0.86%; 0.46%]	-0.03% [95% CI: -1.43%; 1.40%]
AiMP						
Lag 0-1	1,731	0.36% [95% CI: -0.21%; 0.92%]	0.10% [95% CI: -0.54%; 0.73%]	0.47% [95% CI: -0.73%; 1.69%]	-0.39% [95% CI: -1.09%; 0.31%]	-0.15% [95% CI: -1.29%; 1.01%]
Lag 2-4	1,630	**0.73% [95% CI: 0.03%; 1.43%]**	0.45% [95% CI: -0.29%; 1.20%]	2.06% [95% CI: -0.34%; 4.51%]*	**1.16% [95% CI: 0.31%; 2.02%]***	0.73% [95% CI: -1.05%; 2.54%]*
Lag 5-7	1,630	0.00% [95% CI: -0.47%; 0.47%]	0.28% [95% CI: -0.27%; 0.82%]	-0.64% [95% CI: -1.82%; 0.55%]	-0.41% [95% CI: -1.05%; 0.24%]	-0.12% [95% CI: -1.17%; 0.94%]
Lag 0-7	1,399	0.51% [95% CI: -0.16%; 1.20%]	**0.64% [95% CI: 0.04%; 1.24%]**	0.71% [95% CI: -2.04%; 3.53%]*	0.19% [95% CI: -0.52%; 0.92%]	0.28% [95% CI: -0.98%; 1.55%]
AcMP						
Lag 0-1	877	**0.52% [95% CI: 0.04%; 1.01%]**	-0.32% [95% CI: -0.86%; 0.23%]	**2.40% [95% CI: 1.24%; 3.57%]**	0.21% [95% CI: -0.47%; 0.90%]	-0.84% [95% CI: -1.82%; 0.16%]
Lag 2-4	829	1.01% [95% CI: -0.40%; 2.44%]*	**1.18% [95% CI: 0.57%; 1.79%]**	0.36% [95% CI: -2.80%; 3.62%]*	**1.55% [95% CI: 0.86%; 2.25%]**	0.36% [95% CI: -1.68%; 2.44%]
Lag 5-7	830	**0.60% [95% CI: 0.16%; 1.05%]**	**1.00% [95% CI: 0.42%; 1.58%]**	-0.04% [95% CI: -1.56%; 1.51%]	-0.04% [95% CI: -0.69%; 0.61%]	-0.30% [95% CI: -1.25%; 0.66%]
Lag 0-7	704	**1.20% [95% CI: 0.66%; 1.73%]**	**1.13% [95% CI: 0.54%; 1.72%]**	**1.29% [95% CI: 0.04%; 2.55%]**	**0.82% [95% CI: 0.14%; 1.50%]**	0.00% [95% CI: -1.10%; 1.12%]

IQR: Interquartile range; Cardio. HA: cardiovascular disease hospital admission (ICD-10 code: I00-I99); CI: Confidence interval; Heart. HA: Heart disease hospital admission (ICD-10 code: I00-I52); Cerebr. HA: Cerebrovascular disease hospital admission (ICD-10 code: I60-I69); Resp. HA: Respiratory disease hospital admission (ICD-10 code: J00-J99); LRTI HA: Lower Respiratory Tract Infections hospital admission (ICD-10 code: J12-J18 & J20-J22); NC: Number Concentration in a certain size range; NuMP: Nucleation mode particles (10-30nm); AiMP: Aitken mode particles (30-100nm); Accumulation mode particles (100-800 nm); Numbers printed in bold indicate statistical significance ($p < 0.05$).

*: $I^2 > 50\%$ & $p < 0.05$.

†: Pooled analysis for this air pollution without station LTR (no data at this station available).

‡: NO_2 data for Augsburg measured at station A-LfU instead of AFH.

Supplementary Table 8: Percent changes in the pooled relative risk of cause-specific hospital admissions [and 95% confidence intervals] per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollutants. Standardization by IQR facilitates comparison between different pollutants. Pooled estimates, by air pollutant, average lag, and hospital admission endpoint, based on multilevel fixed-effects models adjusting for main model covariates.

Variable	IQR	Cardio. HA [95% CI]	Heart. HA [95% CI]	Cerebr. HA [95% CI]	Resp. HA [95% CI]	LRTI HA [95% CI]
UFP						
Lag 0-1	3,420	**0.52% [95% CI: 0.03%; 1.02%]**	0.50% [95% CI: -0.07%; 1.08%]	-0.11% [95% CI: -1.27%; 1.06%]	-0.18% [95% CI: -0.86%; 0.50%]	0.57% [95% CI: -0.54%; 1.69%]
Lag 2-4	3,220	**0.54% [95% CI: 0.06%; 1.03%]***	0.34% [95% CI: -0.22%; 0.90%]	**1.84% [95% CI: 0.69%; 2.99%]***	**0.88% [95% CI: 0.21%; 1.55%]**	0.53% [95% CI: -0.54%; 1.61%]
Lag 5-7	3,223	-0.19% [95% CI: -0.65%; 0.27%]	0.01% [95% CI: -0.51%; 0.54%]	-0.69% [95% CI: -1.76%; 0.39%]	-0.55% [95% CI: -1.18%; 0.09%]	-0.19% [95% CI: -1.22%; 0.85%]
Lag 0-7	2,804	0.30% [95% CI: -0.19%; 0.79%]	0.45% [95% CI: -0.11%; 1.01%]	0.23% [95% CI: -0.92%; 1.39%]*	-0.03% [95% CI: -0.70%; 0.65%]	0.18% [95% CI: -0.92%; 1.31%]
PNC						
Lag 0-1	3,978	**0.60% [95% CI: 0.10%; 1.11%]**	0.36% [95% CI: -0.22%; 0.95%]	0.52% [95% CI: -0.67%; 1.71%]	-0.12% [95% CI: -0.80%; 0.58%]	0.26% [95% CI: -0.84%; 1.39%]
Lag 2-4	3,744	**0.82% [95% CI: 0.33%; 1.32%]***	**0.59% [95% CI: 0.02%; 1.15%]**	**1.98% [95% CI: 0.82%; 3.15%]***	**1.16% [95% CI: 0.49%; 1.84%]**	0.69% [95% CI: -0.39%; 1.78%]
Lag 5-7	3,747	-0.02% [95% CI: -0.48%; 0.44%]	0.25% [95% CI: -0.28%; 0.78%]	-0.63% [95% CI: -1.70%; 0.46%]	-0.48% [95% CI: -1.10%; 0.16%]	-0.23% [95% CI: -1.25%; 0.80%]
Lag 0-7	3,221	**0.51% [95% CI: 0.02%; 0.99%]**	**0.61% [95% CI: 0.06%; 1.17%]**	0.47% [95% CI: -0.67%; 1.62%]*	0.14% [95% CI: -0.53%; 0.81%]	0.16% [95% CI: -0.93%; 1.26%]
BC						
Lag 0-1	0.90	**0.42% [95% CI: 0.03%; 0.82%]**	-0.28% [95% CI: -0.73%; 0.17%]	**1.63% [95% CI: 0.69%; 2.58%]**	0.10% [95% CI: -0.42%; 0.63%]	**-0.90% [95% CI: -1.72%; -0.07%]**
Lag 2-4	0.88	**0.96% [95% CI: 0.53%; 1.39%]**	**0.70% [95% CI: 0.21%; 1.19%]**	0.89% [95% CI: -0.12%; 1.91%]	**1.13% [95% CI: 0.57%; 1.70%]**	0.02% [95% CI: -0.85%; 0.90%]*
Lag 5-7	0.88	0.26% [95% CI: -0.14%; 0.66%]	**0.54% [95% CI: 0.08%; 1.00%]**	0.00% [95% CI: -0.96%; 0.96%]	0.00% [95% CI: -0.53%; 0.52%]	-0.30% [95% CI: -1.12%; 0.53%]
Lag 0-7	0.77	**0.78% [95% CI: 0.31%; 1.25%]**	0.49% [95% CI: -0.04%; 1.03%]	**1.12% [95% CI: 0.00%; 2.25%]**	**0.63% [95% CI: 0.00%; 1.26%]**	-0.39% [95% CI: -1.36%; 0.59%]
$PM_{2.5}$†						
Lag 0-1	10.78	**0.59% [95% CI: 0.21%; 0.98%]**	0.05% [95% CI: -0.39%; 0.50%]	**1.76% [95% CI: 0.83%; 2.70%]**	**0.64% [95% CI: 0.13%; 1.16%]**	-0.74% [95% CI: -1.55%; 0.07%]
Lag 2-4	10.32	**1.07% [95% CI: 0.66%; 1.49%]***	**1.02% [95% CI: 0.55%; 1.50%]**	0.95% [95% CI: -0.03%; 1.94%]*	**1.25% [95% CI: 0.71%; 1.80%]**	0.19% [95% CI: -0.66%; 1.05%]
Lag 5-7	10.32	**0.78% [95% CI: 0.41%; 1.15%]**	**0.94% [95% CI: 0.51%; 1.37%]**	0.78% [95% CI: -0.12%; 1.69%]	**0.62% [95% CI: 0.12%; 1.11%]**	0.28% [95% CI: -0.51%; 1.06%]
Lag 0-7	9.10	**1.27% [95% CI: 0.81%; 1.74%]**	**1.11% [95% CI: 0.58%; 1.65%]**	**1.69% [95% CI: 0.58%; 2.82%]**	**1.23% [95% CI: 0.61%; 1.85%]**	-0.17% [95% CI: -1.14%; 0.81%]
NO_2†‡						
Lag 0-1	11.80	0.30% [95% CI: -0.25%; 0.86%]	-0.09% [95% CI: -0.73%; 0.55%]	0.92% [95% CI: -0.41%; 2.27%]	0.10% [95% CI: -0.64%; 0.86%]	-0.51% [95% CI: -1.68%; 0.69%]
Lag 2-4	11.00	0.13% [95% CI: -0.42%; 0.68%]	0.06% [95% CI: -0.57%; 0.70%]	0.64% [95% CI: -0.68%; 1.97%]	**1.29% [95% CI: 0.55%; 2.05%]**	0.41% [95% CI: -0.76%; 1.58%]

Lag 5-7	11.00	-0.34% [95% CI: -0.86%; 0.18%]	-0.06% [95% CI: -0.66%; 0.54%]	-0.37% [95% CI: -1.62%; 0.88%]	-0.24% [95% CI: -0.94%; 0.46%]	0.11% [95% CI: -1.01%; 1.23%]
Lag 0-7	9.16	-0.06% [95% CI: -0.70%; 0.59%]	-0.03% [95% CI: -0.77%; 0.71%]	0.27% [95% CI: -1.27%; 1.82%]	0.38% [95% CI: -0.48%; 1.25%]	-0.25% [95% CI: -1.61%; 1.12%]

IQR: Interquartile range; Cardio. HA: cardiovascular disease hospital admission (ICD-10 code: I00-I99); CI: Confidence interval; Heart. HA: Heart disease hospital admission (ICD-10 code: I00-I52); Cerebr. HA: Cerebrovascular disease hospital admission (ICD-10 code: I60-I69); Resp. HA: Respiratory disease hospital admission (ICD-10 code: J00-J99); LRTI HA: Lower Respiratory Tract Infections hospital admission (ICD-10 code: J12-J18 & J20-J22); UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); BC: Black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≤ 2.5µm; NO_2: Nitrogen dioxide. Numbers printed in bold indicate statistical significance ($p < 0.05$).

*: $I^2 > 50\%$ & $p < 0.05$.

†: Pooled analysis for this air pollution without station LTR (no data at this station available).

‡: NO_2 data for Augsburg measured at station A-LfU instead of AFH.

Supplementary Table 9: Percent changes in the pooled relative risk of cause-specific hospital admissions [and 95% confidence intervals] per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in particle metrics. Standardization by IQR facilitates comparison between different pollutants. Pooled estimates, by air pollutant, average lag, and hospital admission endpoint, based on multilevel fixed-effects models adjusting for main model covariates.

Variable	IQR	Cardio. HA [95% CI]	Heart. HA [95% CI]	Cerebr. HA [95% CI]	Resp. HA [95% CI]	LRTI HA [95% CI]
NC 10-20nm						
Lag 0-1	1,245	**0.54% [95% CI: 0.09%; 0.98%]**	**0.70% [95% CI: 0.19%; 1.22%]**	-0.53% [95% CI: -1.56%; 0.52%]	0.03% [95% CI: -0.59%; 0.65%]	1.02% [95% CI: -0.01%; 2.06%]
Lag 2-4	1,150	0.19% [95% CI: -0.24%; 0.63%]*	0.15% [95% CI: -0.35%; 0.65%]	**1.19% [95% CI: 0.16%; 2.23%]***	0.27% [95% CI: -0.34%; 0.88%]	-0.21% [95% CI: -1.20%; 0.79%]
Lag 5-7	1,151	-0.33% [95% CI: -0.76%; 0.09%]	-0.30% [95% CI: -0.78%; 0.20%]	-0.44% [95% CI: -1.44%; 0.56%]	-0.62% [95% CI: -1.21%; -0.02%]	-0.14% [95% CI: -1.12%; 0.85%]*
Lag 0-7	1,042	0.04% [95% CI: -0.43%; 0.52%]	0.22% [95% CI: -0.32%; 0.77%]	-0.07% [95% CI: -1.19%; 1.06%]*	-0.29% [95% CI: -0.95%; 0.37%]	0.00% [95% CI: -1.09%; 1.11%]
NC 20-30nm						
Lag 0-1	716	0.42% [95% CI: -0.02%; 0.86%]	0.52% [95% CI:0.02%; 1.03%]	-0.29% [95% CI: -1.32%; 0.74%]	-0.05% [95% CI: -0.65%; 0.55%]	0.74% [95% CI: -0.23%; 1.71%]
Lag 2-4	653	0.21% [95% CI: -0.23%; 0.65%]	0.07% [95% CI: -0.43%; 0.58%]	**1.41% [95% CI: 0.38%; 2.45%]***	**0.67% [95% CI: 0.07%; 1.27%]**	0.47% [95% CI: -0.48%; 1.43%]
Lag 5-7	654	-0.17% [95% CI: -0.58%; 0.25%]	0.07% [95% CI: -0.41%; 0.55%]	-0.67% [95% CI: -1.65%; 0.31%]	-0.37% [95% CI: -0.95%; 0.20%]	-0.24% [95% CI: -1.17%; 0.70%]
Lag 0-7	568	0.16% [95% CI: -0.30%; 0.62%]	0.36% [95% CI: -0.16%; 0.89%]	0.07% [95% CI: -1.00%; 1.15%]*	-0.02% [95% CI: -0.65%; 0.61%]	0.27% [95% CI: -0.75%; 1.31%]
NC 30-50nm						
Lag 0-1	825	0.44% [95% CI: -0.05%; 0.94%]	0.33% [95% CI: -0.24%; 0.91%]	0.10% [95% CI: -1.06%; 1.28%]	-0.06% [95% CI: -0.75%; 0.62%]	0.61% [95% CI: -0.50%; 1.74%]
Lag 2-4	782	**0.54% [95% CI: 0.04%; 1.04%]***	0.29% [95% CI: -0.28%; 0.87%]	**1.73% [95% CI: 0.56%; 2.91%]***	**1.06% [95% CI: 0.37%; 1.75%]**	0.96% [95% CI: -0.15%; 2.08%]
Lag 5-7	783	-0.10% [95% CI: -0.57%; 0.36%]	0.14% [95% CI: -0.40%; 0.68%]	-0.68% [95% CI: -1.76%; 0.42%]	-0.32% [95% CI: -0.97%; 0.32%]	-0.16% [95% CI: -1.21%; 0.90%]
Lag 0-7	682	0.39% [95% CI: -0.13%; 0.90%]	0.50% [95% CI: -0.09%; 1.09%]	0.33% [95% CI: -0.87%; 1.55%]*	0.22% [95% CI: -0.49%; 0.94%]	0.52% [95% CI: -0.65%; 1.72%]
NC 50-70nm						
Lag 0-1	503	0.34% [95% CI: -0.17%; 0.85%]	0.11% [95% CI: -0.47%; 0.70%]	0.27% [95% CI: -0.92%; 1.47%]	-0.61% [95% CI: -1.31%; 0.09%]	-0.43% [95% CI: -1.55%; 0.70%]
Lag 2-4	471	**0.88% [95% CI: 0.38%; 1.38%]**	0.54% [95% CI: -0.04%; 1.11%]	**2.11% [95% CI: 0.93%; 3.31%]***	**1.31% [95% CI: 0.62%; 2.01%]***	**1.35% [95% CI: 0.23%; 2.48%]**
Lag 5-7	471	0.05% [95% CI: -0.42%; 0.52%]	0.30% [95% CI: -0.24%; 0.84%]	-0.65% [95% CI: -1.74%; 0.46%]	-0.39% [95% CI: -1.04%; 0.26%]	0.06% [95% CI: -0.99%; 1.12%]
Lag 0-7	401	**0.62% [95% CI: 0.10%; 1.14%]**	**0.65% [95% CI: 0.05%; 1.25%]**	0.62% [95% CI: -0.60%; 1.85%]	0.20% [95% CI: -0.52%; 0.92%]	0.53% [95% CI: -0.66%; 1.74%]
NC 70-						

100nm						
Lag 0-1	479	0.26% [95% CI: -0.26%; 0.78%]	-0.29% [95% CI: -0.89%; 0.31%]	1.27% [95% CI:0.04%; 2.51%]	-0.47% [95% CI: -1.17%; 0.24%]	-0.66% [95% CI: -1.77%; 0.47%]
Lag 2-4	449	**1.18% [95% CI: 0.68%; 1.69%]***	**0.85% [95% CI: 0.27%; 1.43%]**	**1.95% [95% CI: 0.75%; 3.16%]***	**1.77% [95% CI: 1.08%; 2.48%]**	**1.76% [95% CI: 0.62%; 2.90%]***
Lag 5-7	448	0.21% [95% CI: -0.26%; 0.69%]	0.54% [95% CI: -0.01%; 1.09%]	-0.63% [95% CI: -1.74%; 0.50%]	-0.33% [95% CI: -0.98%; 0.33%]	0.11% [95% CI: -0.94%; 1.17%]
Lag 0-7	364	**0.81% [95% CI: 0.29%; 1.32%]**	**0.77% [95% CI: 0.17%; 1.36%]**	0.86% [95% CI: -0.35%; 2.09%]	0.50% [95% CI: -0.21%; 1.21%]	0.70% [95% CI: -0.46%; 1.88%]
NuMP						
Lag 0-1	1,921	**0.52% [95% CI: 0.06%; 0.98%]**	0.68% [95% CI: 0.16%; 1.22%]	-0.50% [95% CI: -1.57%; 0.58%]	0.00% [95% CI: -0.63%; 0.64%]	1.02% [95% CI: -0.02%; 2.07%]
Lag 2-4	1,786	0.21% [95% CI: -0.24%; 0.67%]*	0.13% [95% CI: -0.39%; 0.65%]	**1.37% [95% CI: 0.30%; 2.44%]***	0.44% [95% CI: -0.18%; 1.07%]	0.03% [95% CI: -0.98%; 1.05%]
Lag 5-7	1,787	-0.31% [95% CI: -0.75%; 0.12%]	-0.19% [95% CI: -0.69%; 0.31%]	-0.58% [95% CI: -1.59%; 0.45%]	-0.58% [95% CI: -1.18%; 0.03%]	-0.20% [95% CI: -1.19%; 0.80%]
Lag 0-7	1,578	0.07% [95% CI: -0.40%; 0.55%]	0.28% [95% CI: -0.27%; 0.82%]	-0.03% [95% CI: -1.14%; 1.09%]*	-0.20% [95% CI: -0.86%; 0.46%]	0.08% [95% CI: -0.99%; 1.17%]
AiMP						
Lag 0-1	1,731	0.38% [95% CI: -0.14%; 0.90%]	0.10% [95% CI: -0.49%; 0.70%]	0.47% [95% CI: -0.73%; 1.69%]	-0.39% [95% CI: -1.09%; 0.31%]	-0.16% [95% CI: -1.28%; 0.98%]
Lag 2-4	1,630	**0.87% [95% CI: 0.36%; 1.37%]**	0.54% [95% CI: -0.03%; 1.13%]	**2.07% [95% CI: 0.88%; 3.28%]***	**1.28% [95% CI: 0.58%; 1.98%]***	1.10% [95% CI: -0.02%; 2.23%]*
Lag 5-7	1,630	0.00% [95% CI: -0.47%; 0.47%]	0.28% [95% CI: -0.27%; 0.82%]	-0.69% [95% CI: -1.78%; 0.42%]	-0.41% [95% CI: -1.05%; 0.24%]	-0.12% [95% CI: -1.17%; 0.94%]
Lag 0-7	1,399	**0.58% [95% CI: 0.06%; 1.10%]**	**0.64% [95% CI: 0.04%; 1.24%]**	0.58% [95% CI: -0.64%; 1.81%]*	0.19% [95% CI: -0.52%; 0.92%]	0.31% [95% CI: -0.87%; 1.50%]
AcMP						
Lag 0-1	877	**0.53% [95% CI: 0.06%; 1.01%]**	-0.32% [95% CI: -0.86%; 0.23%]	2.42% [95% CI: 1.29%; 3.55%]	0.21% [95% CI: -0.42%; 0.84%]	-0.84% [95% CI: -1.82%; 0.16%]
Lag 2-4	829	**1.45% [95% CI: 0.98%; 1.93%]***	**1.22% [95% CI: 0.67%; 1.76%]**	**1.55% [95% CI: 0.43%; 2.68%]***	**1.59% [95% CI: 0.95%; 2.24%]**	0.90% [95% CI: -0.12%; 1.93%]
Lag 5-7	830	**0.60% [95% CI: 0.16%; 1.05%]**	**1.02% [95% CI: 0.50%; 1.54%]**	-0.17% [95% CI: -1.22%; 0.89%]	-0.04% [95% CI: -0.63%; 0.57%]	-0.30% [95% CI: -1.25%; 0.66%]
Lag 0-7	704	**1.21% [95% CI: 0.71%; 1.71%]**	**1.13% [95% CI: 0.56%; 1.71%]**	**1.29% [95% CI: 0.10%; 2.48%]**	**0.82% [95% CI: 0.14%; 1.50%]**	0.01% [95% CI: -1.07%; 1.10%]

IQR: Interquartile range; Cardio. HA: cardiovascular disease hospital admission (ICD-10 code: I00-I99); CI: Confidence interval; Heart. HA: Heart disease hospital admission (ICD-10 code: I00-I52); Cerebr. HA: Cerebrovascular disease hospital admission (ICD-10 code: I60-I69); Resp. HA: Respiratory disease hospital admission (ICD-10 code: J00-J99); LRTI HA: Lower Respiratory Tract Infections hospital admission (ICD-10 code: J12-J18 & J20-J22); NC: Number Concentration in a certain size range; NuMP: Nucleation mode particles (10-30nm); AiMP: Aitken mode particles (30-100nm); Accumulation mode particles (100-800 nm); Numbers printed in bold indicate statistical significance ($p < 0.05$).

*: $I^2 > 50\%$ & $p < 0.05$.

†: Pooled analysis for this air pollution without station LTR (no data at this station available).

‡: NO_2 data for Augsburg measured at station A-LfU instead of AFH.

Supplementary Table 10: Percent changes in the relative risk [and 95% confidence intervals] of cardiovascular (Cardio. HA, left) and respiratory (Resp. HA, right) hospital admissions per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in UFP or PNC. Standardization by IQR facilitates comparison between different pollutants. Results from the station-specific analysis for the average lags 0-1 (Cardio. HA) and 2-4 (Resp. HA), adjusted for main model covariates.

Variable	IQR	Cardio. HA [95% CI]	IQR	Resp. HA [95% CI]
UFP				
LMI	4,676	**1.27% [95% CI: 0.08%; 2.47%]**	4,329	**1.62% [95% CI: 0.11%; 3.15%]**
LWE	2,833	**2.00% [95% CI: 0.44%; 3.58%]**	2,687	1.15% [95% CI: -0.93%; 3.28%]
LTR	2,826	0.23% [95% CI: -0.83%; 1.30%]	2,684	**1.92% [95% CI: 0.47%; 3.39%]**
DDN	3,920	-0.20% [95% CI: -1.47%; 1.09%]	3,804	0.38% [95% CI: -1.42%; 2.23%]
DDW	2,988	0.40% [95% CI: -0.88%; 1.69%]	2,802	0.36% [95% CI: -1.45%; 2.20%]
AFH	3,275	-0.10% [95% CI: -1.36%; 1.18%]	3,013	-0.66% [95% CI: -2.34%; 1.03%]
Pooled estimate	3,420	0.43% [95% CI: -0.25%; 1.12%]	3,220	0.69% [95% CI: -0.28%; 1.67%]
I^2 & p-value		30.60%, p = 0.206		25.10%, p = 0.246
PNC				
LMI	5,360	**1.33% [95% CI: 0.13%; 2.53%]**	5,004	**1.86% [95% CI: 0.34%; 3.40%]**
LWE	3,184	**1.95% [95% CI: 0.42%; 3.50%]**	2,976	1.64% [95% CI: -0.36%; 3.69%]
LTR	3,347	0.41% [95% CI: -0.70%; 1.53%]	3,189	**2.46% [95% CI: 0.96%; 3.98%]**
DDN	4,550	-0.02% [95% CI: -1.35%; 1.32%]	4,449	0.64% [95% CI: -1.24%; 2.56%]
DDW	3,680	0.54% [95% CI: -0.78%; 1.88%]	3,404	0.78% [95% CI: -1.06%; 2.64%]
AFH	3,747	-0.23% [95% CI: -1.47%; 1.04%]	3,445	-0.64% [95% CI: -2.28%; 1.03%]
Pooled estimate	3,978	0.51% [95% CI: -0.15%; 1.18%]	3,744	0.90% [95% CI: -0.28%; 2.08%]
I^2 & p-value		27.30%, p = 0.230		44.60%, p = 0.108

UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); IQR: Interquartile range; NM: Natural mortality (ICD-10 code: A00-R99); CI: Confidence interval; CVM: Cardiovascular mortality (ICD-10 code: I00-I99); RM: Respiratory mortality (ICD-10 code: J00-J99); LMI: Leipzig-Mitte; LWE: Leipzig-West; LTR: Leipzig-TROPOS; DDN: Dresden-Nord; DDW: Dresden-Winckelmannstr.; AFH: Augsburg-Hochschule; I^2: Test statistic for heterogeneity. Numbers printed in bold indicate statistical significance ($p < 0.05$).

Supplementary Table 11: Percent changes in the pooled relative risk of cause-specific hospital admissions [and 95% confidence intervals] per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollutants. Standardization by IQR facilitates comparison between different pollutants. Results of the pooled main analysis, by air pollutant, average lag, and hospital admission endpoint stratified by station type. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models, adjusted for main model covariates. Green color indicates the results for the urban background stations; black color for the traffic-related stations.

Variable	IQR	Station	Cardio. HA [95% CI]	Heart. HA [95% CI]	Cerebr. HA [95% CI]	Resp. HA [95% CI]	LRTI HA [95% CI]
UFP							
Lag 0-1	2,981	UB	0.49% [95% CI: -0.21%; 1.19%]	0.56% [95% CI: -0.17%; 1.29%]	-0.28% [95% CI: -1.75%; 1.21%]	-0.38% [95% CI: -1.24%; 0.49%]	0.60% [95% CI: -0.78%; 2.01%]
Lag 2-4	2,797	UB	0.00% [95% CI: -1.28%; 1.29%]	-0.18% [95% CI: -0.89%; 0.54%]	1.40% [95% CI: -1.35%; 4.23%]*	0.57% [95% CI: -0.84%; 2.01%]	0.04% [95% CI: -1.93%; 2.04%]
Lag 5-7	2,800	UB	-0.24% [95% CI: -0.83%; 0.35%]	-0.08% [95% CI: -0.76%; 0.60%]	-0.95% [95% CI: -2.35%; 0.46%]	-0.53% [95% CI: -1.56%; 0.51%]	-0.18% [95% CI: -2.58%; 2.27%]*
Lag 0-7	2,395	UB	-0.04% [95% CI: -1.43%; 1.37%]	-0.01% [95% CI: -0.84%; 0.82%]	0.29% [95% CI: -2.73%; 3.41%]	0.13% [95% CI: -0.86%; 1.13%]	0.40% [95% CI: -2.19%; 3.05%]
Lag 0-1	4,298	TR	0.55% [95% CI: -0.79%; 1.90%]	0.20% [95% CI: -2.00%; 2.46%]*	0.09% [95% CI: -1.90%; 2.11%]	0.05% [95% CI: -1.12%; 1.24%]	0.56% [95% CI: -1.36%; 2.52%]
Lag 2-4	4,066	TR	**1.22% [95% CI: 0.38%; 2.07%]**	0.94% [95% CI: -0.24%; 2.14%]	**2.54% [95% CI: 0.32%; 4.81%]**	1.14% [95% CI: 0.00%; 2.30%]	0.59% [95% CI: -2.23%; 3.50%]
Lag 5-7	4,068	TR	-0.15% [95% CI: -0.93%; 0.63%]	0.13% [95% CI: -0.77%; 1.03%]	-0.36% [95% CI: -2.46%; 1.78%]	-0.71% [95% CI: -1.78%; 0.38%]	-0.59% [95% CI: -2.35%; 1.20%]
Lag 0-7	3,623	TR	0.62% [95% CI: -0.16%; 1.41%]	0.90% [95% CI: 0.00%; 1.80%]	1.18% [95% CI: -3.64%; 6.24%]*	-0.16% [95% CI: -1.24%; 0.92%]	-0.26% [95% CI: -2.02%; 1.55%]
PNC							
Lag 0-1	3,490	UB	0.53% [95% CI: -0.16%; 1.22%]	0.37% [95% CI: -0.37%; 1.11%]	0.46% [95% CI: -1.04%; 1.99%]	-0.32% [95% CI: -1.18%; 0.56%]	0.35% [95% CI: -1.03%; 1.74%]
Lag 2-4	3,253	UB	0.25% [95% CI: -1.09%; 1.61%]*	0.12% [95% CI: -0.59%; 0.84%]	1.33% [95% CI: -1.55%; 4.29%]*	0.87% [95% CI: -0.69%; 2.45%]*	0.24% [95% CI: -1.88%; 2.41%]
Lag 5-7	3,255	UB	-0.07% [95% CI: -0.65%; 0.52%]	0.16% [95% CI: -0.51%; 0.84%]	-0.85% [95% CI: -2.32%; 0.64%]	-0.40% [95% CI: -1.46%; 0.67%]	-0.10% [95% CI: -2.25%; 2.08%]
Lag 0-7	2,742	UB	0.20% [95% CI: -1.06%; 1.47%]	0.22% [95% CI: -0.57%; 1.01%]	0.52% [95% CI: -1.61%; 2.71%]	0.37% [95% CI: -0.58%; 1.34%]	0.55% [95% CI: -1.51%; 2.65%]
Lag 0-1	4,955	TR	0.69% [95% CI: -0.51%; 1.92%]	0.14% [95% CI: -1.90%; 2.23%]	0.63% [95% CI: -1.41%; 2.70%]	0.14% [95% CI: -1.05%; 1.35%]	0.17% [95% CI: -1.77%; 2.14%]
Lag 2-4	4,726	TR	**1.48% [95% CI: 0.63%; 2.35%]**	**1.20% [95% CI: 0.08%; 2.33%]**	**2.65% [95% CI: 0.65%; 4.70%]**	**1.40% [95% CI: 0.23%; 2.58%]**	0.67% [95% CI: -2.27%; 3.70%]
Lag 5-7	4,729	TR	0.03% [95% CI: -0.76%; 0.83%]	0.38% [95% CI: -0.53%; 1.30%]	-0.22% [95% CI: -2.52%; 2.14%]	-0.68% [95% CI: -1.76%; 0.42%]	-0.74% [95% CI: -2.51%; 1.06%]
Lag 0-7	4,179	TR	**0.81% [95% CI: 0.02%; 1.60%]**	**1.06% [95% CI: 0.15%; 1.97%]**	1.43% [95% CI: -3.49%; 6.61%]*	-0.04% [95% CI: -1.12%; 1.05%]	-0.38% [95% CI: -2.15%; 1.42%]
BC							
Lag 0-1	0.78	UB	0.31% [95% CI: -0.15%; 0.76%]	-0.35% [95% CI: -0.87%; 0.17%]	1.59% [95% CI: 0.51%; 2.69%]	0.02% [95% CI: -0.58%; 0.62%]	-0.61% [95% CI: -1.54%; 0.32%]
Lag 2-4	0.75	UB	0.46% [95% CI: -0.68%; 1.62%]*	0.32% [95% CI: -0.57%; 1.23%]	0.50% [95% CI: -1.46%; 2.49%]	0.34% [95% CI: -1.03%; 1.72%]*	-0.58% [95% CI: -2.86%; 1.76%]*
Lag 5-7	0.75	UB	0.34% [95% CI: -0.11%; 0.80%]	0.56% [95% CI: 0.04%; 1.08%]	0.30% [95% CI: -1.56%; 2.20%]	-0.18% [95% CI: -0.99%; 0.64%]	-0.17% [95% CI: -1.08%; 0.75%]

Lag 0-7	0.62	UB	0.81% [95% CI: 0.28%; 1.34%]	0.44% [95% CI: -0.15%; 1.03%]	1.43% [95% CI: 0.17%; 2.71%]	0.05% [95% CI: -1.19%; 1.31%]	-0.52% [95% CI: -1.58%; 0.55%]
Lag 0-1	1.15	TR	0.65% [95% CI: -0.12%; 1.43%]	-0.15% [95% CI: -1.03%; 0.73%]	1.74% [95% CI: -0.07%; 3.59%]	0.36% [95% CI: -1.03%; 1.76%]	-1.50% [95% CI: -3.11%; 0.15%]
Lag 2-4	1.15	TR	**1.14% [95% CI: 0.30%; 1.98%]**	**1.02% [95% CI: 0.06%; 1.99%]**	0.74% [95% CI: -1.22%; 2.73%]	**2.06% [95% CI: 0.93%; 3.19%]**	0.74% [95% CI: -1.01%; 2.52%]
Lag 5-7	1.15	TR	0.09% [95% CI: -0.70%; 0.89%]	0.49% [95% CI: -0.42%; 1.41%]	-0.52% [95% CI: -2.39%; 1.39%]	0.14% [95% CI: -0.92%; 1.21%]	-0.59% [95% CI: -2.27%; 1.12%]
Lag 0-7	1.05	TR	0.68% [95% CI: -0.26%; 1.62%]	0.60% [95% CI: -0.47%; 1.68%]	0.50% [95% CI: -1.70%; 2.75%]	**1.28% [95% CI: 0.02%; 2.56%]**	-0.09% [95% CI: -2.08%; 1.94%]
$PM_{2.5}$†							
Lag 0-1	10.37	UB	0.52% [95% CI: 0.01%; 1.03%]	0.02% [95% CI: -0.57%; 0.61%]	1.64% [95% CI: 0.22%; 3.07%]	0.65% [95% CI: -0.03%; 1.33%]	-0.60% [95% CI: -1.65%; 0.46%]
Lag 2-4	9.93	UB	0.88% [95% CI: -0.16%; 1.93%]*	0.88% [95% CI: 0.25%; 1.52%]	0.10% [95% CI: -2.72%; 2.99%]*	1.11% [95% CI: 0.00%; 2.23%]	-0.05% [95% CI: -1.51%; 1.44%]
Lag 5-7	9.93	UB	0.82% [95% CI: 0.27%; 1.37%]	0.96% [95% CI: 0.33%; 1.59%]	0.81% [95% CI: -0.37%; 2.02%]	0.71% [95% CI: 0.06%; 1.37%]	0.55% [95% CI: -0.46%; 1.58%]
Lag 0-7	8.77	UB	1.15% [95% CI: 0.18%; 2.12%]	0.98% [95% CI: 0.24%; 1.73%]	1.32% [95% CI: -0.66%; 3.35%]	1.22% [95% CI: 0.42%; 2.04%]	-0.03% [95% CI: -1.29%; 1.24%]
Lag 0-1	11.40	TR	**0.69% [95% CI: 0.10%; 1.29%]**	0.09% [95% CI: -0.59%; 0.78%]	**1.89% [95% CI: 0.46%; 3.34%]**	0.64% [95% CI: -0.16%; 1.44%]	-0.94% [95% CI: -2.19%; 0.34%]
Lag 2-4	10.90	TR	**1.22% [95% CI: 0.06%; 2.40%]**	**1.21% [95% CI: 0.48%; 1.95%]**	1.40% [95% CI: -1.25%; 4.12%]	**1.33% [95% CI: 0.48%; 2.18%]**	0.36% [95% CI: -0.97%; 1.72%]
Lag 5-7	10.90	TR	**0.76% [95% CI: 0.18%; 1.33%]**	**0.93% [95% CI: 0.26%; 1.60%]**	0.75% [95% CI: -0.64%; 2.15%]	0.50% [95% CI: -0.27%; 1.27%]	-0.10% [95% CI: -1.32%; 1.15%]
Lag 0-7	9.60	TR	**1.44% [95% CI: 0.67%; 2.22%]**	**1.28% [95% CI: 0.45%; 2.11%]**	2.04% [95% CI: -0.19%; 4.33%]	**1.25% [95% CI: 0.28%; 2.22%]**	-0.35% [95% CI: -1.87%; 1.20%]
NO_2†‡							
Lag 0-1	10.83	UB	0.66% [95% CI: -0.14%; 1.45%]	0.09% [95% CI: -0.82%; 1.01%]	1.51% [95% CI: -0.40%; 3.45%]	0.69% [95% CI: -0.54%; 1.93%]	-0.36% [95% CI: -2.34%; 1.66%]
Lag 2-4	10.23	UB	0.27% [95% CI: -1.17%; 1.73%]	0.26% [95% CI: -0.80%; 1.34%]	0.19% [95% CI: -2.85%; 3.33%]	1.58% [95% CI: -0.36%; 3.56%]*	0.16% [95% CI: -2.74%; 3.15%]*
Lag 5-7	10.23	UB	0.09% [95% CI: -0.67%; 0.85%]	0.39% [95% CI: -0.49%; 1.28%]	-0.01% [95% CI: -1.83%; 1.83%]	0.15% [95% CI: -1.03%; 1.34%]	0.16% [95% CI: -1.37%; 1.73%]
Lag 0-7	8.93	UB	0.51% [95% CI: -0.46%; 1.49%]	0.44% [95% CI: -0.68%; 1.57%]	0.72% [95% CI: -1.59%; 3.09%]	1.09% [95% CI: -0.72%; 2.94%]	-0.33% [95% CI: -2.83%; 2.23%]
Lag 0-1	13.25	TR	0.09% [95% CI: -1.18%; 1.37%]	-0.16% [95% CI: -1.50%; 1.19%]	0.92% [95% CI: -3.68%; 5.74%]*	-0.33% [95% CI: -2.04%; 1.42%]	-0.33% [95% CI: -3.50%; 2.94%]
Lag 2-4	12.15	TR	-0.02% [95% CI: -0.80%; 0.76%]	-0.09% [95% CI: -0.98%; 0.80%]	0.84% [95% CI: -1.02%; 2.73%]	**1.17% [95% CI: 0.10%; 2.25%]**	0.42% [95% CI: -2.24%; 3.16%]
Lag 5-7	12.15	TR	-0.63% [95% CI: -1.73%; 0.48%]	-0.42% [95% CI: -1.27%; 0.44%]	-0.68% [95% CI: -2.45%; 1.12%]	-0.51% [95% CI: -1.73%; 0.73%]	0.06% [95% CI: -1.60%; 1.74%]
Lag 0-7	9.50	TR	-0.40% [95% CI: -1.73%; 0.96%]	-0.37% [95% CI: -1.45%; 0.72%]	0.04% [95% CI: -2.57%; 2.72%]	-0.06% [95% CI: -1.36%; 1.26%]	-0.12% [95% CI: -2.03%; 1.82%]
NuMP							
Lag 0-1	1,584	UB	0.47% [95% CI: -0.14%; 1.08%]	0.72% [95% CI: 0.09%; 1.36%]	-0.70% [95% CI: -1.99%; 0.60%]	-0.10% [95% CI: -0.87%; 0.67%]	1.11% [95% CI: -0.14%; 2.38%]
Lag 2-4	1,473	UB	-0.35% [95% CI: -1.28%; 0.59%]	-0.38% [95% CI: -1.01%; 0.26%]	0.86% [95% CI: -1.09%; 2.85%]*	0.26% [95% CI: -0.52%; 1.05%]	-0.48% [95% CI: -2.21%; 1.28%]
Lag 5-7	1,475	UB	-0.34% [95% CI: -0.88%; 0.21%]	-0.28% [95% CI: -0.90%; 0.36%]	-0.73% [95% CI: -2.00%; 0.56%]	-0.70% [95% CI: -1.78%; 0.38%]	-0.29% [95% CI: -2.02%; 1.47%]*

Lag 0-7	1,284	UB	-0.30% [95% CI: -1.24%; 0.65%]	-0.13% [95% CI: -1.04%; 0.79%]	-0.13% [95% CI: -3.31%; 3.16%]	-0.17% [95% CI: -1.14%; 0.81%]	-0.15% [95% CI: -3.12%; 2.90%]
Lag 0-1	2,595	TR	0.57% [95% CI: -0.80%; 1.97%]	0.46% [95% CI: -1.66%; 2.62%]*	-0.27% [95% CI: -2.23%; 1.73%]	0.15% [95% CI: -1.03%; 1.34%]	1.02% [95% CI: -1.06%; 3.15%]
Lag 2-4	2,411	TR	**0.98% [95% CI: 0.15%; 1.82%]**	0.78% [95% CI: -0.38%; 1.96%]	2.32% [95% CI: -0.31%; 5.01%]	0.71% [95% CI: -0.42%; 1.86%]	0.17% [95% CI: -2.35%; 2.75%]
Lag 5-7	2,411	TR	-0.32% [95% CI: -1.10%; 0.46%]	-0.11% [95% CI: -1.01%; 0.79%]	-0.46% [95% CI: -2.28%; 1.40%]	-0.74% [95% CI: -1.81%; 0.34%]	-0.52% [95% CI: -2.29%; 1.27%]
Lag 0-7	2,166	TR	0.44% [95% CI: -0.36%; 1.25%]	0.73% [95% CI: -0.19%; 1.66%]	0.95% [95% CI: -3.75%; 5.88%]*	-0.29% [95% CI: -1.39%; 0.82%]	-0.24% [95% CI: -2.04%; 1.60%]
AiMP							
Lag 0-1	1,576	UB	0.28% [95% CI: -0.35%; 0.93%]	0.11% [95% CI: -0.63%; 0.85%]	0.43% [95% CI: -1.07%; 1.95%]	-0.60% [95% CI: -1.47%; 0.27%]	-0.23% [95% CI: -1.95%; 1.52%]
Lag 2-4	1,475	UB	0.46% [95% CI: -0.72%; 1.67%]*	0.16% [95% CI: -0.57%; 0.89%]	2.06% [95% CI: -1.50%; 5.76%]*	0.96% [95% CI: -1.06%; 3.03%]*	0.66% [95% CI: -2.21%; 3.62%]*
Lag 5-7	1,475	UB	-0.06% [95% CI: -0.65%; 0.54%]	0.17% [95% CI: -0.52%; 0.86%]	-0.83% [95% CI: -2.61%; 0.97%]	-0.29% [95% CI: -1.09%; 0.53%]	0.17% [95% CI: -1.32%; 1.68%]
Lag 0-7	1,236	UB	0.31% [95% CI: -0.64%; 1.27%]	0.20% [95% CI: -0.63%; 1.04%]	0.74% [95% CI: -1.97%; 3.53%]	0.41% [95% CI: -0.59%; 1.41%]	0.81% [95% CI: -1.46%; 3.13%]
Lag 0-1	2,041	TR	0.49% [95% CI: -0.68%; 1.67%]	-0.07% [95% CI: -2.07%; 1.97%]	0.56% [95% CI: -1.50%; 2.67%]	-0.09% [95% CI: -1.31%; 1.14%]	-0.08% [95% CI: -2.07%; 1.94%]
Lag 2-4	1,941	TR	**1.40% [95% CI: 0.53%; 2.27%]**	1.06% [95% CI: -0.19%; 2.31%]	**2.64% [95% CI: 0.62%; 4.72%]**	**1.60% [95% CI: 0.41%; 2.80%]**	1.24% [95% CI: -1.81%; 4.39%]
Lag 5-7	1,941	TR	0.09% [95% CI: -0.71%; 0.90%]	0.44% [95% CI: -0.49%; 1.37%]	-0.28% [95% CI: -2.61%; 2.11%]	-0.60% [95% CI: -1.71%; 0.52%]	-0.63% [95% CI: -2.46%; 1.22%]
Lag 0-7	1,725	TR	**0.88% [95% CI: 0.05%; 1.71%]**	1.13% [95% CI: 0.18%; 2.09%]	1.28% [95% CI: -3.44%; 6.22%]*	0.01% [95% CI: -1.13%; 1.17%]	-0.28% [95% CI: -2.17%; 1.65%]
AcMP							
Lag 0-1	820	UB	0.32% [95% CI: -0.41%; 1.06%]	-0.42% [95% CI: -1.09%; 0.26%]	2.17% [95% CI: 0.13%; 4.26%]	0.09% [95% CI: -0.94%; 1.13%]	-0.56% [95% CI: -1.77%; 0.67%]
Lag 2-4	772	UB	0.96% [95% CI: -0.35%; 2.28%]*	0.96% [95% CI: 0.16%; 1.76%]	0.39% [95% CI: -2.79%; 3.68%]*	1.25% [95% CI: -0.32%; 2.86%]	0.50% [95% CI: -1.78%; 2.84%]
Lag 5-7	773	UB	0.51% [95% CI: -0.05%; 1.07%]	0.86% [95% CI: 0.10%; 1.62%]	-0.44% [95% CI: -2.32%; 1.47%]*	0.04% [95% CI: -0.93%; 1.01%]	0.09% [95% CI: -1.08%; 1.26%]
Lag 0-7	634	UB	0.98% [95% CI: 0.27%; 1.71%]	0.84% [95% CI: 0.12%; 1.58%]	1.18% [95% CI: -0.32%; 2.71%]	1.01% [95% CI: 0.09%; 1.94%]	0.61% [95% CI: -0.78%; 2.03%]
Lag 0-1	990	TR	0.78% [95% CI: -0.03%; 1.60%]	-0.16% [95% CI: -1.08%; 0.78%]	**2.37% [95% CI: 0.47%; 4.30%]**	0.44% [95% CI: -1.15%; 2.06%]	-1.31% [95% CI: -3.02%; 0.42%]
Lag 2-4	944	TR	**1.66% [95% CI: 0.14%; 3.20%]**	**1.54% [95% CI: 0.58%; 2.50%]**	**2.02% [95% CI: 0.12%; 3.96%]**	**1.64% [95% CI: 0.55%; 2.75%]**	0.87% [95% CI: -1.09%; 2.87%]
Lag 5-7	943	TR	0.76% [95% CI: 0.00%; 1.53%]	**1.24% [95% CI: 0.36%; 2.13%]**	0.20% [95% CI: -1.58%; 2.01%]	-0.23% [95% CI: -1.26%; 0.80%]	-0.95% [95% CI: -2.59%; 0.72%]
Lag 0-7	845	TR	**1.53% [95% CI: 0.68%; 2.39%]**	**1.60% [95% CI: 0.62%; 2.59%]**	1.68% [95% CI: -1.20%; 4.65%]	0.57% [95% CI: -0.59%; 1.74%]	-0.89% [95% CI: -2.74%; 1.00%]

IQR: Interquartile range; Cardio. HA: cardiovascular disease hospital admission (ICD-10 code: I00-I99); CI: Confidence interval; Heart. HA: Heart disease hospital admission (ICD-10 code: I00-I52); Cerebr. HA: Cerebrovascular disease hospital admission (ICD-10 code: I60-I69); Resp. HA: Respiratory disease hospital admission (ICD-10 code: J00-J99); LRTI HA: Lower Respiratory Tract Infections hospital admission (ICD-10 code: J12-J18 & J20-J22); UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); BC: Black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≤ 2.5µm; NO_2: Nitrogen dioxide. Numbers printed in bold indicate statistical significance ($p < 0.05$).

*: $I^2 > 50\%$ & $p < 0.05$.
†: Pooled analysis for this air pollution without station LTR (no data at this station available).
‡: NO_2 data for Augsburg measured at station A-LfU instead of AFH.

Supplementary Table 12: Percent changes in relative risk of respiratory hospital admissions [and 95% confidence intervals] per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in average Lag 2-4 UFP (left) and PNC (right) exposures. Results of the two-pollutant and effect modification analysis. Standardization by IQR facilitates comparison between different pollutants. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models, adjusted for main model covariates.

Analysis	IQR	UFP	IQR	PNC
Main analysis	3,220	0.69% [95% CI: -0.28%; 1.67%]	3,744	0.90% [95% CI: -0.28%; 2.08%]
Two-pollutant model				
+ adj. BC	3,220	0.54% [95% CI: -0.49%; 1.59%]	3,744	0.65% [95% CI: -0.60%; 1.92%]
+ adj. $PM_{2.5}$*	3,327	0.50% [95% CI: -0.25%; 1.26%]	3,856	0.53% [95% CI: -0.25%; 1.31%]
+ adj. NO_2†	3,077	-0.17% [95% CI: -1.26%; 0.92%]	3,569	-0.04% [95% CI: -1.71%; 1.67%]
Effect modification				
Female	3,220	0.58% [95% CI: -0.78%; 1.97%]	3,744	0.74% [95% CI: -0.74%; 2.24%]
Male	3,220	0.85% [95% CI: 0.00%; 1.71%]	3,744	**1.12% [95% CI: 0.09%; 2.15%]**
0-17 years	3,220	2.54% [95% CI: -0.47%; 5.63%]	3,744	2.19% [95% CI: -0.99%; 5.47%]
18-64 years	3,220	0.94% [95% CI: -0.16%; 2.06%]	3,744	**1.27% [95% CI: 0.16%; 2.41%]**
65+ years	3,220	-0.19% [95% CI: -1.11%; 0.75%]	3,744	0.30% [95% CI: -0.64%; 1.25%]
Apr.-Sep.	3,220	-0.54% [95% CI: -1.55%; 0.48%]	3,744	-0.37% [95% CI: -1.52%; 0.79%]
Oct.-Mar.	3,220	**1.47% [95% CI: 0.25%; 2.70%]**	3,744	**1.60% [95% CI: 0.26%; 2.95%]**

UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); IQR: Interquartile range; Adj.: adjustment; BC: Black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≤ 2.5µm; NO_2: Nitrogen dioxide. Apr.: April; Sep.: September; Oct.: October; Mar.: March; Numbers printed in bold indicate statistical significance ($p < 0.05$).

*: Pooled analysis without station LTR (no data at this station available).
†: Pooled analysis without station LTR (no data at this station available) and LMI (Spearman correlation coefficient ≥ 0.7).

Supplementary Table 13: Percent changes in the pooled relative risk of cause-specific hospital admissions [and 95% confidence intervals] per fixed-unit increase in air pollutants. Pooled estimates, by air pollutant, average lag, and hospital admission endpoint, based on multilevel random-effects models adjusting for main model covariates.

Variable	Fixed-unit increase	Cardio. HA [95% CI]	Heart. HA [95% CI]	Cerebr. HA [95% CI]	Resp. HA [95% CI]	LRTI HA [95% CI]
UFP						
Lag 0-1	10,000	1.26% [95% CI: -0.74%; 3.31%]	1.31% [95% CI: -0.88%; 3.54%]	-0.33% [95% CI: -3.67%; 3.12%]	-0.54% [95% CI: -2.50%; 1.47%]	1.67% [95% CI: -1.57%; 5.01%]
Lag 2-4	10,000	0.77% [95% CI: -2.38%; 4.03%]*	1.05% [95% CI: -0.68%; 2.81%]	4.99% [95% CI: -4.50%; 15.42%]*	2.16% [95% CI: -0.87%; 5.28%]	0.86% [95% CI: -3.58%; 5.52%]
Lag 5-7	10,000	-0.59% [95% CI: -2.00%; 0.83%]	0.04% [95% CI: -1.58%; 1.70%]	-1.93% [95% CI: -5.65%; 1.94%]	-1.69% [95% CI: -3.61%; 0.27%]	-0.49% [95% CI: -4.67%; 3.88%]
Lag 0-7	10,000	0.68% [95% CI: -2.16%; 3.60%]	1.61% [95% CI: -0.40%; 3.67%]	1.41% [95% CI: -3.80%; 6.89%]*	-0.10% [95% CI: -2.49%; 2.34%]	0.28% [95% CI: -4.71%; 5.55%]
PNC						
Lag 0-1	10,000	1.29% [95% CI: -0.37%; 2.99%]	0.81% [95% CI: -0.91%; 2.56%]	1.30% [95% CI: -1.67%; 4.36%]	-0.28% [95% CI: -2.02%; 1.49%]	0.66% [95% CI: -2.11%; 3.52%]
Lag 2-4	10,000	1.38% [95% CI: -1.22%; 4.05%]*	1.38% [95% CI: -0.42%; 3.22%]	4.11% [95% CI: -4.14%; 13.06%]*	2.41% [95% CI: -0.73%; 5.65%]	1.01% [95% CI: -3.11%; 5.30%]
Lag 5-7	10,000	-0.06% [95% CI: -1.28%; 1.17%]	0.67% [95% CI: -0.74%; 2.10%]	-1.37% [95% CI: -4.92%; 2.31%]	-1.27% [95% CI: -2.94%; 0.43%]	-0.53% [95% CI: -3.94%; 3.01%]
Lag 0-7	10,000	1.37% [95% CI: -0.69%; 3.47%]	**1.92% [95% CI: 0.18%; 3.69%]**	2.01% [95% CI: -2.77%; 7.03%]*	0.44% [95% CI: -1.62%; 2.55%]	0.15% [95% CI: -4.40%; 4.91%]
BC						
Lag 0-1	1	**0.47% [95% CI: 0.03%; 0.91%]**	-0.31% [95% CI: -0.81%; 0.19%]	**1.81% [95% CI: 0.77%; 2.87%]**	0.12% [95% CI: -0.48%; 0.72%]	-1.00% [95% CI: -1.91%; -0.08%]
Lag 2-4	1	0.74% [95% CI: -0.30%; 1.78%]	**0.77% [95% CI: 0.18%; 1.37%]**	0.64% [95% CI: -1.07%; 2.38%]	0.79% [95% CI: -0.90%; 2.52%]	-0.67% [95% CI: -3.42%; 2.16%]*
Lag 5-7	1	0.29% [95% CI: -0.16%; 0.75%]	**0.61% [95% CI: 0.09%; 1.14%]**	0.47% [95% CI: -1.56%; 2.54%]	-0.01% [95% CI: -0.60%; 0.60%]	-0.34% [95% CI: -1.27%; 0.61%]
Lag 0-7	1	**1.02% [95% CI: 0.38%; 1.66%]**	0.64% [95% CI: -0.06%; 1.34%]	1.49% [95% CI: -0.06%; 3.06%]	0.40% [95% CI: -1.37%; 2.21%]	-0.51% [95% CI: -1.76%; 0.77%]
$PM_{2.5}$†						
Lag 0-1	10	**0.55% [95% CI: 0.19%; 0.91%]**	0.05% [95% CI: -0.36%; 0.46%]	**1.57% [95% CI: 0.48%; 2.68%]**	**0.59% [95% CI: 0.12%; 1.07%]**	-0.69% [95% CI: -1.44%; 0.06%]
Lag 2-4	10	0.91% [95% CI: -0.18%; 2.01%]*	**0.97% [95% CI: 0.46%; 1.49%]**	0.18% [95% CI: -2.77%; 3.22%]*	**1.12% [95% CI: 0.32%; 1.93%]**	0.18% [95% CI: -0.64%; 1.02%]
Lag 5-7	10	**0.76% [95% CI: 0.39%; 1.12%]**	**0.91% [95% CI: 0.48%; 1.35%]**	0.76% [95% CI: -0.12%; 1.64%]	**0.60% [95% CI: 0.09%; 1.10%]**	0.27% [95% CI: -0.49%; 1.03%]
Lag 0-7	10	**1.36% [95% CI: 0.48%; 2.26%]**	**1.22% [95% CI: 0.63%; 1.81%]**	1.66% [95% CI: -0.48%; 3.85%]	**1.35% [95% CI: 0.67%; 2.04%]**	-0.18% [95% CI: -1.25%; 0.89%]
NO_2†‡						
Lag 0-1	10	0.30% [95% CI: -0.31%; 0.91%]	-0.07% [95% CI: -0.64%; 0.50%]	0.87% [95% CI: -1.01%; 2.78%]	0.21% [95% CI: -1.02%; 1.45%]	-0.14% [95% CI: -1.89%; 1.65%]
Lag 2-4	10	0.08% [95% CI: -0.61%; 0.78%]	0.04% [95% CI: -0.61%; 0.69%]	0.58% [95% CI: -0.62%; 1.79%]	**1.17% [95% CI: 0.06%; 2.29%]**	0.04% [95% CI: -2.26%; 2.40%]

Lag 5-7	10	-0.23% [95% CI: -0.92%; 0.46%]	-0.05% [95% CI: -0.60%; 0.50%]	-0.34% [95% CI: -1.47%; 0.80%]	-0.19% [95% CI: -0.87%; 0.49%]	0.10% [95% CI: -0.92%; 1.12%]
Lag 0-7	10	0.03% [95% CI: -0.88%; 0.96%]	-0.04% [95% CI: -0.84%; 0.78%]	0.29% [95% CI: -1.38%; 1.99%]	0.57% [95% CI: -0.64%; 1.79%]	-0.28% [95% CI: -1.76%; 1.23%]
NC 10-20nm						
Lag 0-1	10,000	3.60% [95% CI: -1.76%; 9.25%]	**5.37% [95% CI: 0.01%; 11.03%]**	-4.16% [95% CI: -11.88%; 4.25%]	0.22% [95% CI: -4.66%; 5.35%]	8.48% [95% CI: -0.05%; 17.75%]
Lag 2-4	10,000	-0.72% [95% CI: -8.72%; 7.97%]*	0.67% [95% CI: -4.64%; 6.27%]	7.36% [95% CI: -12.53%; 31.76%]*	2.01% [95% CI: -3.95%; 8.35%]	-3.84% [95% CI: -16.29%; 10.45%]
Lag 5-7	10,000	-2.83% [95% CI: -6.63%; 1.13%]	-2.53% [95% CI: -6.61%; 1.73%]	-3.80% [95% CI: -11.85%; 4.98%]	-7.74% [95% CI: -16.34%; 1.74%]	-5.32% [95% CI: -20.05%; 12.13%]*
Lag 0-7	10,000	0.11% [95% CI: -5.46%; 6.00%]	1.78% [95% CI: -3.94%; 7.83%]	-4.03% [95% CI: -29.43%; 30.50%]*	-2.77% [95% CI: -8.78%; 3.63%]	-1.65% [95% CI: -15.90%; 15.02%]
NC 20-30nm						
Lag 0-1	10,000	5.94% [95% CI: -0.67%; 12.99%]	7.28% [95% CI: -1.11%; 16.37%]	-3.87% [95% CI: -17.05%; 11.40%]	-0.75% [95% CI: -8.74%; 7.94%]	10.82% [95% CI: -3.12%; 26.76%]
Lag 2-4	10,000	1.54% [95% CI: -9.59%; 14.04%]	-0.69% [95% CI: -11.37%; 11.29%]	24.70% [95% CI: -3.85%; 61.72%]*	**10.34% [95% CI: 0.18%; 21.53%]**	7.21% [95% CI: -7.60%; 24.38%]
Lag 5-7	10,000	-2.23% [95% CI: -8.91%; 4.94%]	1.10% [95% CI: -6.18%; 8.94%]	-9.65% [95% CI: -22.56%; 5.41%]	-5.56% [95% CI: -13.56%; 3.18%]	-3.66% [95% CI: -16.51%; 11.18%]
Lag 0-7	10,000	2.04% [95% CI: -9.92%; 15.59%]	6.60% [95% CI: -2.82%; 16.92%]	6.43% [95% CI: -28.08%; 57.50%]*	-0.35% [95% CI: -10.84%; 11.37%]	4.93% [95% CI: -12.48%; 25.81%]
NC 30-50nm						
Lag 0-1	10,000	5.29% [95% CI: -1.40%; 12.43%]	3.31% [95% CI: -5.83%; 13.33%]	1.24% [95% CI: -12.12%; 16.62%]	-0.77% [95% CI: -8.68%; 7.83%]	7.66% [95% CI: -5.96%; 23.25%]
Lag 2-4	10,000	6.60% [95% CI: -0.64%; 14.37%]	3.03% [95% CI: -5.19%; 11.97%]	10.91% [95% CI: -31.44%; 79.44%]*	8.83% [95% CI: -10.38%; 32.16%]	9.33% [95% CI: -9.88%; 32.64%]
Lag 5-7	10,000	-1.32% [95% CI: -7.02%; 4.74%]	1.84% [95% CI: -4.93%; 9.09%]	-8.14% [95% CI: -20.46%; 6.10%]	-4.05% [95% CI: -11.67%; 4.22%]	-2.00% [95% CI: -14.38%; 12.16%]
Lag 0-7	10,000	5.60% [95% CI: -2.71%; 14.62%]	7.59% [95% CI: -1.33%; 17.32%]	6.56% [95% CI: -31.81%; 66.52%]*	3.30% [95% CI: -6.98%; 14.70%]	7.56% [95% CI: -10.35%; 29.05%]
NC 50-70nm						
Lag 0-1	10,000	6.92% [95% CI: -3.46%; 18.41%]	2.27% [95% CI: -9.02%; 14.96%]	5.47% [95% CI: -16.74%; 33.61%]	-11.52% [95% CI: -23.03%; 1.71%]	-7.02% [95% CI: -28.70%; 21.25%]
Lag 2-4	10,000	13.18% [95% CI: -11.31%; 44.43%]	11.74% [95% CI: -1.43%; 26.66%]	45.38% [95% CI: -10.41%; 135.93%]*	20.75% [95% CI: -16.50%; 74.63%]*	20.42% [95% CI: -26.80%; 98.09%]
Lag 5-7	10,000	1.02% [95% CI: -8.56%; 11.61%]	6.52% [95% CI: -5.06%; 19.50%]	-11.71% [95% CI: -32.79%; 15.98%]	-8.02% [95% CI: -19.90%; 5.61%]	1.28% [95% CI: -19.07%; 26.75%]
Lag 0-7	10,000	**16.47% [95% CI: 1.95%; 33.06%]**	**17.39% [95% CI: 0.80%; 36.70%]**	17.98% [95% CI: -33.35%; 108.84%]	5.04% [95% CI: -12.26%; 25.75%]	14.17% [95% CI: -15.14%; 53.62%]
NC 70-100nm						
Lag 0-1	10,000	5.50% [95% CI: -CI: -5.37%; 17.61%]	-5.87% [95% CI: -16.97%; 6.71%]	**30.07% [95% CI: 0.95%; 67.58%]**	-9.25% [95% CI: -23.72%; 7.96%]	-11.88% [95% CI: -32.35%; 14.80%]

Lag 2-4	10,000	18.41% [95% CI: -12.52%; 60.28%]*	14.35% [95% CI: -10.89%; 46.74%]	36.37% [95% CI: -21.62%; 137.26%]*	35.33% [95% CI: -CI: -5.23%; 93.25%]	29.69% [95% CI: -25.46%; 125.66%]*
Lag 5-7	10,000	4.86% [95% CI: -CI: -5.75%; 16.66%]	12.36% [95% CI: -1.43%; 28.08%]	-9.12% [95% CI: -37.62%; 32.39%]	-7.03% [95% CI: -19.71%; 7.64%]	2.40% [95% CI: -19.09%; 29.59%]
Lag 0-7	10,000	**23.53% [95% CI: 5.52%; 44.62%]**	**23.09% [95% CI: 4.34%; 45.20%]**	27.89% [95% CI: -27.91%; 126.87%]	14.67% [95% CI: -5.62%; 39.31%]	21.23% [95% CI: -11.88%; 66.77%]
NuMP						
Lag 0-1	10,000	2.39% [95% CI: -0.86%; 5.75%]	3.27% [95% CI: -0.62%; 7.32%]	-2.58% [95% CI: -7.89%; 3.04%]	0.01% [95% CI: -3.24%; 3.36%]	5.40% [95% CI: -0.12%; 11.23%]
Lag 2-4	10,000	-0.86% [95% CI: -7.72%; 6.52%]*	0.21% [95% CI: -3.25%; 3.80%]	6.69% [95% CI: -6.38%; 21.59%]*	2.17% [95% CI: -1.83%; 6.34%]	-0.17% [95% CI: -6.24%; 6.29%]
Lag 5-7	10,000	-1.66% [95% CI: -4.40%; 1.16%]	-1.07% [95% CI: -3.81%; 1.75%]	-3.10% [95% CI: -9.00%; 3.17%]	-3.39% [95% CI: -6.97%; 0.32%]	-2.85% [95% CI: -13.31%; 8.88%]
Lag 0-7	10,000	0.02% [95% CI: -4.33%; 4.56%]	1.51% [95% CI: -2.26%; 5.43%]	-1.21% [95% CI: -20.54%; 22.83%]*	-1.27% [95% CI: -5.30%; 2.93%]	-0.16% [95% CI: -8.73%; 9.22%]
AiMP						
Lag 0-1	10,000	2.07% [95% CI: -1.19%; 5.43%]	0.56% [95% CI: -3.07%; 4.31%]	2.77% [95% CI: -4.13%; 10.17%]	-2.26% [95% CI: -6.15%; 1.80%]	-0.84% [95% CI: -7.24%; 5.99%]
Lag 2-4	10,000	**4.55% [95% CI: 0.17%; 9.12%]**	2.80% [95% CI: -1.75%; 7.56%]	13.31% [95% CI: -2.07%; 31.11%]*	**7.33% [95% CI: 1.92%; 13.03%]***	4.54% [95% CI: -6.29%; 16.63%]*
Lag 5-7	10,000	0.01% [95% CI: -2.84%; 2.94%]	1.70% [95% CI: -1.63%; 5.14%]	-3.89% [95% CI: -10.67%; 3.41%]	-2.46% [95% CI: -6.27%; 1.51%]	-0.73% [95% CI: -6.95%; 5.90%]
Lag 0-7	10,000	3.73% [95% CI: -1.18%; 8.87%]	**4.66% [95% CI: 0.30%; 9.21%]**	5.16% [95% CI: -13.70%; 28.12%]*	1.39% [95% CI: -3.68%; 6.73%]	2.00% [95% CI: -6.78%; 11.59%]
AcMP						
Lag 0-1	10,000	**6.15% [95% CI: 0.43%; 12.21%]**	-3.53% [95% CI: -9.34%; 2.64%]	31.07% [95% CI: 15.13%; 49.21%]	2.47% [95% CI: -5.24%; 10.81%]	-9.14% [95% CI: -18.93%; 1.82%]
Lag 2-4	10,000	12.85% [95% CI: -4.76%; 33.71%]*	**15.18% [95% CI: 7.12%; 23.84%]**	4.41% [95% CI: -29.03%; 53.60%]*	**20.43% [95% CI: 10.86%; 30.82%]**	4.40% [95% CI: -18.45%; 33.66%]
Lag 5-7	10,000	**7.51% [95% CI: 1.89%; 13.45%]**	**12.72% [95% CI: 5.19%; 20.80%]**	-0.47% [95% CI: -17.29%; 19.78%]	-0.51% [95% CI: -8.03%; 7.62%]	-3.55% [95% CI: -14.03%; 8.20%]
Lag 0-7	10,000	**18.37% [95% CI: 9.87%; 27.52%]**	**17.30% [95% CI: 8.03%; 27.36%]**	**19.92% [95% CI: 0.56%; 43.01%]**	**12.34% [95% CI: 2.08%; 23.62%]**	0.02% [95% CI: -14.57%; 17.09%]

Cardio. HA: cardiovascular disease hospital admission (ICD-10 code: I00-I99); CI: Confidence interval; Heart. HA: Heart disease hospital admission (ICD-10 code: I00-I52); Cerebr. HA: Cerebrovascular disease hospital admission (ICD-10 code: I60-I69); Resp. HA: Respiratory disease hospital admission (ICD-10 code: J00-J99); LRTI HA: Lower Respiratory Tract Infections hospital admission (ICD-10 code: J12-J18 & J20-J22); UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); BC: Black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≤ 2.5µm; NO_2: Nitrogen dioxide. Numbers printed in bold indicate statistical significance ($p < 0.05$).

*: $I^2 > 50\%$ & $p < 0.05$.

†: Pooled analysis for this air pollution without station LTR (no data at this station available).

‡: NO_2 data for Augsburg measured at station A-LfU instead of AFH.

Supplementary Table 14: Percent changes in relative risk of respiratory hospital admissions [and 95% confidence intervals] per fixed-unit increase in average Lag 2-4 UFP (left) and PNC (right) exposures. Results of the two-pollutant and effect modification analysis. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models, adjusted for main model covariates.

Analysis	Fixed-unit increase	UFP	Fixed-unit increase	PNC
Main analysis	10,000	2.16% [95% CI: -0.87%; 5.28%]	10,000	2.41% [95% CI: -0.73%; 5.65%]
Two-pollutant model				
+ adj. BC	10,000	1.70% [95% CI: -1.52%; 5.03%]	10,000	1.75% [95% CI: -1.61%; 5.21%]
+ adj. $PM_{2.5}$*	10,000	1.51% [95% CI: -0.75%; 3.83%]	10,000	1.38% [95% CI: -0.64%; 3.44%]
+ adj. NO_2†	10,000	-0.56% [95% CI: -4.03%; 3.03%]	10,000	-0.10% [95% CI: -4.72%; 4.75%]
Effect modification				
Female	10,000	1.83% [95% CI: -2.40%; 6.24%]	10,000	2.00% [95% CI: -1.95%; 6.10%]*
Male	10,000	**2.67% [95% CI: 0.00%; 5.41%]**	10,000	**3.01% [95% CI: 0.24%; 5.86%]**
0-17 years	10,000	8.08% [95% CI: -1.44%; 18.53%]*	10,000	5.95% [95% CI: -2.63%; 15.28%]*
18-64 years	10,000	2.96% [95% CI: -0.51%; 6.55%]	10,000	**3.44% [95% CI: 0.41%; 6.56%]**
65+ years	10,000	-0.58% [95% CI: -3.41%; 2.34%]	10,000	0.80% [95% CI: -1.70%; 3.36%]
Apr.-Sep.	10,000	-1.68% [95% CI: -4.74%; 1.49%]	10,000	-1.00% [95% CI: -4.02%; 2.12%]
Oct.-Mar.	10,000	**4.63% [95% CI: 0.77%; 8.64%]**	10,000	**4.33% [95% CI: 0.71%; 8.08%]***

UFP: Particle number concentration of particles in the ultrafine range (10-100nm); PNC: Total particle number concentration (10-800nm); IQR: Interquartile range; Adj.: adjustment; BC: Black carbon; $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≤ 2.5µm; NO_2: Nitrogen dioxide. Apr.: April; Sep.: September; Oct.: October; Mar.: March; Numbers printed in bold indicate statistical significance ($p < 0.05$).

*: Pooled analysis without station LTR (no data at this station available).
†: Pooled analysis without station LTR (no data at this station available) and LMI (Spearman correlation coefficient ≥ 0.7).

Supplementary Table 15: Percent changes in the pooled relative risk of cause-specific hospital admissions [and 95% confidence intervals] per an interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in UFP (20-100nm) and PNC (20-800nm). Results of the pooled main analysis, stratified by air pollutant, average lag, and hospital admission endpoint. Standardization by IQR facilitates comparison between different pollutants. All estimates represent the pooled analysis of the measurement stations multilevel random-effects models, adjusted for main model covariates.

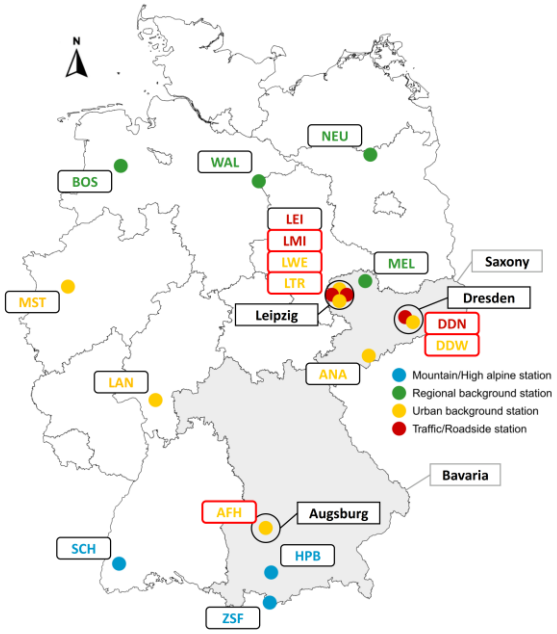
Variable	IQR	Cardio. HA [95% CI]	Heart. HA [95% CI]	Cerebr. HA [95% CI]	Resp. HA [95% CI]	LRTI HA [95% CI]
UFP						
Lag 0-1	2,377	0.37% [95% CI: -0.13%; 0.88%]	0.20% [95% CI: -0.39%; 0.80%]	0.19% [95% CI: -0.98%; 1.37%]	-0.21% [95% CI: -0.89%; 0.48%]	0.37% [95% CI: -0.73%; 1.48%]
Lag 2-4	2,233	0.44% [95% CI: -0.38%; 1.26%]*	0.24% [95% CI: -0.54%; 1.02%]	2.02% [95% CI: -0.59%; 4.71%]*	0.90% [95% CI: -0.68%; 2.50%]*	1.08% [95% CI: -0.20%; 2.37%]
Lag 5-7	2,234	-0.05% [95% CI: -0.50%; 0.41%]	0.25% [95% CI: -0.28%; 0.78%]	-0.64% [95% CI: -1.90%; 0.64%]	-0.44% [95% CI: -1.07%; 0.19%]	-0.19% [95% CI: -1.21%; 0.84%]
Lag 0-7	1,915	0.32% [95% CI: -0.44%; 1.09%]	0.53% [95% CI: -0.04%; 1.10%]	0.67% [95% CI: -1.39%; 2.78%]*	0.21% [95% CI: -0.48%; 0.90%]	0.45% [95% CI: -0.67%; 1.59%]
PNC						
Lag 0-1	3,090	0.47% [95% CI: -0.05%; 0.99%]	0.05% [95% CI: -0.54%; 0.64%]	0.95% [95% CI: -0.26%; 2.17%]	-0.07% [95% CI: -0.77%; 0.64%]	0.06% [95% CI: -1.05%; 1.19%]
Lag 2-4	2,879	0.70% [95% CI: -0.27%; 1.69%]*	0.58% [95% CI: -0.18%; 1.35%]	1.79% [95% CI: -0.85%; 4.49%]*	1.18% [95% CI: -0.82%; 3.21%]*	1.16% [95% CI: -0.23%; 2.58%]
Lag 5-7	2,879	0.17% [95% CI: -0.30%; 0.63%]	**0.54% [95% CI: 0.01%; 1.08%]**	-0.47% [95% CI: -1.85%; 0.93%]	-0.34% [95% CI: -0.97%; 0.30%]	-0.23% [95% CI: -1.24%; 0.80%]
Lag 0-7	2,442	0.48% [95% CI: -0.50%; 1.47%]	**0.75% [95% CI: 0.18%; 1.32%]**	0.86% [95% CI: -0.54%; 2.28%]	0.44% [95% CI: -0.24%; 1.12%]	0.40% [95% CI: -0.71%; 1.53%]

IQR: Interquartile range; Cardio. HA: cardiovascular disease hospital admission (ICD-10 code: I00-I99); CI: Confidence interval; Heart. HA: Heart disease hospital admission (ICD-10 code: I00-I52); Cerebr. HA: Cerebrovascular disease hospital admission (ICD-10 code: I60-I69); Resp. HA: Respiratory disease hospital admission (ICD-10 code: J00-J99); LRTI HA: Lower Respiratory Tract Infections hospital admission (ICD-10 code: J12-J18 & J20-J22); UFP: Particle number concentration of particles in the ultrafine range (20-100nm); PNC: Total particle number concentration (20-800nm). Numbers printed in bold indicate statistical significance ($p < 0.05$).

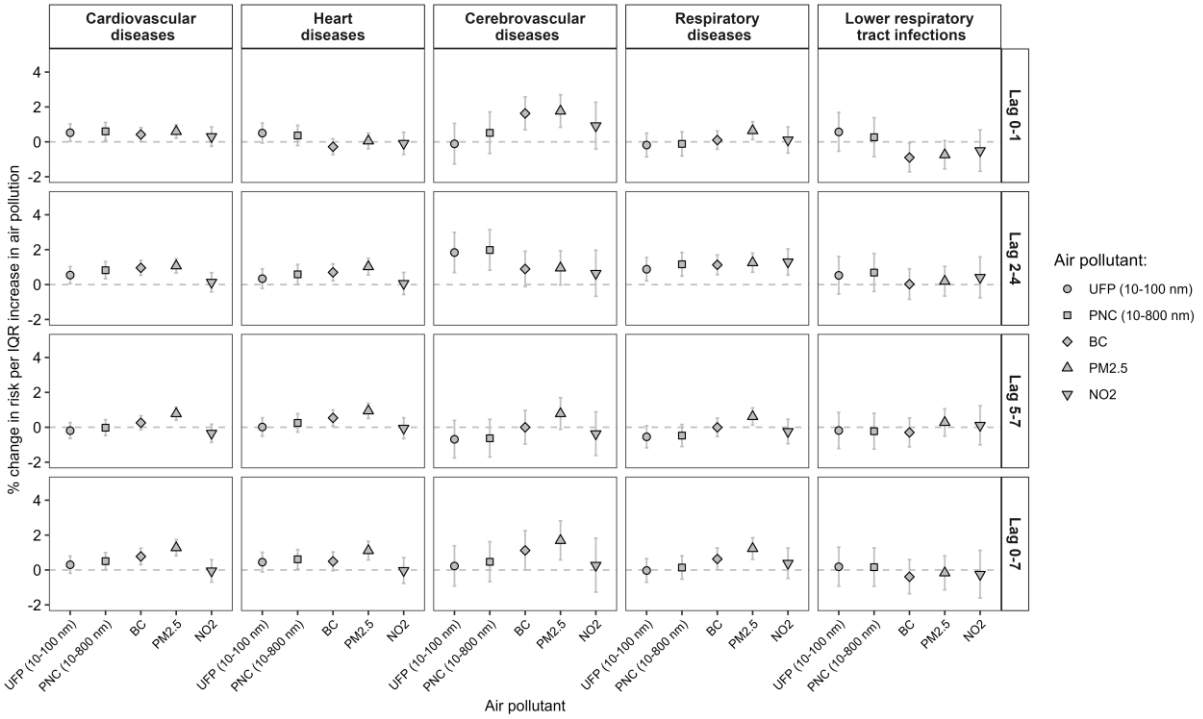
*: $I^2 > 50\%$ & $p < 0.05$.

Supplementary figures:

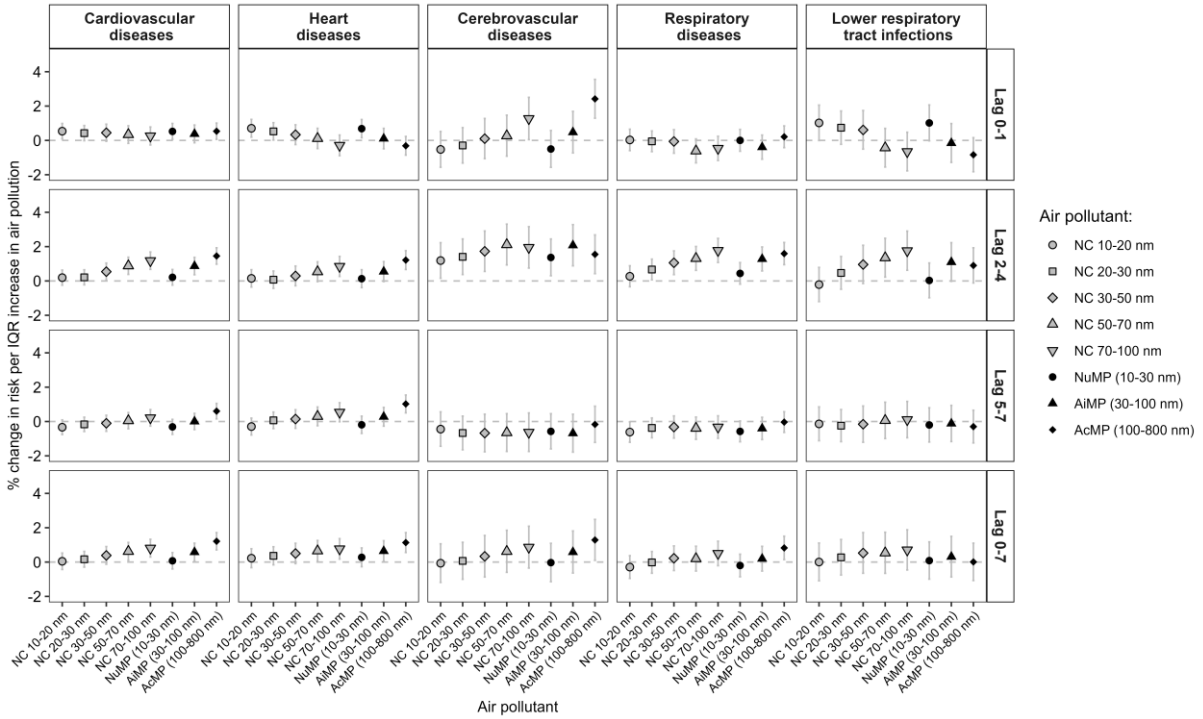
Abbreviation	Station name
ANA	Annaberg-Buchholz
AFH	Augsburg
BOS	Bösel
DDN	Dresden-Nord
DDW	Dresden-Winckelmannstraße
HPB	Hohenpeißenberg
LAN	Langen
LEI	Leipzig-Eisenbahnstraße
LMI	Leipzig-Mitte
LTR	Leipzig-TROPOS
LWE	Leipzig-West
MEL	Melpitz
MST	Mülheim-Styrum
NEU	Neuglobsow
SCH	Schauinsland
WAL	Waldhof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



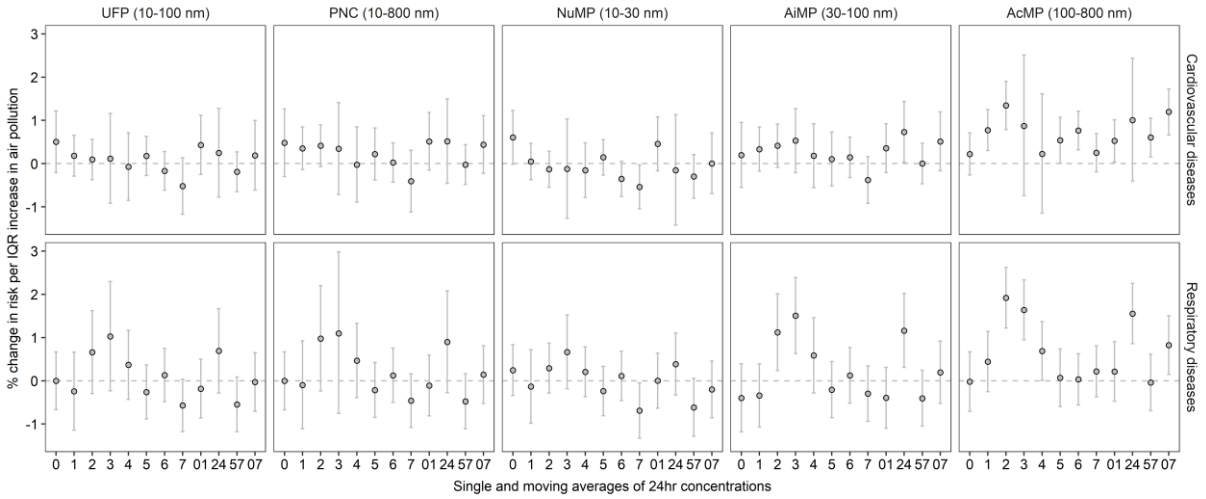
Supplementary Figure 1: Location of German Ultrafine Aerosol Network stations across Germany (divided by federal states) and classification according to station type. Stations used for this analysis are highlighted with red boxes. Map adapted from (Birmili et al. 2016) and (Sun et al. 2019).



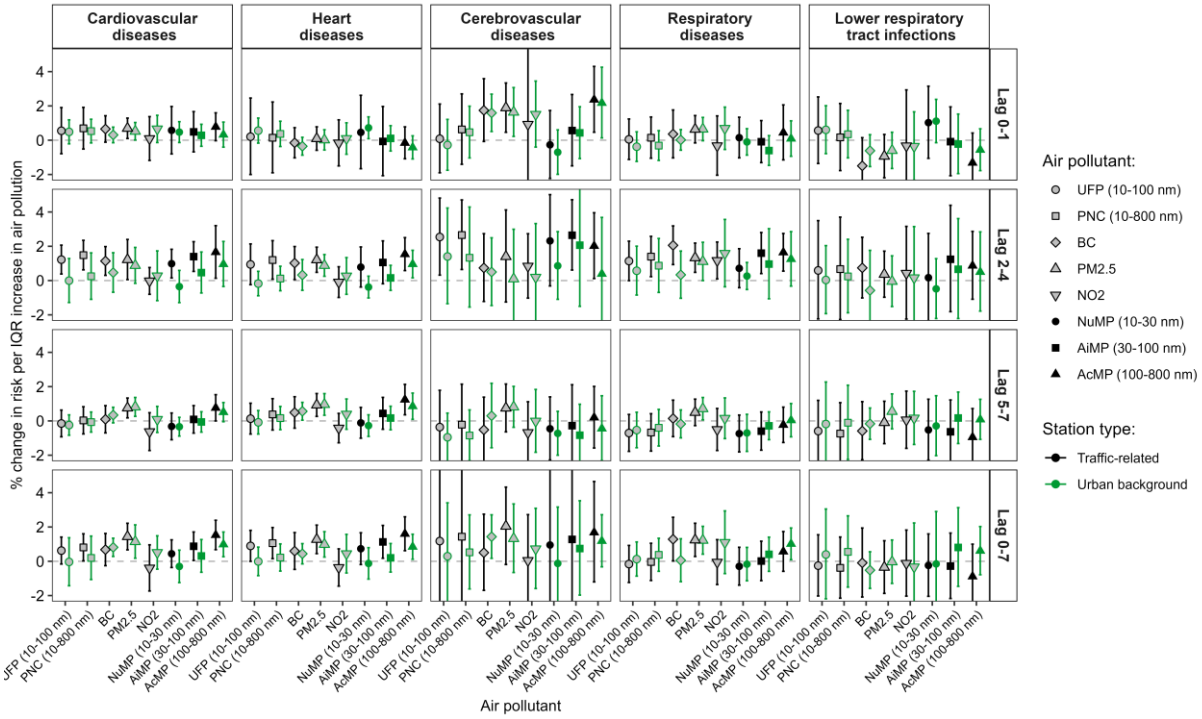
Supplementary Figure 2: Percent changes in the pooled relative risk [and 95% confidence intervals] per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollution concentration for cardiovascular disease- (left), heart disease- (second from left), cerebrovascular disease- (middle), respiratory disease- (second from right), and lower respiratory tract infection hospital admission (right). Standardization by IQR facilitates comparison between different pollutants. The x-axis and the shape show the type of pollutant. The y-axis represents the percent change of risk per interquartile range increase in air pollution concentration (left side) per average lag concentration of air pollutants (right side). All estimates represent the pooled analysis of the measurement stations using fixed-effects models and were adjusted for main model covariates.



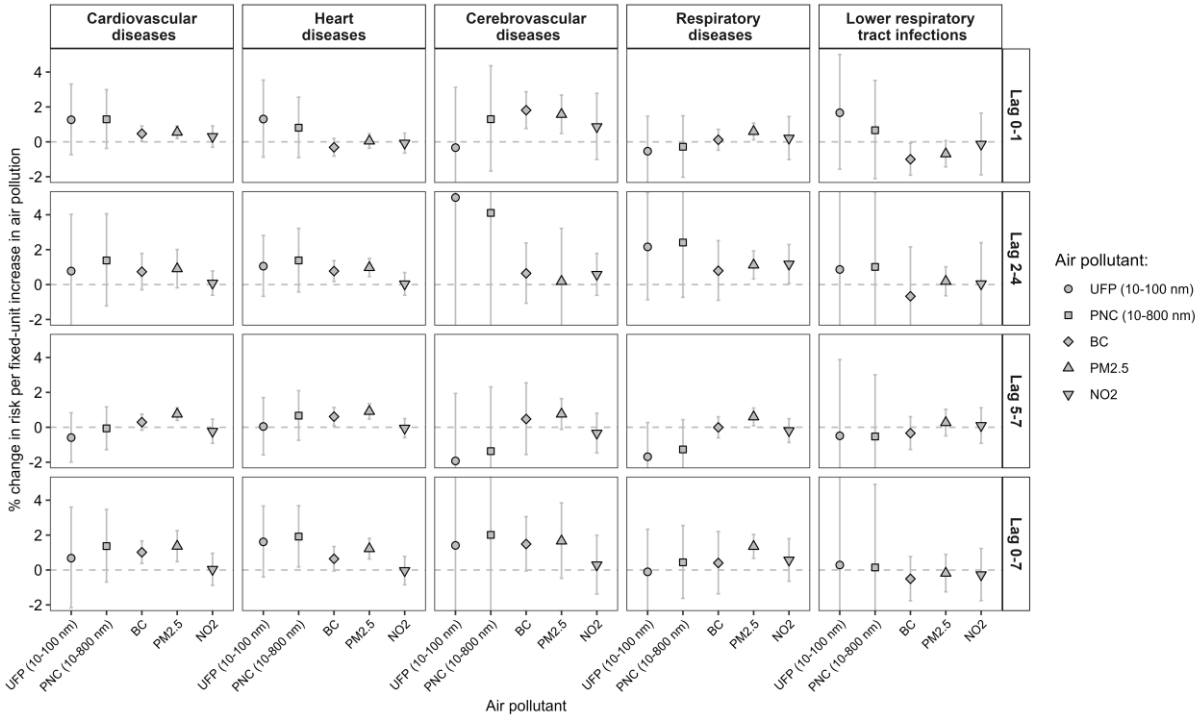
Supplementary Figure 3: Percent changes in the pooled relative risk [and 95% confidence intervals] per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in particle metrics for cardiovascular disease- (left), heart disease- (second from left), cerebrovascular disease- (middle), respiratory disease- (second from right), and lower respiratory tract infection hospital admission (right). Standardization by IQR facilitates comparison between different pollutants. The x-axis and the shape show the type of pollutant. The y-axis represents the percent change of risk per interquartile range increase in air pollution concentration (left side) per average lag concentration of air pollutants (right side). All estimates represent the pooled analysis of the measurement stations using fixed-effects models and were adjusted for main model covariates.



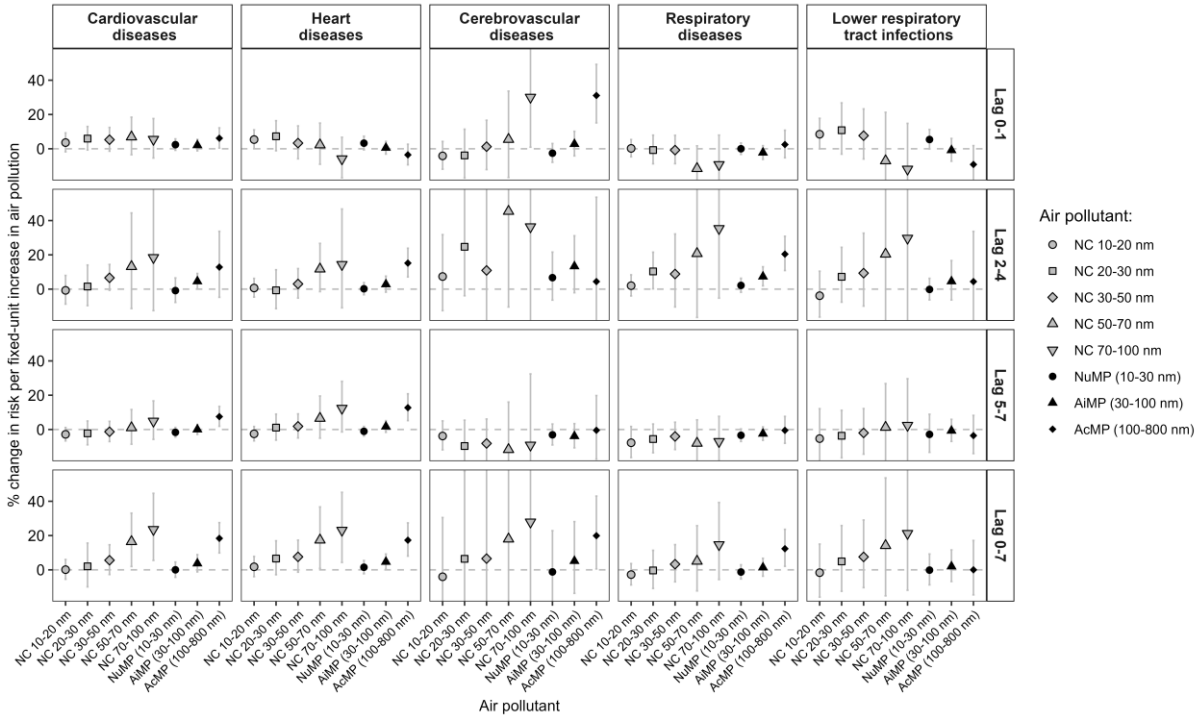
Supplementary Figure 4: Percent changes in the pooled relative risk of cardiovascular disease (top) - and respiratory disease hospital admission (bottom) [and 95% confidence intervals] risk per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollution concentration. Standardization by IQR facilitates comparison between different pollutants. The x-axis shows the single and average lags of air pollutants. The y-axis represents the percent changes of risk per interquartile range increase in air pollution concentration. All estimates represent the pooled multilevel random-effects analysis of the measurement stations and were adjusted for main model covariates.



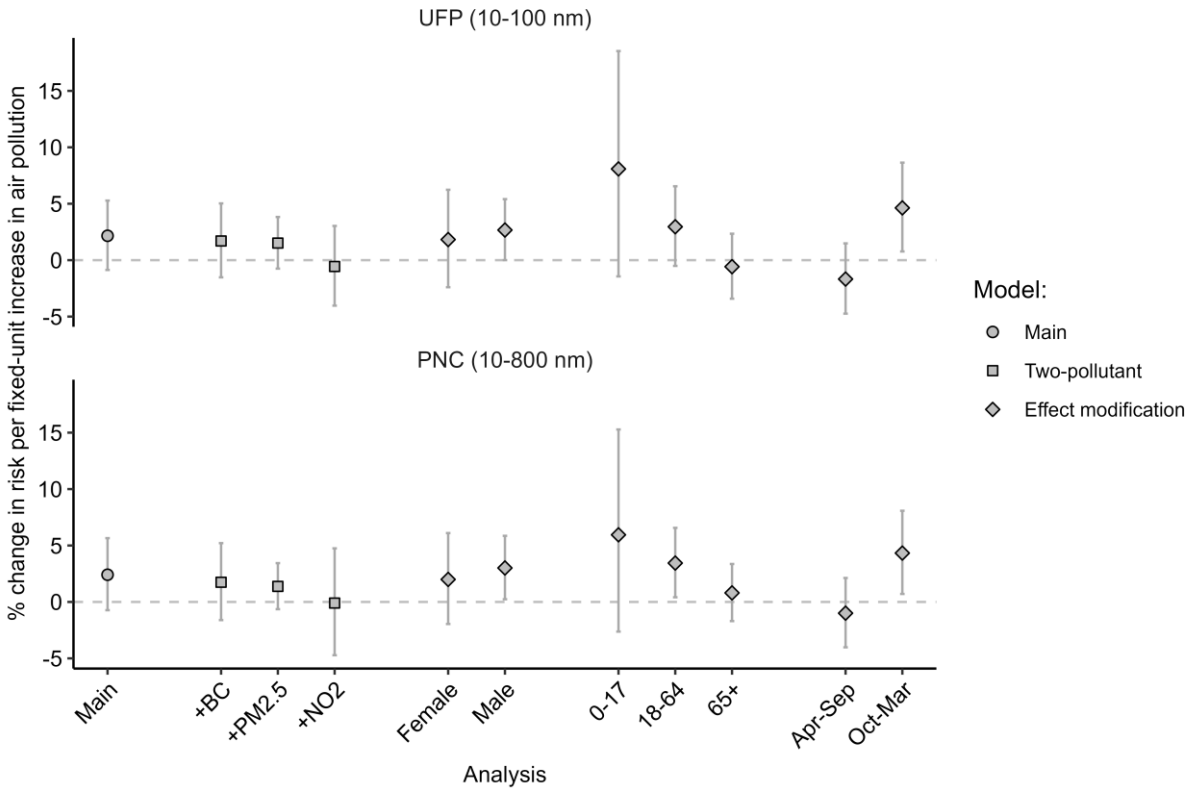
Supplementary Figure 5: Percent changes in the pooled relative risk [and 95% confidence intervals] per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollution concentration for cardiovascular disease- (left), heart disease- (second from left), cerebrovascular disease- (middle), respiratory disease- (second from right), and lower respiratory tract infection hospital admission (right). Standardization by IQR facilitates comparison between different pollutants. The x-axis and the shape show the type of pollutant. The y-axis represents the percent change of risk per interquartile range increase in air pollution concentration (left side) per average lag concentration of air pollutants (right side). Estimates for urban background stations are displayed in green and estimates for traffic-related stations are displayed in black. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates.



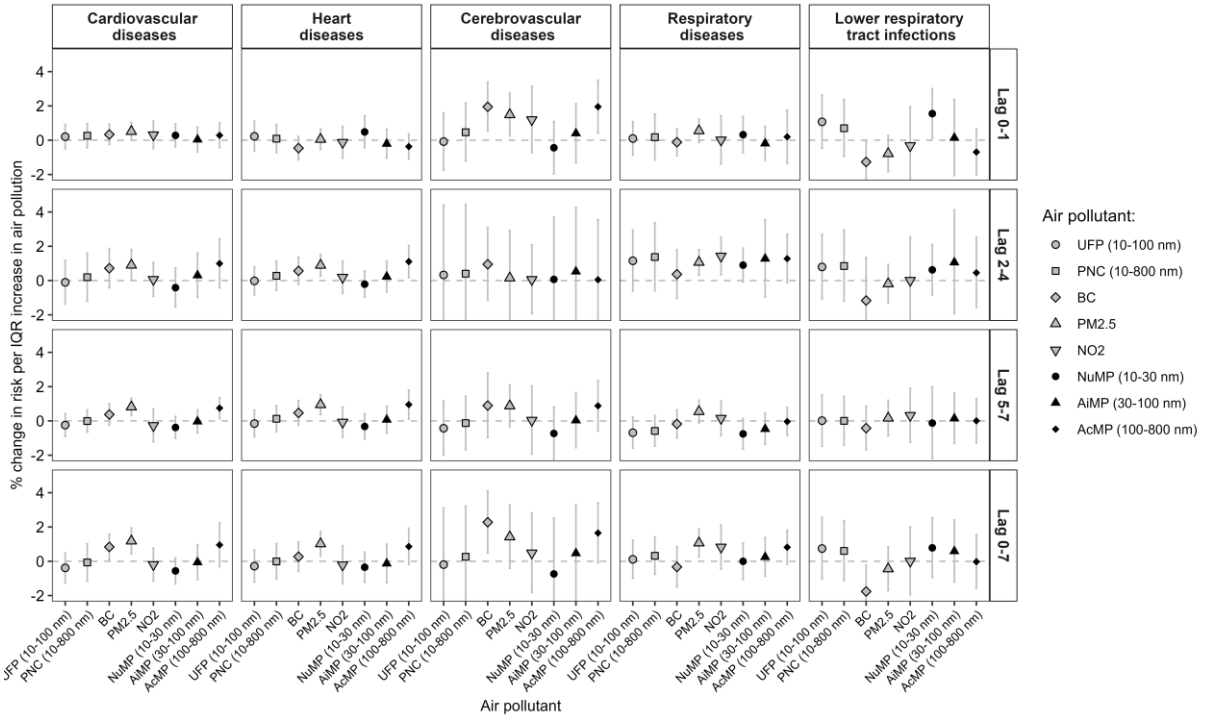
Supplementary Figure 6: Percent changes in the pooled relative risk [and 95% confidence intervals] per fixed-unit increase in air pollution concentration for cardiovascular disease- (left), heart disease- (second from left), cerebrovascular disease- (middle), respiratory disease- (second from right), and lower respiratory tract infection hospital admission (right). The x-axis and the shape show the type of pollutant. The y-axis represents the percent change of risk per interquartile range increase in air pollution concentration (left side) per average lag concentration of air pollutants (right side). We used standardized increments according to the literature of 10,000 particles/cm^3 (UFP and PNC), 1 µg/m^3 (BC), and 10 µg/m^3 ($PM_{2.5}$ and NO_2). All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models, adjusted for main model covariates.



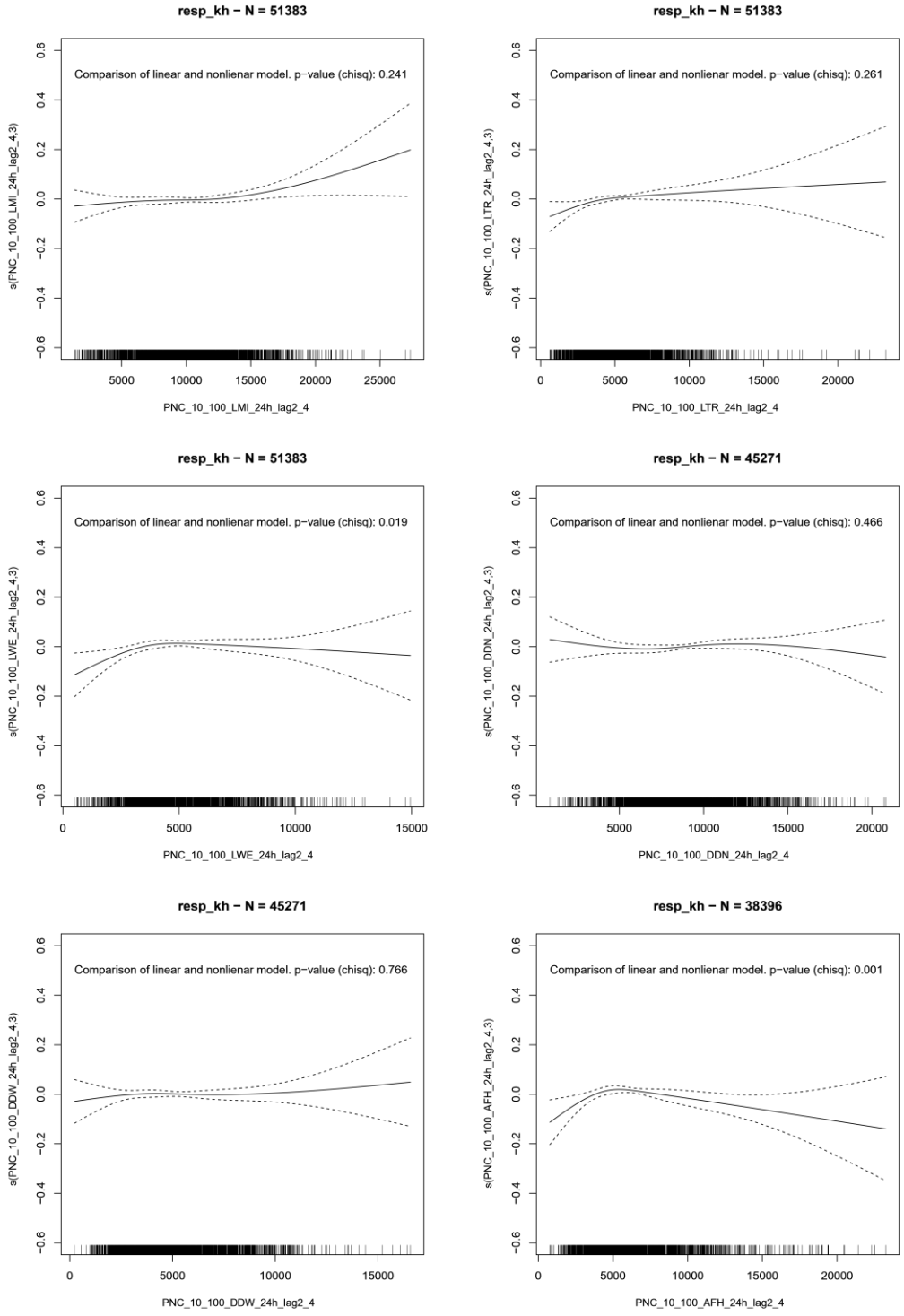
Supplementary Figure 7: Percent changes in the pooled relative risk [and 95% confidence intervals] per fixed-unit increase in particle metrics for cardiovascular disease- (left), heart disease- (second from left), cerebrovascular disease- (middle), respiratory disease- (second from right), and lower respiratory tract infection hospital admission (right). The x-axis and the shape show the type of pollutant. The y-axis represents the percent change of risk per interquartile range increase in air pollution concentration (left side) per average lag concentration of air pollutants (right side). We used standardized increments according to the literature of 10,000 particles/cm^3 (UFP and PNC), 1 µg/m^3 (BC), and 10 µg/m^3 ($PM_{2.5}$ and NO_2). All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates.



Supplementary Figure 8: Percent changes in the relative risk of respiratory hospital admission and 95% confidence intervals per fixed-unit increase in ultrafine particles (10-100nm; UFP; top panel) and total particle number concentrations (10-800nm; PNC; bottom panel) (Lag 2-4). The x-axis shows the results for the main (displayed as dot), two-pollutant (displayed as rectangle), and effect modification analysis (displayed as diamond). The y-axis represents the percent change of risk per fixed-unit increase in air pollution concentration. We used standardized increments according to the literature of 10,000 particles/cm^3 (UFP and PNC), 1 µg/m^3 (BC), and 10 µg/m^3 ($PM_{2.5}$ and NO_2). All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models, adjusted for main model covariates. It should be noted that for the two-pollutant models $PM_{2.5}$ and NO_2, the station Leipzig-TROPOS was not included in the model (no air pollution data). Additionally, the station Leipzig-Mitte was not included in the NO_2 model because Spearman correlation coefficients were above 0.7.



Supplementary Figure 9: Percent changes in the pooled relative risk [and 95% confidence intervals] per interquartile range (IQR: difference between the 75th and 25th percentile; corresponds to the spread of the middle 50% of the data) increase in air pollution concentration for cardiovascular disease- (left), heart disease- (second from left), cerebrovascular disease- (middle), respiratory disease- (second from right), and lower respiratory tract infection hospital admission (right). Standardization by IQR facilitates comparison between different pollutants. The x-axis and the shape show the type of pollutant. The y-axis represents the percent change of risk per interquartile range increase in air pollution concentration (left side) per average lag concentration of air pollutants (right side). Estimates are pooled using city-specific exposure concentrations according to the APHEA protocol. All estimates represent the pooled analysis of the measurement stations using multilevel random-effects models and were adjusted for main model covariates.



Supplementary Figure 10: Exposure-response functions for Leipzig-Mitte (top left), Leipzig-West (top right), Leipzig-TROPOS (middle left), Dresden-Nord (middle right), Dresden-Winckelmannstr. (bottom left), and Augsburg (bottom right). Smooth functions with three degrees of freedom (represented by black lines) were used for respiratory hospitalization (Lag 2-4) and number concentrations of particles in the ultrafine range (UFP, 10-100nm). Dotted lines indicate 95% confidence intervals. The models were adjusted for main model covariates.

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Appendix: Manuscript 3

Title:	Temporal Variations in the Short-Term Effects of Ambient Air Pollution on Cardiovascular and Respiratory Mortality in 380 Urban Areas during a 22-Year Period
Authors:	Maximilian Schwarz, Annette Peters, Massimo Stafoggia, Francesca De'Donato, Francesco Sera, Michelle L. Bell, Yuming Guo, Yasushi Honda, Veronika Huber, Jouni J. K. Jaakkola, Aleš Urban, Ana Maria Vicedo-Cabrera, Pierre Masselot, Eric Lavigne, Haidong Kan, Samuel Osorio, Souzana Achilleos, Jan Kyselý, Hans Orru, Ene Indermitte, Marek Maasikmets, Niilo Ryti, Mathilde Pascal, Klea Katsouyanni, Antonis Analitis, Evangelia Samoli, Alireza Entezari, Fatemeh Mayvaneh, Masahiro Hashizume, Yoonhee Kim, Chris Fook Sheng Ng, Barrak Alahmad, Magali Hurtado Diaz, Eunice Elizabeth Félix Arellano, Shilpa Rao, Alfonso Diz-Lois Palomares, Susana das Neves Pereira da Silva, Joana Madureira, Noah Scovronick, Fiorella Acquaotta, Rebecca M. Garland, Ho Kim, Whanhee Lee, Aurelio Tobias, Carmen Íñiguez, Bertil Forsberg, Martina S. Ragettli, Yue Leon Guo, Shih-Chun Pan, Shanshan Li, Ben Armstrong, Antonella Zanobetti, Joel Schwartz, Antonio Gasparrini, Alexandra Schneider, and Susanne Breitner
Year:	2024
Journal:	The Lancet Planetary Health
Status:	Submitted (Published at time of thesis publication)
Volume:	Volume 8, Issue 9
Page:	e657-e665
DOI:	https://doi.org/10.1016/S2542-5196(24)00168-2
Publishing license:	Creative Commons Attribution License 4.0 (CC BY 4.0 DEED; https://creativecommons.org/licenses/by/4.0/)
Journal Impact Factor:	25.7 (according to *Journal Citation Reports™* 2022)
Rank by Journal Impact Factor:	5/275 in the category 'Environmental Sciences' (according to *Journal Citation Reports™* 2022)

Temporal Variations in the Short-Term Effects of Ambient Air Pollution on Cardiovascular and Respiratory Mortality in 380 Urban Areas during a 22-Year Period

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Author contributions. MSc, SBr, AS, FdD, MSt, AG, and FS were involved in the design of the study. MSc and SBr analyzed the data and wrote the first version of the manuscript. AS, FdD, MSt, FS, and AG provided assistance with the methodological framework, and the rest of the MCC Collaborative Research Network provided the country-specific air pollution and mortality data. All authors contributed to the interpretation and visualization of the results, have read the manuscript, and approved its final version.

Data sharing: The mortality data is not publicly available due to restrictions imposed by data usage agreements with the respective data providers of the included countries.

Acknowledgments: AG was supported by the European Union's Horizon 2020 Project Exhaustion (Grant ID: 820655). FS was supported by the Italian Ministry of University and Research, Department of Excellence project 2023-2027 ReDS "Rethinking Data Science" - Department of Statistics, Computer Science and Applications - University of Florence. AMVC acknowledges funding from the Swiss National Science Foundation (TMSGI3_211626)

Word count main text: 3656

No. of references: 28

No. of tables: 2

No. of figures: 3

KEYWORDS: Temporal variation; Air pollution; Particulate matter; Nitrogen dioxide; Mortality

RESEARCH IN CONTEXT

Evidence before this study. We conducted a literature search in PubMed without restrictions by language, including the following search terms: "air pollution" AND ("NO_2" OR "PM_{10}" OR "$PM_{2·5}$") AND "mortality" AND ("temporal variation" OR "temporal variability" OR "temporal*"). In addition, we restricted the publication date between January 1, 2013, and June 30, 2023, and included studies with a length of the respective study period of five or more years. The search revealed that previous epidemiological studies reported inconsistent associations over time and were mainly conducted in single cities or countries. In addition, these studies have shown substantial heterogeneity in factors such as geographic location, population demographics, socioeconomic factors, and statistical methods.

Added value of this study. This study of 380 cities across 24 countries provides global risk estimates of how the associations between short-term exposures to three commonly studied air pollutants and mortality have changed over 22 years. To our knowledge, this is the first study to apply a comprehensive and standardized analytical framework for a global set of cities to reduce bias and increase the comparability of results. Overall, the effect estimates for NO_2 and PM_{10} and mortality did not exhibit a significant temporal change, although exposure concentrations have decreased over the past decades. However, a significant temporal change in the effect estimate for $PM_{2·5}$ and cardiovascular mortality was seen. The effects may vary by geographic region and co-pollutant adjustment, although the overall heterogeneity was rather moderate.

Implications of all the available evidence. The results suggest that a reduction in air pollution concentrations does not necessarily lead to a change in the association between air pollution and mortality or a reduction in the slope of the exposure-response function. This finding is consistent with a non-linear relationship when high air pollution concentrations were included. Influencing factors such as the sources and composition of pollutants, social and economic determinants, but also human behavior and changes in population distribution warrant further research. Given the variation in risk over time, it may be necessary to adapt and expand public health policies to attribute the risk of air pollution accurately, especially at low concentrations where mitigation measures are successful.

ABSTRACT

BACKGROUND. Ambient air pollution, including particulate matter with diameters ≤10 µm (PM_{10}) or ≤2·5 µm ($PM_{2·5}$) and nitrogen dioxide (NO_2), has been linked to mortality. It is unclear whether populations' vulnerability to these pollutants has changed over time, and studies lack multi-center analyses. We therefore evaluated whether changes in exposure were associated with changes in mortality effect estimates over time.

METHODS. We examined over 21·6 million cardiovascular and 7·8 million respiratory deaths in 380 cities across 24 countries between 1995 and 2016. We applied a two-stage approach to analyze the short-term effects of NO_2, PM_{10}, and $PM_{2·5}$ on cause-specific mortality using city-specific time series regression analyses and multilevel random-effects meta-analysis. We assessed changes over time using a longitudinal meta-regression with time as a linear fixed term and explored potential sources of heterogeneity.

FINDINGS. All three air pollutants showed decreasing concentrations over time. The pooled results suggested no significant temporal change in the effect estimates per unit exposure for PM_{10} or NO_2 and mortality. However, the risk of cardiovascular mortality associated with a 10 µg/m^3 increase in $PM_{2·5}$ changed from 0·14% (95%CI: -0·32%-0·61%) in 1998 to 0·77% (95%CI: 0·35%-1·19%) in 2012. Regional analyses indicated stronger associations in the regions of the Americas.

INTERPRETATION. Although air pollution levels have decreased, the effect sizes per unit increase have not changed. This might be due to the composition and toxicity, sources of air pollution, but also other factors, such as a non-linear exposure-response function, socioeconomic determinants, or changes in population distribution and susceptibility.

FUNDING.-

Word count abstract: 250/250 words

INTRODUCTION

Ambient air pollution, especially particulate matter (PM) with diameters of 2.5 µm or 10 µm or less ($PM_{2.5}$ and PM_{10}, respectively), is a major environmental risk factor affecting the global mortality burden[1] and also significantly impacting the economy.[2] Epidemiological studies have extensively studied associations over the past decades, showing evidence of increased morbidity[3-5] and mortality.[3,5-8] These research efforts led to the implementation of evidence-based recommendations and legal public health policies, such as reference and target values, to reduce ambient air pollution levels and the related health burden in societies.[9] However, $PM_{2.5}$ and nitrogen dioxide (NO_2) have been associated with mortality even at low exposure concentrations near or below the recommended target levels.[10]

Epidemiological short-term studies used to propose these recommended levels have mostly assumed a constant health risk over time, and potential temporal trends in associations were less often explicitly examined; thus, the legislative decisions based on those studies were made under this assumption. Furthermore, not considering temporal variations, e.g., in absolute exposure concentration or exposure mixture, limits the accurate representation of the health burden and could mask the positive impacts of technological improvements and past public health policies. In addition, changes in human behavior and/or temporal shifts in the underlying population distribution (e.g., epidemiological transition towards increasing life expectancy, aging populations, and chronic diseases) could contribute further to shifts in effect estimates by different exposure-response functions for subpopulations. Finally, understanding the temporal trends of air pollution effects is necessary to accurately estimate the future health benefits/detriments of different emissions scenarios. This is particularly relevant for studies of co-impacts ("co-benefits") for air quality and climate change mitigation policies.[11]

To date, large multi-country studies on temporal variations of short-term air pollution effects are still lacking; only single-country studies have explicitly addressed this research question. In general, although the concentrations of PM and NO_2 have decreased, studies reported inconclusive results regarding the temporal trend in their effect estimates per unit increase in air pollution.[12-18] Studies from Japan, China, Switzerland, South Korea, Greece, and Italy reported mixed results showing either an increase[12,13,15-18], a decrease[12,17,18], or no temporal trend[14,18] in the effect estimates between PM fractions or NO_2 and cardio-respiratory mortality. However, the comparability between studies, as well as the overall generalizability, is limited because different geographic regions and populations were analyzed, including locally prevailing air pollutant mixtures and different statistical approaches. In addition, a potential non-linearity in the

relationship between exposure and response may give the illusion of a change in risk following a change in air pollution concentration.

Therefore, this study aimed to examine temporal variations of ambient NO_2, PM_{10}, and $PM_{2.5}$ exposure concentrations using the large international Multi-Country Multi-City (MCC) Collaborative Research Network database over 22 years between 1995 and 2016. We hypothesized that changes over time also changed the associations between air pollution and mortality during the study period. In addition, we investigated temporal variations in the cause-specific mortality effect size estimates over the same period in two ways and evaluated the interdependencies of co-pollutants. Further, we assessed potential heterogeneity factors, such as the geographic region according to the World Health Organization (WHO) classification.

METHODS

Data sources and selection of urban areas

We retrieved data from the MCC database, which has been previously analyzed and described in more detail.[7,8,19] We *a priori* defined the study period between 1995 and 2016 because of limited available data before and after these years and excluded cities without available air pollution data from the dataset. Mortality data were obtained as daily counts from local authorities in each city and were classified according to the International Classification of Diseases, 10th Revision (ICD-10). In each city, we collected daily death counts due to cardiovascular (ICD-10 codes I00-I99) and respiratory (ICD-10 codes J00-J99) diseases. Air pollution data included 24-hour average NO_2, PM_{10}, and $PM_{2.5}$ concentrations. In addition, daily averages of air temperature and relative humidity were also included in the dataset. We incorporated additional indicators from the OECD Regional and Metropolitan Database[20], such as population density or gross domestic product (GDP) per capita, and calculated climate variables based on location-specific distributions (e.g., temperature range).

We made further constraints to the original data to improve data quality regarding the analysis of temporal variations: 1) We removed city years with less than two-thirds of available data for that year. 2) We included cities with a minimum of five years of valid air pollution data 3) We excluded cities with more than 50% missing outcome data. The geographic distribution can be found in the appendix (Figure S1), with a more detailed description of the data collection per country.

Statistical analysis

We used a two-stage modeling framework to analyze the associations between daily air pollution concentrations and cause-specific mortality.[21] In the first stage, we obtained city-specific risk estimates using a linear quasi-Poisson regression model. To be consistent with previous MCC analyses on PM fractions[7] and NO_2[8], we controlled for similar confounder models: long-term trends and seasonality, day of the week, temperature, and relative humidity. We used a natural spline with seven degrees of freedom (df) per year for time trends, indicator terms for day of week, a natural spline of the four-day moving average concentrations using six df for temperature, and a natural spline using three df for same day relative humidity levels and present the results of lag 1 for NO_2 and lag 0-1 for PM fractions. In the second stage, we pooled the city-specific results using a multilevel random-effects meta-analysis that accounted for variation in effect estimates by nested random terms of cities and countries.[22] The corresponding I^2 statistics and p-values (Cochran's Q test) were reported as measures of heterogeneity. All results are presented as percent change in daily mortality and 95% confidence intervals (CI) per 10 $\mu g/m^3$ increase in the air pollutant concentration.

The temporal variation in mortality effect estimates was assessed through the following general modeling strategy. We divided the overall time series into three periods of approximately seven years (first stage) and pooled the city- and period-specific estimates using a longitudinal multilevel meta-regression with time (midyear of each period) as a linear fixed term (second stage).[21,23] Based on the model results, we predicted the yearly estimates over the study period and tested for the presence of a temporal difference by comparing the model with and without the linear term for time using a Wald-Test. As an alternative approach, we compared the effect estimates for each period separately by calculating city-specific interactions in the first stage, followed by the general modeling procedure without the longitudinal meta-regression for each period separately (second stage) to obtain an overall estimate for each period.

On an exploratory basis, we carried out several secondary analyses: 1) we replaced the linear term with a non-linear term of time in the longitudinal analysis; 2) we considered two-pollutant models to assess the potential confounding of co-pollutants by adding another primary pollutant as a second linear term in the main model. Therefore, we restricted our two-pollutant analysis to cities with data for both pollutants and followed the general modeling procedure; 3) we applied a multivariable meta-regression analysis that involved a set of nine meta-predictors (WHO regions, GDP per capita, Köppen climate zones, average temperature and total temperature range, average air pollution concentration, total population, population density, and proportion of old population) to investigate causes of heterogeneity affecting the longitudinal meta-regression results. In brief, we used a stepwise forward selection based on the Akaike

information criterion (AIC) to identify models that described most of the heterogeneity and reported the stratified results if the meta-predictor significantly improved the model fit.

We conducted a series of sensitivity analyses to assess the robustness of our findings (e.g., changing model parameters, confounding variables, or further restrictions to the dataset).

All statistical analyses were performed in R software, version 4.1.2 (R Foundation for Statistical Computing), using the packages *mgcv* (first stage), *mixmeta* (second stage), and *ggplot2* (visualization).

A more detailed description of data collection and the statistical analysis can be found in the appendix.

ROLE OF THE FUNDING SOURCE

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or drafting of the manuscript.

RESULTS

Descriptive analyses

We analyzed more than 21·6 million cardiovascular and 7·8 million respiratory deaths in 380 cities across 24 countries worldwide over an average study period of 12·2 years (Table 1). More detailed information, such as city-specific data or geographic distribution, can be found in the appendix (Tables S1-S4; Figure S1). Average concentrations (5^{th}-95^{th} percentiles) of NO_2, PM_{10}, and $PM_{2·5}$ were 27·5 μg/m^3 (11·4-50·0), 31·3 μg/m^3 (12·3-62·2), and 13·5 μg/m^3 (4·5-29·4), respectively, and exhibited high heterogeneity within and between countries (Tables S1-S4). During the study period, there was a substantial reduction in NO_2 and PM_{10} concentrations, whereas $PM_{2·5}$ showed smaller decreases in concentrations (Figure 1; Figure S2). PM fractions were highly correlated (mean correlations over all cities) with each other and moderately correlated with NO_2 (Table S5). Over time, correlations between PM_{10} and $PM_{2·5}$ have increased and remained relatively stable for NO_2. However, some countries have shown changing correlations (Figures S3-S5).

Time-series regression analyses

We observed robust positive pooled associations with cardiovascular and respiratory mortality for all three air pollutants over the entire study period (Figure S6). For example, an increase of 10 μg/m^3 in $PM_{2·5}$

concentrations was associated with a 1·07% (95% confidence interval [CI]: 0·74%-1·39%) increased risk of respiratory mortality (Table 2).

In the pooled longitudinal analyses, no significant change in the effect estimates for NO_2 and PM_{10} was observed over the years (Figure 2). However, slightly larger estimates were seen at the end of the study period. In contrast, we observed a statistically significant temporal difference for $PM_{2·5}$ and cardiovascular mortality (p=0·022) (Figure 2; Table 2). A 10 µg/m^3 increase in $PM_{2·5}$ resulted in a 0·14% (95% CI: -0·32%-0·61%) higher risk of cardiovascular mortality in 1998 and 0·45% (95% CI: 0·10%-0·81%), and 0·77% (95% CI: 0·35%-1·19%) in 2005 and 2012, respectively (Figure 2; Table 2). PM_{10} and NO_2 are characterized by higher precision (smaller CIs) but smaller magnitude of effects. The regression slopes ranged from 0·005%/per year for cardiovascular mortality and PM_{10} to 0·046%/per year for respiratory mortality and $PM_{2·5}$. The country-specific results (Figures S7-S12) showed evidence of (moderate) heterogeneity (highest for cardiovascular mortality and PM_{10}: I^2 = 30·58%, p<0·001) and different patterns between countries. The pooled exposure-response functions indicated no large deviation from linearity, although substantially fewer cities with high air pollution levels affected the precision at the upper end of the exposure-response functions (e.g., $PM_{2.5}$ > 100 µg/m^3) (Figure S13).

When a non-linear term replaced the linear term for time in the pooled longitudinal analyses, the overall pattern remained similar (Figure S14). An alternative assessment of temporal variation by separately comparing the three sub-periods indicated overall comparable results, although the observed trend for $PM_{2·5}$ and cardiovascular mortality was not as pronounced (Table 2; Figure S15). The association indicated a slight increase between the first and third periods, although the number of cities contributing to these periods changed.

Secondary analyses

Including PM size fractions in the NO_2 models generally showed an increasing trend for the NO_2 effect estimates for cardiovascular and respiratory mortality (Figure 3). In contrast to the NO_2 single-pollutant models, no associations were observed at the beginning of the study period. However, a significantly increased temporal trend for mortality was observed over the study period (cardiovascular mortality: NO_2+$PM_{2·5}$; respiratory mortality: NO_2+PM_{10}). The associations remained nearly unchanged when NO_2 was added to the PM_{10} or $PM_{2·5}$ models. However, it should be noted that the underlying number of cities has been reduced due to the simultaneous availability of both pollutants.

The results from the exploratory meta-regression models can be found in Figure S16. Generally, stratification by the WHO region significantly improved the model fit and explained parts of the

heterogeneity in some longitudinal models. The association between PM_{10} and both causes of mortality, as well as between $PM_{2.5}$ and cardiovascular mortality, exhibited higher levels in the region of the Americas and a slight increase in the Western Pacific Region (Figure S16). However, except for GDP per capita (NO_2 and respiratory mortality), none of the other meta-predictors significantly improved the models.

Sensitivity analyses

The results of the sensitivity analyses can be found in the appendix (Figures S17-S23). In general, excluding cities that exhibit high correlations among model variables, excluding relative humidity as a confounder, or using different numbers of df for the time trend or using alternative temperature adjustments did not affect the direction and only slightly the magnitude of the associations over time (Figures S17-S22). Excluding the US cities generally indicated an increasing trend in the association with cardiovascular mortality, but no differences for respiratory mortality (Figure S23).

DISCUSSION

This multi-country, multi-city study provides evidence that there have been no significant temporal changes in the associations between NO_2 or PM_{10} and cardio-respiratory mortality. However, a tendency of a temporal increase in the effect estimate was found for $PM_{2.5}$ and cardiovascular mortality. Including a second pollutant in the main model showed no major changes for the PM fractions, although the effect estimates tended to increase over time for NO_2. The evaluation of spatial heterogeneity using nine explanatory meta-predictors indicated larger effect estimates in the Americas and Western Pacific regions than in Europe, with overall moderate heterogeneity.

Until now, most analyses of temporal variations in the effects of air pollution on mortality have been limited to individual countries or even cities. For example, two studies conducted in Seoul, South Korea, examined temporal trends from 1998-2015.[13,17] Both studies found slightly increasing associations between $PM_{2.5}$ or PM_{10} exposure and cardio-respiratory mortality over time, although Choi et al. (2018) reported a decrease in the effects of PM_{10} during the latest period (2011-2015).[17] Our country-specific analysis of seven South Korean cities indicated only slight increases in the PM_{10} effects on cardio-respiratory mortality over time. A time-series study in Switzerland over 16 years (1995-2010) found a significantly increasing trend for PM_{10} and cardiovascular mortality.[12] Also, Perez et al. (2015) reported a slight decrease in the association between NO_2 and respiratory mortality, especially among older people (65y+). Our findings differ from these results as we found no significant differences for either PM_{10} or NO_2

effects over time, indicating relatively stable effect sizes. Moreover, our country-specific estimates suggest a slight decreasing non-significant trend for NO_2 and cardiovascular mortality in Switzerland. However, the analyses might not be directly comparable because of differences in the included cities (eight major cities vs. 21 Swiss cantons) and statistical methods. A single-city study conducted in Rome, Italy, for the period 1998-2014 reported no consistent trends over time in the effects of NO_2, PM_{10}, and $PM_{2·5}$ on non-accidental mortality. However, the strongest associations were seen in the most recent periods, except for NO_2. Furthermore, the results remained constant when additional meta-regressors (e.g., temperature) were included in the models.[14] Finally, a recent study conducted in ten Japanese cities found evidence of a negative linear trend for suspended PM and cardiovascular mortality over 39 years (1977-2015), contrary to our country-specific findings.[18] However, the authors found the highest estimates in the earliest period (1977-1980), which is not included in our analysis and may have contributed to the different results. In addition, Nishikawa et al. (2023) reported increased associations with respiratory mortality in the most recent periods and observed no temporal changes when examining gaseous pollutants, consistent with our findings.[18]

In recent decades, air pollution concentrations have generally declined in most regions, particularly North America and Europe.[3,5,24] However, in our analyses, 17·3%-49·0% of days still exceeded the current 24-hour WHO air quality standards. In addition, some regions showed opposite trends, with increasing air pollution levels[9], some of which may be attributed to wildfires.[25] Therefore, in our secondary analyses, we aimed to examine spatial heterogeneity and dependencies of multiple pollutants. Our models indicated low to moderate spatial heterogeneity ranging from 5·74% ($PM_{2·5}$ and respiratory mortality) to 30·58% (PM_{10} and cardiovascular mortality). In addition, we identified the WHO regions as a factor that may have contributed significantly to this variability. We observed higher estimates in the regions of the Americas compared to Europe and mixed results for the Western Pacific region. Liu et al. (2019) previously reported similar heterogeneity in PM effects on total mortality.[7] Possible contributors to these variations include susceptibility and health behavior of the population, lower concentrations in North America, different lengths of study periods or different local climate pattern.[7] In future research, it will be important to disentangle the co-impacts/co-benefits of air quality and climate change mitigation policies, along with the health benefits and harms of different emission scenarios in the context of climate change and rising global temperatures.[11]

Breitner et al. (2009) discussed two competing factors contributing to changes in association with changes in exposure concentration: 1) alterations in the effect estimate due to a non-linear exposure-response relationship, or 2) a linear exposure-response relationship but the measured pollutant marks changes in

the exposure mixture or source composition.[26] Our exposure-response functions indicated no evidence contradicting our linear model assumptions, although we cannot completely rule out the possibility that non-linearity may have affected the results. Furthermore, technological advancements, such as particle filters or new combustion engine technologies, could reduce PM mass from, e.g., diesel engines[27], but not necessarily gaseous emissions. Moreover, PM consists of several components that have changed over time, contributing to the decrease in $PM_{2·5}$ concentrations.[5] A multi-country, multi-city study investigated the differential health effects of $PM_{2·5}$ composition and examined yearly differences in $PM_{2·5}$ components between regions and over time. While some countries showed relatively stable $PM_{2·5}$ compositions, others exhibited slight changes and a wide temporal variability (e.g., reduction of sulfate (SO_4^{2-}) content in the UK).[28] In addition, the authors reported a greater proportion of nitrate in Northern and Central European countries and SO_4^{2-} in countries with higher temperatures, which are the two largest contributors to $PM_{2·5}$, and are linked to fossil fuel combustion.[28] The reported relative risks indicated an increasing mortality risk for all components, although changes in the proportion modified the risk.[28] We also observed changing correlations between PM fractions and NO_2, which may have contributed to different associations over time. However, given the remaining issues of co-pollutant models (e.g., multicollinearity, differentiation of direct effects of one pollutant in the presence of others) and different PM compositions, the interpretation of the results is not straightforward. Further, we cannot rule out the presence of residual confounding because air pollution is a complex mixture of different pollutants and components.

However, considering changes in $PM_{2.5}$ composition over time and its associations with mortality, as reported by Masselot at al. (2022), a changing exposure mix or composition may have contributed to our findings. In addition, changing demographics (e.g., children or older people), health behaviors (e.g., using face masks, air purifiers, or spending more time outdoors), or population vulnerabilities (e.g., chronic diseases) may be among the factors driving changes over time.

In summary, the complexity of a changing environment over time emphasizes the need for further analyses of temporal variations across multiple countries and cities with a unified analytical approach to explain observed differences and further verify our findings. Future research should include more spatially and temporally resolved meta-predictors and chemical composition data in the context of changing populations and complex exposure-response relationships.

To our knowledge, this is the first multi-country, multi-city study specifically designed to examine differences in air pollution effects over time. The large sample size provides good statistical power and stability to analyze effects even for cause-specific mortality endpoints. We applied comprehensive and standardized state-of-the-art analytical methods to account for city- and country-specific differences. We

thoroughly constrained our dataset to increase internal validity and comparability across cities and time periods and were able to validate previous findings with this dataset.

However, it is important to acknowledge several limitations. First, although our final dataset included 380 cities in 24 countries worldwide, some regions, such as the Middle East, Latin America, and Africa, were underrepresented, and thus generalizations should be made with caution. Second, the spatial resolution and representativeness of data collected from fixed monitoring stations might be limited, which could result in exposure misclassification. Additionally, it should be noted that extrapolating the results to an entire country is inaccurate because some countries provided data from only one city. Moreover, numerous cities had exposure settings that were primarily urban or suburban, which could differ from rural areas in terms of chemical composition. In addition, it is important to consider that certain cities and countries contributed at different time periods during the study period. Third, more detailed exposure information was unavailable, such as the chemical composition of PM (e.g., sulfate or nitrate content) or different PM sub-fractions (e.g., ultrafine particles), which may be key factors in toxicity and overall PM risk. Fourth, the study relied on city-level time-series data without more detailed analysis at the individual level (e.g., age or biological sex). Furthermore, the potential for exposure measurement error over past decades (e.g., relocation of monitoring stations) or the ecological fallacy could have impacted the results; however, visual inspection of the individual time series (data not shown) suggested this to be marginal. Finally, we only analyzed the primary coded cardiovascular and respiratory mortality endpoints. However, air pollution exposure is also related to non-fatal disease endpoints. For example, it has been associated with temporal changes in hospitalizations.[11] A more detailed investigation was beyond the scope of this paper and warrants further research.

In conclusion, this study provides evidence that although air pollution levels have decreased over a 22-year period, the related effects on mortality have not changed. This might be due to the overall toxicity of the air pollution mix, differences in socioeconomic factors, changes in population distribution or susceptibility. Future research is required to understand how temporal variations in these factors influence the health impacts of air pollution. Understanding the factors that drive temporal trends in the associations between air pollution and cardio-respiratory mortality are particularly important to support mitigation measures to allow reaching the updated WHO air quality guidelines.

DECLARATION OF INTEREST

The authors report no conflicts of interest.

Table 1. Total death counts due to cardiovascular and respiratory causes by country and study period.

	Dataset: NO_2				Dataset: PM_{10}				Dataset: $PM_{2·5}$			
Country	Cities (N)	Period	CVD (N)	RESP (N)	Cities (N)	Period	CVD (N)	RESP (N)	Cities (N)	Period	CVD (N)	RESP (N)
Canada	25	1995-2015	826,003	224,702	7	2000-2011	153,068	40,410	25	1997-2015	673,436	187,688
China	2	1996-2008	76,689	44,549	2	1996-2008	76,689	44,549	-	-	-	-
Colombia	1	1998-2013	123,780	46,328	1	2002-2013	95,588	36,514	-	-	-	-
Cyprus	4	2010-2016	12,607	2,879	5	2005-2016	22,263	4,666	2	2010-2016	4,804	1,139
Czech Republic	1	1995-2009	102,835	9,094	1	1995-2009	102,835	9,094	-			
Estonia	4	2003-2016	42,485	2,824	4	2003-2016	42,485	2,824	3	2009-2016	10,917	718
Finland	1	1995-2014	54,366	9,226	1	1995-2014	54,366	9,226	1	1995-2014	54,366	9,226
France	18	2000-2015	255,222	66,657	18	2007-2015	234,413	62,250	15	2007-2015	200,895	53,136
Greece	1	2001-2010	136,194	28,771	1	2001-2010	136,194	28,771	-	-	-	-
Iran	1	2002-2015	316,976	52,649	1	2002-2015	316,976	52,649	-	-	-	-
Japan	44	1995-2016	1,176,249	625,020	40	1995-2016	1,114,447	588,611	26	2001-2016	610,505	346,247
Kuwait	-	-	-	-	1	2010-2016	15,962	3,170	-	-	-	-
Mexico	-	-	-	-	6	2000-2012	492,867	185,735	2	2004-2012	269,157	96,373
Norway	-	-	-	-	1	2000-2016	23,503	7,152	1	2000-2016	23,503	7,152
Portugal	6	1995-2016	297,057	87,784	5	1999-2016	238,172	73,264	3	2004-2016	106,124	30,614
South Africa	-	-	-	-	2	2004-2013	62,203	48,086	1	2007-2013	14,721	13,713
South Korea	7	1999-2015	389,590	106,209	7	1999-2015	389,590	106,209	-	-	-	-
Spain	48	2001-2014	516,250	191,989	34	2001-2014	376,387	146,017	2	2004-2014	87,540	38,337
Sweden	1	1995-2010	66,455	11,697	1	1995-2010	66,434	11,695	1	2001-2010	37,873	6,707
Switzerland	8	1995-2013	90,744	16,015	8	1995-2013	86,906	15,382	4	1998-2009	39,568	6,394
Taiwan	3	1995-2014	257,553	113,269	3	1995-2014	257,553	113,269	3	2007-2014	117,402	58,942
Thailand	16	1999-2008	150,329	99,509	16	1999-2008	151,824	100,179	-	-	-	-
UK	33	1995-2016	1,309,605	580,669	30	1995-2016	1,235,377	547,036	28	1998-2016	577,277	277,262
USA	114	1995-2006	3,768,420	1,134,984	54	1995-2006	1,336,061	424,075	77	1999-2006	1,725,612	533,461
Overall	338	1995-2016	9,969,409	3,454,824	249	1995-2016	7,082,163	2,660,833	194	1995-2016	4,553,700	1,667,109

N: Number of cities and mortality cases over the respective period; CVD: cardiovascular disease mortality; RESP: respiratory disease mortality; NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm.

Table 2. Pooled percent change in daily cause-specific mortality (95% CI) per 10 µg/m^3 increase in air pollutants using the temporal variation analyses i) by study period and ii) by midyear of each period for the longitudinal meta-regression analysis. Models were adjusted for main model covariates using multilevel random-effects meta-analysis.

	Temporal variation analysis by period			
	1995-2001 (period 1)	2002-2008 (period 2)	2009-2016 (period 3)	Total study period
Cardiovascular mortality				
NO_2	0·35% (0·16% - 0·54%)	0·37% (0·25% - 0·49%)	0·35% (0·17% - 0·52%)	0·35% (0·22% - 0·48%)
PM_{10}	0·23% (0·02% - 0·44%)	0·32% (0·19% - 0·44%)	0·16% (0·01% - 0·32%)	0·27% (0·14% - 0·39%)
$PM_{2·5}$	0·39% (-0·06% - 0·85%)	0·59% (0·22% - 0·97%)	0·50% (0·02% - 1·03%)	0·60% (0·33% - 0·87%)
Respiratory mortality				
NO_2	0·39% (-0·01% - 0·78%)	0·55% (0·24% - 0·86%)	0·36% (0·12% - 0·59%)	0·48% (0·22% - 0·73%)
PM_{10}	0·33% (-0·05% - 0·71%)	0·46% (0·18% - 0·74%)	0·35% (0·07% - 0·63%)	0·40% (0·21% - 0·59%)
$PM_{2·5}$	0·67% (0·02% - 1·32%)	1·13% (0·68% - 1·59%)	1·18% (0·70% - 1·65%)	1·07% (0·74% - 1·39%)
	Temporal variation analysis by longitudinal meta-regression			
	At midyear period 1: 1998	At midyear period 2: 2005	At midyear period 3: 2012	
Cardiovascular mortality				
NO_2	0·32% (0·19% - 0·45%)	0·38% (0·27% - 0·49%)	0·44% (0·30% - 0·59%)	
PM_{10}	0·25% (0·07% - 0·42%)	0·29% (0·16% - 0·42%)	0·32% (0·15% - 0·50%)	
$PM_{2·5}$	**0·14% (-0·32% - 0·61%)**	**0·45% (0·10% - 0·81%)**	**0·77% (0·35% - 1·19%)**	
Respiratory mortality				
NO_2	0·30% (0·00% - 0·61%)	0·45% (0·23% - 0·67%)	0·60% (0·30% - 0·89%)	
PM_{10}	0·31% (-0·02% - 0·63%)	0·41% (0·21% - 0·62%)	0·52% (0·22% - 0·82%)	
$PM_{2·5}$	0·68% (0·15% - 1·22%)	1·01% (0·69% - 1·32%)	1·33% (0·86% - 1·81%)	

Numbers printed in bold indicated a statistically significant presence of a temporal difference measured by comparing the model with and without a term for time using a Wald-Test; NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm; CI: confidence interval.
a: $I^2 > 50\%$ & $p < 0·05$.

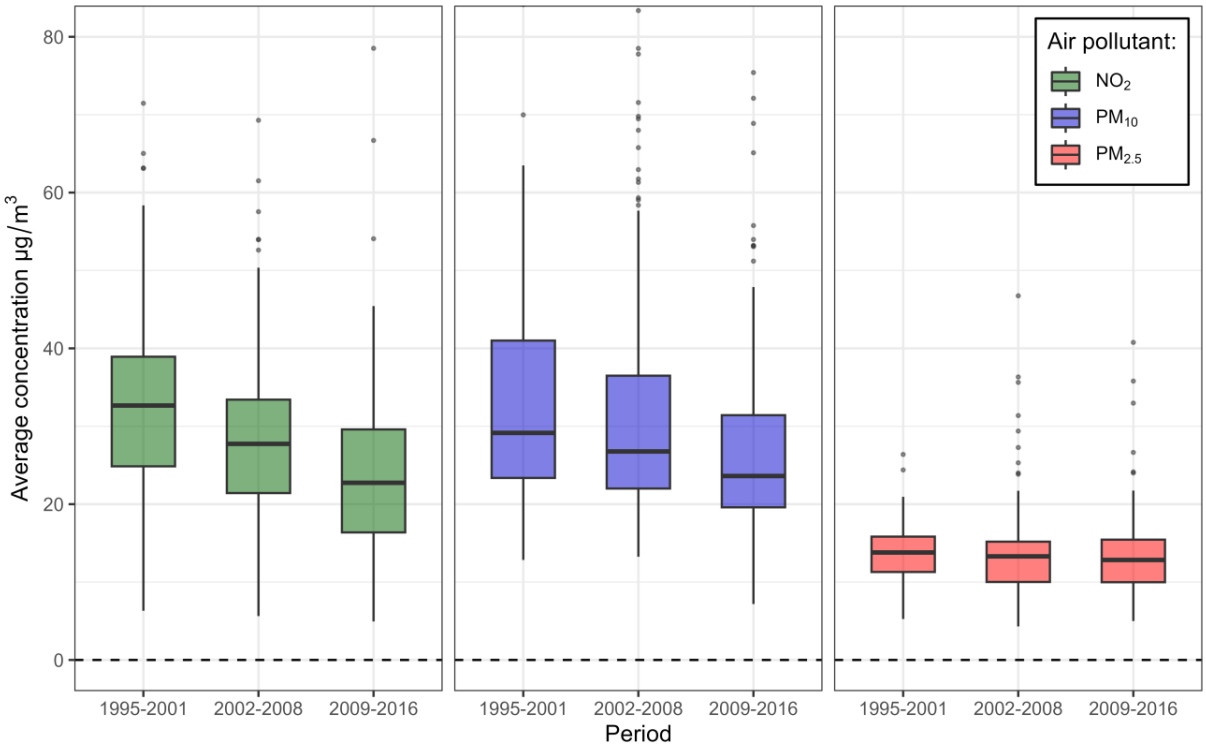

Figure 1. Boxplots of 24-hour average concentrations, in µg/m^3, of NO_2 (green, left panel), PM_{10} (blue, middle panel), and $PM_{2.5}$ (red, right panel) stratified per study period (Boxplots of yearly data can be found in the appendix).

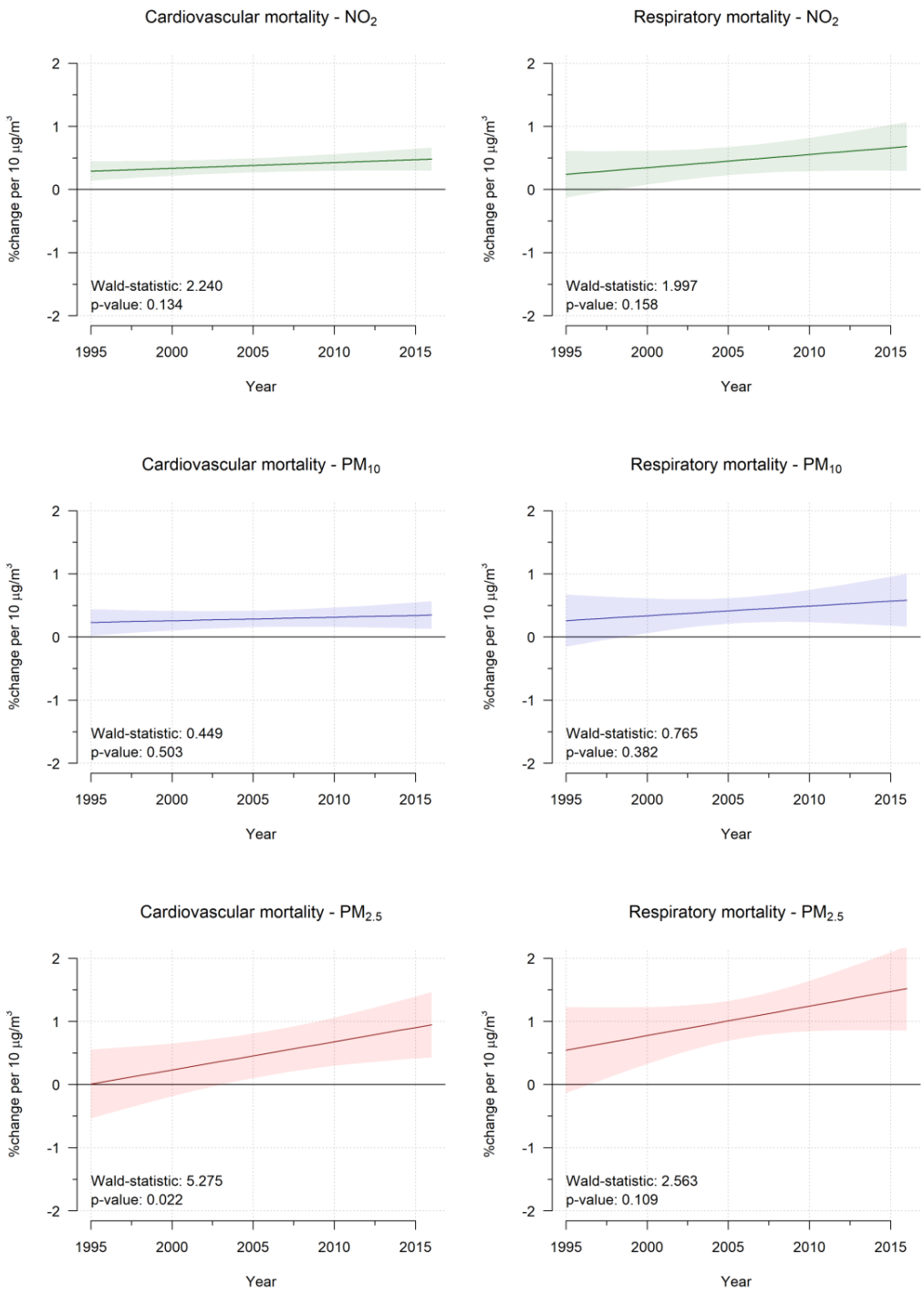

Figure 2. Percent change in daily cardiovascular (left column) and respiratory (right column) mortality and 95% CI (shaded area) per 10 µg/m^3 increase in NO_2 (top panel, at lag1), PM_{10} (middle panel, at lag01), and $PM_{2.5}$ (bottom panel, at lag 01) over the study period 1995-2016. The graph represents the result of the pooled longitudinal meta-regression using time as a linear term. The p-value of the related Wald-Test indicate a significant difference of the model with the linear term for time.

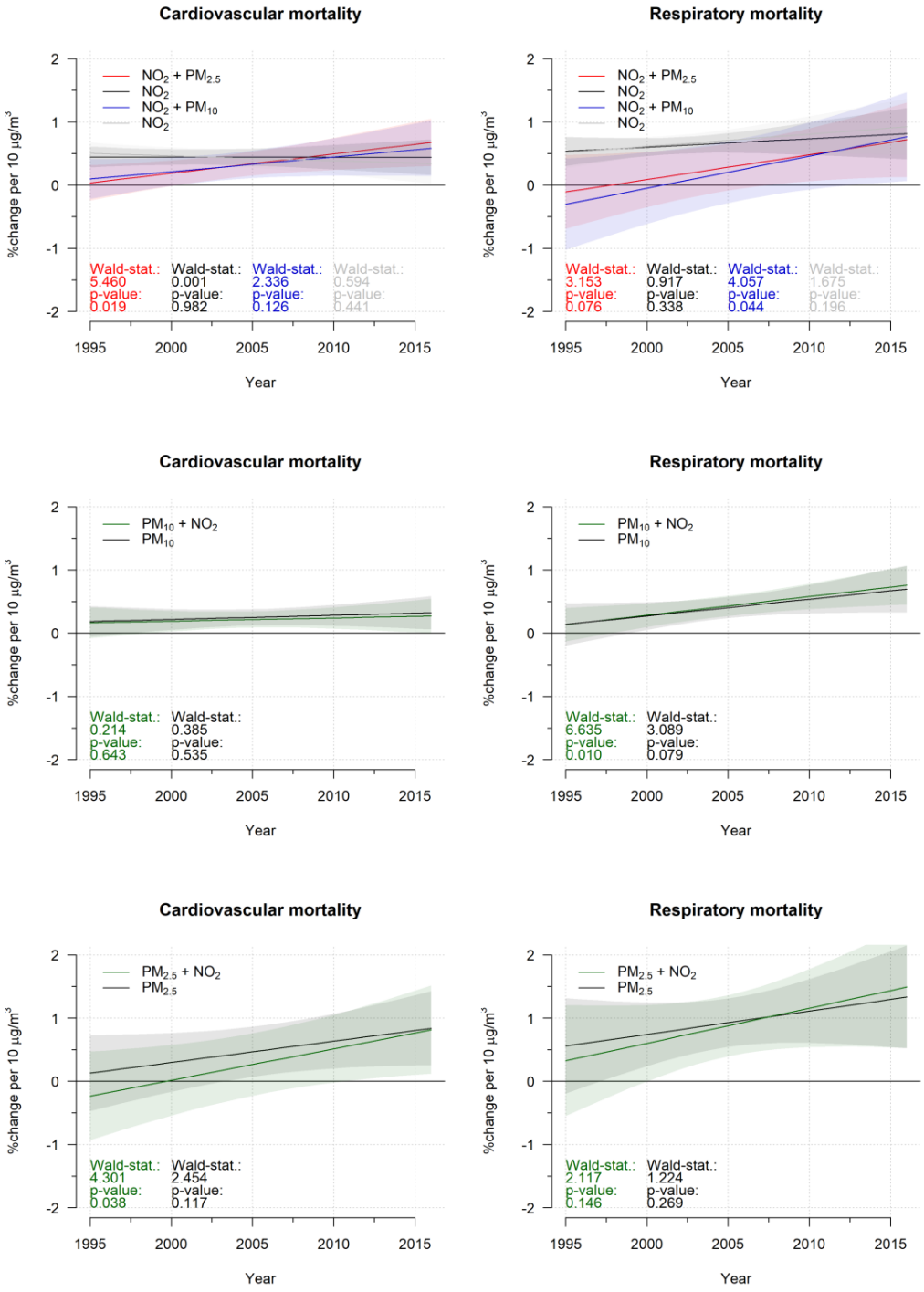

Figure 3. Percent change in daily cardiovascular (left column) and respiratory (right column) mortality and 95% CI (shaded area) per 10 µg/m^3 increase in NO_2 (top panel, at lag1), PM_{10} (middle panel, at lag01), and $PM_{2.5}$ (bottom panel, at lag 01) over the study period 1995-2016. The colored graph represents the result of the pooled two-pollutant longitudinal meta-regression using time as a linear term. The black/grey graph represents the single-pollutant model (restricted dataset including both pollutants). The p-value of the related Wald-Test indicate a significant difference of the model with the linear term for time; NO_2 models were adjusted for additional PM fractions, PM models for NO_2.

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Temporal Variations in the Short-Term Effects of Ambient Air Pollution on Cardiovascular and Respiratory Mortality in 380 Urban Areas during a 22-Year Period

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ONLINE SUPPLEMENT

SUPPLEMENTARY METHODS:

Additional information on data collection

In total, 21,605,272 deaths from cardiovascular causes and 7,782,766 deaths from respiratory causes were analyzed occurring in 380 individual cities from 24 countries:

Asia (China: 2 cities; Iran: 1 city; Japan: 44 cities; Kuwait: 1 city; South Korea: 7 cities; Taiwan: 3 cities; Thailand: 16 cities); Europe (Cyprus: 5 cities; Czech Republic: 1 city; Estonia: 4 cities; Finland: 1 city; France: 18 cities; Greece: 1 city; Norway: 1 city; Portugal: 6 cities; Spain: 48 cities; Sweden: 1 city; Switzerland: 8 cities; UK: 36 cites), South Africa (2 cities), South and Central America (Colombia: 1 city; Mexico: 4 cities); and North America (Canada: 25 cities; U.S.: 144 cities).

Because of differences in the availability of air pollutants in the total dataset, we decided to follow a general data management strategy but extract three individual datasets for the main air pollutants NO_2, PM_{10}, and $PM_{2·5}$.

The following section reports details on country-specific data, such as data collection and instrumentation.

Canada: Daily mortality data was obtained from Statistics Canada through access to the Canadian Mortality Database. Mean daily temperature (in ℃), computed as the 24-hour average based on hourly measurements, was obtained from Environment Canada. A single weather station was selected for each city using the airport monitoring station located closest to the CMA center. Hourly measures of PM_{10}, $PM_{2·5}$, O_3, and NO_2 were collected from monitors located in urban areas of the National Air Pollution Surveillance (NAPS) network of Environment Canada, a government institution that operates ground monitoring stations across Canada. Daily PM_{10}, $PM_{2·5}$, and NO_2 levels were computed as the 24-h average and O_3 as the daily maximum 8-hour running average from hourly measurements in different stations and then averaged across stations within the same CMA with no missing data, with an average of 4 stations per city.

China: Daily mortality data was obtained from the Municipal Center for Disease Control. Mean daily temperature (in ℃), computed as the 24-hour average from hourly measurements, was collected from the meteorological departments of each city. Measures of PM_{10}, $PM_{2·5}$, O_3, and NO_2 were collected from urban monitoring stations run by China National Environmental Monitoring Center. Daily PM_{10}, $PM_{2·5}$, O_3, and NO_2 levels were computed as the 24-h average.

Colombia: Daily mortality data was obtained from Administrativo Nacional de Estadistica (DANE). Mean daily temperature (in ℃), computed as the 24-hour average based on hourly measurements, was obtained from the Instituto de Hidrología, Meteorología y Estudios Ambientales de Colombia (IDEAM). A single

weather station was selected for each city. Measurements for PM_{10}, NO_2, and O_3 were available from the Environmental Secretary of Bogotá. Monitoring stations measured hourly air pollutants for each station, and 24-h averages were calculated. For each city, the average among monitoring stations was calculated.

Cyprus: Daily mortality used in this study was collected by the Health Monitoring Unit of the Ministry of Health of Cyprus. The ideas and opinions expressed herein are those of the author. Endorsement of these ideas and opinions by the Ministry of Health of Cyprus is not intended nor should it be inferred. Deaths refer to citizens of each city. Daily mean air temperature data are provided by the Department of Meteorology, Ministry of Agriculture, Rural Development, and the Environment. Air pollution daily concentrations are provided by the Air Quality and Strategic Planning Section, Department of Labour Inspection, Ministry of Labour, Welfare and Social Insurance. These come from one traffic station in each city, PM concentrations are gravimetric, and all concentrations are expressed in $\mu g/m^3$.

Czech Republic: Daily mortality data was obtained from the Czech Statistical Office and the Institute of Health Information and Statistics. Mean daily temperature (in ℃), computed as the average of observations in standard climatic terms (7:00, 14:00, and 21:00 local time), was collected by the Czech Hydrometeorological Institute. The average value was calculated according to the formula (T07 + T14 + 2*T21)/4. Information about daily PM_{10} and NO_2 levels, computed as 24-hour averages and the maximum 8-hour running average for O_3, were provided by the Czech Hydrometeorological Institute. The daily values were calculated from 4 stations (2 urban + 2 suburban).

Estonia: Daily mortality data was obtained from the Estonian Causes of Death Registry. Mean daily temperature (in ℃) was computed as the 24-h average of hourly measurements collected from the Estonian Environment Agency. A single weather station located nearby the urban area was selected for each city. Hourly measurements of PM_{10}, $PM_{2.5}$, NO_2, and O_3 were collected from urban background stations run by the Estonian Environmental Research Centre. Daily PM_{10}, $PM_{2.5}$ and NO_2 levels were computed as 24-hour averages and O_3 as the daily maximum 8-hour running average from hourly measurements; for each pollutant, the city average among monitoring stations was calculated.

Finland: The daily number of deaths was obtained from Statistics Finland. A dataset containing weather variables was obtained from Helsinki Region Environmental Services Authority. Measures of PM_{10}, $PM_{2.5}$, O_3, and NO_2 were extracted, from a nationwide dataset compiled by the Finnish Meteorological Institute, for a single coordinate at Helsinki city center using GIS.

France: Daily mortality data was obtained from the French National Institute of Health and Medical Research (CepiDC). Mean daily temperature (in ℃), computed as the mean of the minimum and maximum

temperature, and relative humidity (%) was obtained from Meteo France. Hourly measurements of PM_{10} and O_3 were collected through the French local air quality monitoring network (Associations Agréées de Surveillance de la Qualité de l'Air AASQA). For PM_{10}, we used only urban stations, and for O_3, urban and peri-urban stations. Daily PM_{10} levels were computed as 24-h averages and O_3 as the daily maximum 8-hour running average from hourly measurements. Measurements were obtained from multiple stations (with different numbers for each city).

Greece: Daily mortality data was collected by Hellenic Statistical Authority. Mean daily temperature (in ℃) and relative humidity (%) were computed as the 24-h average based on hourly measurements collected from the National Observatory of Athens from site "Thisio", located in the city of Athens. Hourly measurements of PM_{10}, $PM_{2.5}$, NO_2, and O_3 were obtained from the Ministry of Environment and Energy fixed-site monitoring network. Urban or suburban fixed monitoring background or traffic sites were selected. Daily PM_{10}, $PM_{2.5}$, and NO_2 levels were computed as 24-hour averages and O_3 as the daily maximum 8-hour running average from hourly measurements.

Iran: Daily mortality of all causes was provided by the Ferdows organization of Mashhad Municipality. Mean, maximum, and minimum daily temperature (in ℃) and relative humidity (in %), computed as the 24-hour average based on hourly measurements collected from IRAN Meteorological Organization (IRIMO) (http://www.irimo.ir). Twenty four-hour averages are used as daily values for PM_{10} and NO_2.

Japan: Daily mortality data was obtained from computerized death certificate data from the Ministry of Health, Labour and Welfare, Japan. Mean daily temperature (in ℃), computed as the 24-h average based on hourly measurements, was obtained from the Japan Meteorological Agency. A single weather station located within the urban area of the city was selected. Hourly measurements of PM_{10}, $PM_{2.5}$, O_3, and NO_2 were collected from the urban monitors within the capital cities maintained by the Ministry of the Environment of Japan. Daily PM_{10}, $PM_{2.5}$, and NO_2 levels were computed as 24-hour averages and O_3 as the daily maximum 8-hour running average from hourly measurements.

Kuwait: Hourly measurements of PM_{10} and O_3 were obtained from measurement stations of the Environmental Public Authority, Kuwait (KEPA). Daily PM_{10} levels were computed as the 24-hour mean and the daily maximum 8-hour running average for O_3 from hourly measurements.

Mexico: Daily mortality data was obtained from the National Institute of Statistics, Geography and Informatics. Mean daily temperature (in ℃) were computed as the 24-hour average based on hourly measurements collected through the Servicio Meteorológico Nacional (SMN) and the Instituto Nacional de Ecología y Cambio Climático (INECC). Hourly measurements of PM_{10}, $PM_{2.5}$, and O_3 were obtained from

urban monitors of the local monitoring network. Daily PM_{10}, $PM_{2·5}$, and NO_2 levels were computed as 24-hour averages and O_3 as the daily maximum 8-hour running average from hourly measurements.

Norway: Aggregated daily mortality data was obtained from the Cause of Death Registry of Norway. Daily mean air temperatures on a 1 km grid across Norway were obtained from the observationally gridded se-norge 2 datasets of the Norwegian Meteorological Institute (MET Norway). The dataset is continuously updated based on measurement data from stations. Daily values for Norway of PM_{10}, $PM_{2·5}$, O_3, and NO_2 at a 1 km resolution were sourced from the Nordic DEHM-UBM (Danish Eulerian Hemispheric Model-Urban Background Model) setup (insert reference). Daily PM_{10}, $PM_{2·5}$, and NO_2 levels were computed as 24-hour averages and O_3 as the daily maximum 8-hour running average from hourly measurements.

Portugal: Daily mortality was obtained from Statistics Portugal. Mean daily temperature (in ℃) was computed as the 24-h average based on hourly measurements collected from the National Oceanic and Atmospheric Administration (NOAA). Hourly measurements of pollutants were gathered from the "online database of air quality" through the Portuguese Environment Agency from urban monitors. Daily PM_{10}, $PM_{2·5}$, and NO_2 levels were computed as 24-hour averages and O_3 as the daily maximum 8-hour running average from hourly measurements. The year 2016 was removed from the analysis due to anomalies in the mortality data.

South Africa: Daily mortality data was obtained from Statistics South Africa. Mean daily temperature (in ℃) was computed as the average between daily minimum and maximum temperature collected from the Agricultural Research Council of South Africa and the National Oceanic and Atmospheric Administration (NOAA). Hourly measurements of PM_{10}, $PM_{2·5}$, NO_2, and O_3 were collected at sites managed by the Department of Environmental Affairs (DEA). Daily PM_{10} levels were computed as the 24-hour mean, and O_3 as the daily maximum 8-hour running average from the respective provided hourly measurements. The average 24-hour mean or daily maximum 8-hour running average values per district municipality (DM) were then calculated from all sites within each DM. Except for the ESKOM run stations, all air quality data were accessed through SAAQIS (http://www.saaqis.org.za/), which is run and hosted by the South African Weather Service.

South Korea: Daily mortality was obtained from the Korea National Statistics Office. Mean daily temperature (in ℃) was computed as the 24-h average based on hourly measurements. Measures of PM_{10}, $PM_{2·5}$, O_3, and NO_2 were available from monitors of the National Institute of Environmental Research. Daily PM_{10}, $PM_{2·5}$, and NO_2 levels were computed as 24-hour averages and O_3 as the daily maximum 8-hour running average from hourly measurements.

Spain: Daily mortality was obtained from the Spain National Institute of Statistics. Mean daily temperature (in ℃), computed as the 24-h average based on hourly measurements, was obtained from weather stations of the Spain National Meteorology Agency. A single weather station, located within the urban area or at the near airport, was selected for each city. Hourly measurements of PM_{10}, $PM_{2.5}$, O_3, and NO_2 were collected from the free national repository (Magrama) from urban and suburban monitors. Daily PM_{10}, $PM_{2.5}$, and NO_2 levels were computed as 24-hour averages and O_3 as the daily maximum 8-hour running average from hourly measurements.

Sweden: Daily mortality data was obtained from the Swedish Cause of Death Register at the Swedish National Board of Health and Welfare. Mean daily temperature (in °C), computed as the 24-hour average based on hourly measurements, was obtained from the Environment and Health Administration. A single weather station, located at Torkel Knutssongatan in Central Stockholm, was selected. Hourly measurements of PM_{10}, $PM_{2.5}$, and NO_2 were collected from the main urban background (roof-top level) monitor run by the local monitoring network. Daily PM_{10}, $PM_{2.5}$, and NO_2 levels were computed as 24-hour averages and O_3 as the daily maximum 8-hour running average from hourly measurements.

Switzerland: Daily mortality data was provided by the Federal Office of Statistics (Switzerland). Mean daily temperature (in °C), computed as the 24-h average based on hourly measurements, was obtained from the IDAWEB database (a service provided by MeteoSwiss, the Swiss Federal Office of Meteorology and Climatology). A single weather station located within or near the urban area was selected for each city. Hourly measurements of PM_{10}, $PM_{2.5}$, O_3, and NO_2 were provided by the Immissionsdatenbank Luft (IDB, Federal Office of the Environment, Bern, Switzerland). Daily PM_{10}, $PM_{2.5}$, and NO_2 levels were computed as 24-hour averages and O_3 as the daily maximum 8-hour running average from hourly measurements from urban monitoring stations.

Taiwan: Daily mortality data was obtained from the Department of Health in Taiwan. Mean daily temperature (in ℃) was computed as the 24-h average based on hourly measurements. Hourly measurements of PM_{10}, $PM_{2.5}$, O_3, and NO_2 were obtained from urban monitors of the local monitoring network. Daily PM_{10}, $PM_{2.5}$, and NO_2 levels were computed as 24-hour averages and O_3 as the daily maximum 8-hour running average from hourly measurements. Measurements were obtained from multiple stations (with different numbers for each city).

Thailand: Daily mortality data was obtained from the Ministry of Public Health, Thailand. Mean daily temperature (in ℃), computed as the average between the daily minimum and maximum temperature, was obtained from the Meteorological Department, Ministry of Information and Communication Technology,

Thailand. Daily data on PM_{10}, $PM_{2.5}$, O_3, and NO_2 were obtained from the Pollution Control Department, Ministry of Natural Resources and Environment. For each city and air pollutant, daily concentrations were averaged by fixed air quality monitoring stations within the city. If monitored data for a particular pollutant were insufficient to calculate a daily average, all measurements from that day were excluded for that pollutant and monitor.

United Kingdom: Daily mortality data was gathered from the Office for National Statistics. Mean daily temperature (in ℃) was obtained from the British Atmospheric Data Centre. Daily PM_{10}, $PM_{2.5}$, O_3, and NO_2 levels were obtained from the Automatic Urban and Rural Network (AURN) repository, the Welsh Air Quality Network (WAQN) archive and the King's College London (KCL) dataset. The urban and sub-urban monitoring stations within the selected boundaries were considered. Those classified as “Roadside/Trac”, “Industrial”, “Portable/ Mobile”, and “Indoor” were excluded due to the unrepresentative nature of the average exposure.

United States: Daily mortality data was obtained from the National Center for Health Statistics (NCHS). Mean daily temperature (in ℃), computed as the 24-h average based on hourly measurements, was obtained from the National Climatic Data Center (NCDC) of the National Oceanic and Atmospheric Administration (NOAA). Hourly measurements of PM_{10}, $PM_{2.5}$, O_3, and NO_2 were gathered from the US Environmental Protection Agency (EPA) Air Quality System (AQS), from urban and sub-urban monitoring stations. Daily PM_{10}, $PM_{2.5}$, and NO_2 levels were computed as 24-hour averages and O_3 as the daily maximum 8-hour running average, from urban monitoring stations from monitors located in the county or set of contiguous counties in which the city is located.

Further data management:

The start of the overall study period was set to 1995 and ended in 2016 because of limited data quality before and after these years (e.g., data of only one country). However, city- and country-specific periods could vary among the datasets. In addition, we set one single individual year to NA, if less than 2/3 of the main air pollution data of that year was available. Furthermore, we restricted the analyses to cities with at least 5+ years of valid air pollution data, to better display changes in risk over time. Last, we excluded cities with more than 50% NA for mortality endpoints. The resulting air pollution-specific datasets comprised 338 cities (9,969,409 cardiovascular and 3,454,824 respiratory deaths) for the NO_2 analysis, 249 cities (7,082,163 cardiovascular and 2,660,833 respiratory deaths) for PM_{10}, and 194 cities (4,553,700

cardiovascular and 1,667,109 respiratory deaths) contributed to the analysis of $PM_{2·5}$ association. The final datasets comprised 380 cities or urban areas in 24 countries.

Additional information on the statistical analyses:

Basic descriptive statistics of mortality counts, and air pollution concentrations were expressed as mean (5^{th}-95^{th} percentile of air pollution range) concentrations. In addition, we calculated the Spearman correlation coefficient r_S between the main air pollutants of the analyses, and among the individual variables of the main regression models. We considered values $r_S \geq 0{\cdot}7$ as high correlations since previous studies used 0·7 as a reasonable tradeoff value between investigating temporal variations among model variables/cities and considering potential multicollinearity.

The main analysis was based on a two-stage modeling design to analyze the associations between air pollution concentrations and cause-specific mortality and was further extended to examine temporal variations. This advanced statistical design has recently been used in other multicity studies.[1-3] Because of differences in the availability of primary air pollutants, we analyzed each pollutant in separate analyses.

First stage model:

In the first stage, we applied linear city-specific confounder-adjusted generalized additive models (GAM) following a quasi-Poisson distribution and allowing for overdispersion. We selected the confounder variables based on the published analyses by Liu and colleagues[1] and Meng and colleagues[2], who analyzed associations between PM fractions and NO_2.with (cause-specific) mortality in initial MCC analyses. PM and NO_2 were assumed to have linear associations.

$$Y_t \sim quasi\_Poisson(E(Y_t))$$

$$\log\big(E(Y_t)\big) = \beta_0 + \beta_1 AP_l + ns(date, df = 7 \times years) + factor(day\_of\_week) + ns(tmean_{l03}, df = 6) + ns(rhum, df = 3)$$

where Y_t corresponds to the observed (cause-specific) death counts on a specific day t. $E(Y_t)$ denotes the expected (cause-specific) death counts on day t. β_0 is the intercept and $\beta_1$represents the log-relative risk (RR) for a one-unit increase (µg/m^3) in air pollution (AP) concentration at a specific lag day l. $ns()$ denotes a natural smooth spline term including seven degrees of freedom (df) per year to control for long-term

time trends and seasonal variations, six df for air temperature at lag 0-3, and three df for relative humidity (where applicable). Day of the week was entered to the models as an indicator term.

Second stage model:

In the second stage, we used a novel multilevel random-effects meta-analytical model to pool the city-specific results.[4,5] This method accounted for different nested hierarchical structures of the risks between countries and cities (as random terms in the multilevel model). We applied the restricted maximum likelihood (REML) estimator in the multilevel meta-analysis and extracted the best linear unbiased prediction (BLUP) for the global estimates between air pollutants and mortality. We also obtained country-specific estimates using the same approach for country-level data without the country term in the meta-analysis model. The BLUP borrows information within and/or between hierarchical levels, resulting in more precise estimates while accounting for heterogeneity.[5,6] Finally, we extracted the corresponding I^2 statistic and p-value as a measure of heterogeneity, where I^2 > 50% and p-value < 0·05 were considered as substantial heterogeneity.

On an exploratory basis, we modeled the pooled exposure-response functions to check our model assumptions of a linear relationship between air pollution and mortality. Therefore, we exchanged the linear air pollution term in the first stage with a quintic polynomial parameter to decrease the sensitivity of the estimates across the whole variable range.[3] In the second stage, the resulting city-specific estimates were then pooled according to the general modeling strategy.

Assessment of temporal variation:

We assessed the temporal variation in associations between air pollutants and mortality in two different ways by making some changes to the aforementioned two-stage design. First, we divided the overall study period into three sub-periods of approximately seven years. The three periods are: 1995-2001, 2002-2008, 2009-2016. The choice of these periods was based on a reasonable individual length of the period itself (increased power and lager number of cities contributing to those periods) as well as the possibility to consider the onset of the global economic crisis and its consequences around 2008. In addition, we used predefined time periods for all cities rather than city-specific periods to examine comparable overall/global patterns, although this resulted in a reduction in the number of cities. We then subset the city-specific data in stage one and pooled the resulting city- and period-specific data using a longitudinal multilevel meta-regression in stage two, where we modeled time as a linear fixed term (entered as midyear of the respective study period) to the model. The results of the second stage were used to predict the overall yearly estimates over the study period. In addition, we tested for a temporal trend by comparing the model

to a model without the linear time term using a Wald test. Second, we used the same periods as for the longitudinal analyses but compared the mortality risks separately between the periods by calculating interactions between the air pollution concentrations and the periods in the first stage. In the second stage, we followed the general modeling strategy of pooling the city- and period-specific estimates without the longitudinal meta-regression to obtain an overall estimate for each period.

Further, secondary analyses:

On an exploratory basis, we conducted three secondary analyses based on our main (longitudinal) approach: 1) We conducted the main longitudinal analysis but modeled the term of time nonlinearly. 2) We assessed interdependencies between the main air pollutants in two pollutant models, where we included the second pollutant as additional linear term into the first stage (e.g., PM+NO_2/NO_2+PM). Consequently, we further restricted our dataset only using cities that included both air pollutants simultaneously and performed the single- and two-pollutant model on that dataset. 3) We applied a multivariable meta-regression to further investigate sources of heterogeneity that affected the results of the longitudinal meta-regression. We therefore used a set of nine meta-predictors, which were either calculated from variables in the MCC dataset (e.g., climate variables such as total temperature range) or derived from the OECD Regional and Metropolitan Database. The following variables were included:

- WHO region
- GDP per capita (in USD)
- Köppen climate zone (main climates)
- Average temperature
- Total temperature range
- Average (main) air pollution concentration
- Total population
- Population density
- Proportion of old population (65+ years)

We applied a stepwise forward selection on an empty model of the second-stage longitudinal multilevel meta-regression (without any meta-predictors and fitting the models by Maximum Likelihood estimation (ML)) to identify further potential influential variables based on the Akaike information criterion (final model). We then used a likelihood ratio test to evaluate whether the identified meta-predictors of the final model improved the model fit significantly. Significant categorical meta-predictors were added directly into the model and continuous variables were categorized before into terciles to have a sufficient number of cities in each stratum.

Sensitivity analyses:

To test the robustness of our results, we conducted a series of sensitivity analyses:

- We excluded cities where the Spearman correlation coefficient r_S indicated high correlations (r_S > 0·7) between the model variables
- We excluded relative humidity from the main model (first stage)
- We modeled time trend with ten df per year
- We modeled time trend with four df per year
- We adjusted for air temperature by using a distributed lag nonlinear model (DLNM) according to O'Brien and colleagues[3]
- We adjusted for high and low temperature separately according to Chen and colleagues[7]
- We excluded the US cities from the dataset

SUPPLEMENTARY RESULTS:

Supplementary tables:

Table S1: Basic descriptive statistics of NO_2 data, stratified by country.

Country	Cities (N)	Period	Years (mean)	CVD (N)	RESP (N)	Mean NO_2 (5^{th}-95^{th} percentile) (µg/m³)	% of days above WHO limit
Canada	25	1995-2015	20·2	826,003	224,702	23·4 (7·6-47·0)	38·3%
China	2	1996-2008	6	76,689	44,549	40·5 (21·1-65·0)	65·2%
Colombia	1	1998-2013	16	123,780	46,328	31·5 (15·5-49·6)	71·4%
Cyprus	4	2010-2016	7	12,607	2,879	28·9 (13·4-47·6)	58·4%
Czech Republic	1	1995-2009	15	102,835	9,094	32·1 (16·6-52·7)	71·1%
Estonia	4	2003-2016	10·5	42,485	2,824	13·0 (4·0-27·8)	12·5%
Finland	1	1995-2014	20	54,366	9,226	8·7 (2·4-21·6)	2·7%
France	18	2000-2015	10·3	255,222	66,657	26·3 (9·8-49·8)	47·1%
Greece	1	2001-2010	10	136,194	28,771	51·5 (28·6-80·6)	97·8%
Iran	1	2002-2015	14	316,976	52,649	88·5 (37·7-179·4)	99·4%
Japan	44	1995-2016	8·3	1,176,249	625,020	18·9 (7·6-36·2)	23·6%
South Korea	7	1999-2015	17	389,590	106,209	46·5 (22·4-79·9)	88·1%
Portugal	6	1995-2016	14·7	297,057	87,784	15·8 (5·2-31·6)	19·8%
Spain	48	2001-2014	12·4	516,250	191,989	27·7 (13·3-46·5)	54·9%
Switzerland	8	1995-2013	19	90,744	16,015	33·9 (15·1-58·3)	65·7%
Sweden	1	1995-2010	16	66,455	11,697	28·4 (11·9-48·5)	57·6%
Thailand	16	1999-2008	9·4	150,329	99,509	25·3 (10·8-47·9)	40·6%
Taiwan	3	1995-2014	20	257,553	113,269	43·6 (20·8-73·1)	86·8%
UK	33	1995-2016	18·1	1,309,605	580,669	27·3 (10·4-52·0)	49·8%
USA	114	1995-2006	11·6	3,768,420	1,134,984	30·4 (12·2-54·6)	56·5%
Overall	338	1995-2016	13·8	9,969,409	3,454,824	27·5 (11·4-50·0)	49·0%

N: Number of cities and mortality cases over the respective period; CVD: cardiovascular disease mortality; RESP: respiratory disease mortality; NO_2: Nitrogen dioxide; WHO: World Health Organization; 24-hour limit according to WHO air quality guideline[8]: 25 µg/m³; Air pollutants measured in µg/m³.

Table S2: Basic descriptive statistics of PM_{10} data, stratified by country.

Country	Cities (N)	Period	Years (mean)	CVD (N)	RESP (N)	Mean PM_{10} (5^{th}-95^{th} percentile) (µg/m³)	% of days above WHO limit
Canada	7	2000-2011	11·7	153,068	40,410	17·6 (6·2-37·8)	3·7%
China	2	1996-2008	6	76,689	44,549	91·9 (33·8-174·8)	73·0%
Colombia	1	2002-2013	12	95,588	36,514	62·7 (34·1-97·6)	81·2%
Cyprus	5	2005-2016	10·8	22,263	4,666	44·2 (21·5-78·0)	33·2%
Czech Republic	1	1995-2009	15	102,835	9,094	34·3 (12·0-77·2)	21·2%
Estonia	4	2003-2016	10·5	42,485	2,824	17·0 (4·8-38·7)	3·3%
Finland	1	1995-2014	20	54,366	9,226	19·8 (4·7-52·0)	7·6%

France	18	2007-2015	9	234,413	62,250	23·7 (9·8-47·9)	6·6%
Greece	1	2001-2010	10	136,194	28,771	43·9 (18·5-83·3)	38·5%
Iran	1	2002-2015	14	316,976	52,649	87·5 (30·1-164·2)	86·1%
Japan	40	1995-2016	8·5	1,114,447	588,611	29·0 (10·0-59·5)	15·0%
South Korea	7	1999-2015	17	389,590	106,209	52·2 (20·8-101·7)	51·3%
Kuwait	1	2010-2016	7	15,962	3,170	191·0 (60·7-539·5)	98·3%
Mexico	6	2000-2012	11·7	492,867	185,735	57·5 (24·5-104·9)	60·8%
Norway	1	2000-2016	17	23,503	7,152	22·1 (8·3-45·9)	5·6%
Portugal	5	1999-2016	14·8	238,172	73,264	23·1 (7·7-51·5)	9·1%
South Africa	2	2004-2013	8·5	62,203	48,086	61·6 (24·8-116·9)	63·7%
Spain	34	2001-2014	11·1	376,387	146,017	27·9 (13·6-49·1)	10·3%
Switzerland	8	1995-2013	17·9	86,906	15,382	25·1 (7·8-56·0)	10·6%
Sweden	1	1995-2010	16	66,434	11,695	14·9 (6·0-32·1)	1·0%
Thailand	16	1999-2008	9·5	151,824	100,179	51·1 (22·6-104·3)	45·8%
Taiwan	3	1995-2014	20	257,553	113,269	62·8 (25·3-118·4)	62·2%
UK	30	1995-2016	17	1,235,377	547,036	21·2 (8·6-43·0)	4·3%
USA	54	1995-2006	8·6	1,336,061	424,075	25·6 (9·0-50·4)	9·4%
Overall	249	1995-2016	12·7	7,082,163	2,660,833	31·3 (12·3-62·2)	17·3%

N: Number of cities and mortality cases over the respective period; CVD: cardiovascular disease mortality; RESP: respiratory disease mortality; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; WHO: World Health Organization; 24-hour limit according to WHO air quality guideline[8]: 45 µg/m³; Air pollutants measured in µg/m³.

Table S3: Basic descriptive statistics of $PM_{2·5}$ data, stratified by country.

Country	Cities (N)	Period	Years (mean)	CVD (N)	RESP (N)	Mean $PM_{2·5}$ (5^{th}-95^{th} percentile) (µg/m³)	% of days above WHO limit
Canada	25	1997-2015	16·1	673,436	187,688	8·1 (2·2-18·8)	10·8%
Cyprus	2	2010-2016	6·5	4,804	1,139	20·1 (9·0-34·5)	66·0%
Estonia	3	2009-2016	7·3	10,917	718	7·7 (1·2-18·8)	10·3%
Finland	1	1995-2014	20	54,366	9,226	16·8 (3·9-43·5)	41·5%
France	15	2007-2015	8·3	200,895	53,136	16·3 (5·2-38·2)	41·0%
Japan	26	2001-2016	6·2	610,505	346,247	14·7 (4·8-29·9)	39·9%
Mexico	2	2004-2012	9	269,157	96,373	26·9 (12·0-46·5)	87·4%
Norway	1	2000-2016	17	23,503	7,152	10·8 (4·6-21·8)	16·5%
Portugal	3	2004-2016	12·3	106,124	30,614	10·1 (3·2-22·5)	18·4%
South Africa	1	2007-2013	7	14,721	13,713	36·0 (14·6-71·0)	94·2%
Spain	2	2004-2014	8	87,540	38,337	16·3 (7·0-30·9)	43·3%
Switzerland	4	1998-2009	11·2	39,568	6,394	19·7 (5·9-45·0)	56·0%
Sweden	1	2001-2010	10	37,873	6,707	8·2 (3·1-19·4)	9·2%
Taiwan	3	2007-2014	8	117,402	58,942	34·4 (12·7-65·1)	89·4%
UK	28	1998-2016	8	577,277	277,262	12·1 (4·1-30·2)	24·0%
USA	77	1999-2006	7·3	1,725,612	533,461	13·2 (4·5-28·0)	32·0%
Overall	194	1995-2016	10·1	4,553,700	1,667,109	13·5 (4·5-29·4)	31·9%

N: Number of cities and mortality cases over the respective period; CVD: cardiovascular disease mortality; RESP: respiratory disease mortality; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5μm; WHO: World Health Organization; 24-hour limit according to WHO air quality guideline[8]: 15 μg/m³; Air pollutants measured in μg/m³.

Table S4: Basic descriptive statistics of NO_2, PM_{10}, and $PM_{2·5}$ data per city.

Country	City	Period	Years (N)	Mean concentration of air pollutant (5^{th}-95^{th} percentile) (μg/m³)	% of days above WHO limit
				NO_2	
Canada	Abbotsford	1995-2015	21	21·3 (9·1-36·5)	30·9%
Canada	Calgary	1995-2015	21	37·3 (11·2-69·9)	73·1%
Canada	Edmonton	1995-2015	21	34·2 (11·5-69·0)	63·8%
Canada	Halifax	1995-2015	21	27·1 (9·9-48·0)	52·8%
Canada	Hamilton	1995-2015	21	29·8 (9·9-56·0)	57·9%
Canada	Kingston	2007-2013	7	8·7 (3·7-18·1)	1·4%
Canada	Kitchener-Waterloo	1995-2015	21	21·0 (5·6-46·0)	30·6%
Canada	London Ontario	1995-2014	20	24·7 (6·9-53·3)	41·2%
Canada	Montreal	1995-2015	21	27·9 (10·5-52·8)	51·6%
Canada	Oakville	1995-2015	21	25·3 (6·5-51·3)	45·4%
Canada	Oshawa	1995-2015	21	24·6 (5·0-57·3)	40·4%
Canada	Ottawa	1995-2015	21	23·8 (4·8-55·6)	39·8%
Canada	Regina	1995-2013	19	22·9 (8·9-44·7)	35·4%
Canada	Sarnia	1995-2015	21	23·7 (6·4-50·2)	38·3%
Canada	Sudbury	1995-2015	21	15·1 (4·2-34·7)	14·1%
Canada	Saint John NB	1995-2015	21	12·0 (2·3-28·8)	8·2%
Canada	St. John's NFL	1998-2015	18	13·0 (3·1-29·5)	9·0%
Canada	Sault Ste. Marie	1995-2015	21	13·7 (3·3-34·2)	12·6%
Canada	Saskatoon	1995-2015	21	21·0 (7·4-42·4)	29·7%
Canada	Thunder Bay	1995-2015	21	18·8 (5·6-41·0)	24·1%
Canada	Toronto	1995-2015	21	37·0 (15·2-65·2)	75·8%
Canada	Victoria	1995-2015	21	17·6 (5·9-35·9)	18·4%
Canada	Vancouver	1995-2015	21	29·3 (15·0-46·8)	64·3%
Canada	Windsor	1995-2015	21	33·4 (13·5-61·3)	66·6%
Canada	Winnipeg	1995-2015	21	21·2 (5·7-45·1)	31·6%
China	Hong Kong	1996-2002	7	58·2 (30·4-93·8)	98·5%
China	Taiyuan	2004-2008	5	22·7 (11·8-36·3)	31·9%
Colombia	Bogota	1998-2013	16	31·5 (15·5-49·6)	71·4%
Cyprus	Larnaka	2010-2016	7	28·4 (14·0-47·6)	56·8%
Cyprus	Limassol	2010-2016	7	32·7 (16·4-51·3)	74·4%
Cyprus	Nicosia	2010-2016	7	32·3 (14·4-54·2)	70·0%
Cyprus	Pafos	2010-2016	7	22·2 (8·6-37·3)	32·4%
Czech Republic	Prague	1995-2009	15	32·1 (16·6-52·7)	71·1%
Estonia	Kohtla-Jarve linn	2003-2016	14	6·4 (1·3-15·7)	1·1%

Estonia	Narva linn	2009-2016	8	10·6 (3·4-23·8)	4·4%
Estonia	Tallinn	2005-2016	12	22·6 (7·2-44·0)	37·5%
Estonia	Tartu linn	2009-2016	8	12·4 (4·0-27·7)	7·0%
Finland	Helsinki	1995-2014	20	8·7 (2·4-21·6)	2·7%
France	Bordeaux	2007-2015	9	20·0 (5·9-40·9)	28·8%
France	Clermont-Ferrand	2000-2015	16	26·3 (8·0-56·5)	43·6%
France	Dijon	2000-2015	16	26·9 (9·3-49·4)	50·9%
France	Grenoble	2007-2015	9	24·7 (8·2-50·4)	40·5%
France	Le Havre	2007-2015	9	22·8 (7·0-47·0)	35·2%
France	Lille	2004-2015	12	27·4 (10·6-50·5)	50·3%
France	Lens-Douai	2007-2015	9	23·6 (7·0-47·5)	38·6%
France	Lyon	2007-2015	9	32·0 (11·7-62·9)	60·2%
France	Montpellier	2007-2015	9	28·1 (10·0-52·3)	54·7%
France	Marseille	2007-2015	9	34·4 (13·0-60·0)	69·3%
France	Nice	2007-2015	9	27·3 (14·0-43·0)	54·6%
France	Nancy	2007-2015	9	28·6 (13·0-50·2)	55·8%
France	Nantes	2007-2015	9	18·0 (5·5-38·5)	22·5%
France	Paris	2007-2015	9	35·5 (15·6-60·0)	74·6%
France	Rennes	2007-2015	9	19·3 (5·8-39·7)	26·0%
France	Rouen	2007-2015	9	26·3 (11·3-48·0)	46·4%
France	Strasbourg	2000-2015	16	30·9 (13·2-53·5)	63·2%
France	Toulouse	2007-2015	9	21·6 (6·7-45·4)	32·6%
Greece	Athens	2001-2010	10	51·5 (28·6-80·6)	97·8%
Iran	Tehran	2002-2015	14	88·5 (37·7-179·4)	99·4%
Japan	Akita	2012-2016	5	11·4 (4·5-23·7)	3·6%
Japan	Chiba	2011-2016	6	25·6 (10·0-52·9)	42·4%
Japan	Fukushima	2011-2016	6	16·7 (5·2-35·5)	17·1%
Japan	Fukuoka	1995-2016	22	20·0 (7·8-36·7)	27·3%
Japan	Fukui	2011-2016	6	14·0 (5·2-28·3)	7·9%
Japan	Gifu	2011-2016	6	15·6 (6·1-28·6)	10·0%
Japan	Hiroshima	2012-2016	5	20·9 (8·7-36·8)	28·6%
Japan	Kagoshima	2011-2016	6	20·1 (7·5-37·9)	26·8%
Japan	Kumamoto	2011-2016	6	18·1 (6·7-36·7)	22·0%
Japan	Kanazawa	2011-2016	6	13·6 (6·2-25·6)	5·9%
Japan	Kobe	2011-2016	6	33·4 (13·1-60·9)	66·9%
Japan	Kochi	2011-2016	6	10·7 (4·0-23·1)	3·2%
Japan	Kofu	2011-2016	6	21·9 (9·1-46·3)	30·9%
Japan	Kitakyushu	1995-2008	14	20·6 (9·3-33·9)	28·4%
Japan	Kyoto	2011-2016	6	23·7 (10·3-45·0)	36·9%
Japan	Matsue	2011-2016	6	5·1 (1·9-10·5)	0·1%
Japan	Maebashi	2011-2016	6	14·4 (4·5-28·8)	9·3%
Japan	Mito	2011-2016	6	14·6 (6·7-26·4)	6·4%
Japan	Morioka	2011-2016	6	16·3 (5·1-38·6)	17·6%
Japan	Matsuyama	2011-2016	6	23·0 (11·2-41·7)	34·0%
Japan	Nagano	2011-2016	6	15·2 (5·9-33·7)	14·5%

Japan	Nagoya	1995-2016	22	28·3 (12·7-47·7)	57·4%
Japan	Nara	2011-2016	6	17·3 (6·0-35·7)	18·2%
Japan	Nagasaki	2011-2016	6	14·0 (6·0-24·4)	4·2%
Japan	Niigata	2011-2016	6	14·4 (6·0-28·8)	8·9%
Japan	Oita	2011-2016	6	14·4 (6·7-26·1)	6·2%
Japan	Okayama	2011-2016	6	22·1 (9·5-40·1)	33·2%
Japan	Osaka	1995-2016	22	33·1 (14·7-58·2)	69·1%
Japan	Otsu	2011-2016	6	19·2 (6·7-38·9)	24·1%
Japan	Saga	2011-2016	6	14·9 (5·8-30·9)	11·7%
Japan	Saitama	2011-2016	6	29·8 (11·8-56·6)	57·8%
Japan	Sendai	1995-2016	22	14·0 (5·3-26·5)	6·8%
Japan	Shimonoseki	2012-2016	5	6·9 (1·3-15·7)	0·6%
Japan	Shizuoka	2011-2016	6	19·5 (9·4-32·7)	19·8%
Japan	Sapporo	1995-2016	22	21·3 (8·1-44·0)	28·1%
Japan	Takamatsu	2011-2016	6	23·5 (8·6-47·3)	36·3%
Japan	Tokushima	2011-2016	6	12·3 (5·6-22·7)	3·2%
Japan	Tokyo	1995-2016	22	31·9 (14·4-55·9)	67·5%
Japan	Toyama	2011-2016	6	13·0 (5·3-25·7)	5·7%
Japan	Tsu	2011-2016	6	16·0 (6·6-32·3)	12·8%
Japan	Utsunomiya	2011-2016	6	22·7 (11·0-41·2)	33·3%
Japan	Wakayama	2011-2016	6	16·4 (7·8-29·1)	10·2%
Japan	Yokohama	2011-2016	6	31·2 (10·6-59·2)	61·2%
Japan	Yamagata	2011-2016	6	18·7 (7·3-41·0)	20·6%
South Korea	Busan	1999-2015	17	42·3 (20·8-70·8)	88·1%
South Korea	Daegu	1999-2015	17	45·6 (20·6-80·6)	88·9%
South Korea	Daejeon	1999-2015	17	39·6 (17·9-72·5)	79·3%
South Korea	Gwangju	1999-2015	17	38·9 (17·4-68·7)	81·0%
South Korea	Incheon	1999-2015	17	53·1 (25·0-93·4)	94·9%
South Korea	Seoul	1999-2015	17	67·5 (34·7-109·9)	99·6%
South Korea	Ulsan	1999-2015	17	38·8 (20·3-63·4)	85·1%
Portugal	Beja	2005-2014	10	5·1 (1·9-10·4)	0·0%
Portugal	Coimbra	2003-2016	14	16·4 (4·7-33·0)	16·0%
Portugal	Castelo Branco	2005-2016	12	5·9 (2·0-10·2)	0·0%
Portugal	Faro	2005-2016	12	11·1 (3·8-22·0)	2·4%
Portugal	Lisboa	1995-2016	22	30·5 (10·0-63·0)	54·1%
Portugal	Porto	1999-2016	18	26·0 (9·0-50·8)	45·9%
Spain	A Coruna	2006-2014	9	28·2 (9·9-51·9)	54·4%
Spain	Albacete	2001-2013	13	15·2 (4·1-32·0)	12·2%
Spain	Alicante	2001-2014	14	31·0 (17·5-48·0)	72·4%
Spain	Almeria	2006-2014	9	22·4 (10·8-37·2)	34·1%
Spain	Avila	2001-2014	14	23·0 (11·4-36·4)	35·4%
Spain	Badajoz	2002-2014	13	10·1 (2·5-24·5)	4·7%
Spain	Bilbao	2001-2014	14	37·1 (20·0-58·8)	84·8%
Spain	Barcelona	2001-2014	14	45·5 (22·6-72·1)	92·5%
Spain	Burgos	2001-2014	14	25·1 (11·7-45·0)	42·9%

Spain	Cadiz	2007-2014	8	19·2 (5·4-38·5)	25·2%
Spain	Caceres	2002-2014	13	12·2 (2·8-28·4)	8·0%
Spain	Ciudad Real	2008-2014	7	10·7 (2·2-28·3)	8·0%
Spain	Cordoba	2001-2014	14	30·2 (20·1-42·3)	77·0%
Spain	Castellon	2002-2014	13	40·9 (25·8-57·7)	95·8%
Spain	Cuenca	2008-2014	7	17·8 (3·3-40·2)	22·4%
Spain	Guadalajara	2001-2014	14	26·4 (6·3-53·4)	48·1%
Spain	Girona	2005-2014	10	32·4 (23·5-42·7)	90·5%
Spain	Granada	2001-2014	14	39·9 (21·4-63·4)	89·1%
Spain	Huesca	2004-2014	11	19·9 (4·6-38·2)	27·1%
Spain	Jaen	2004-2014	11	20·1 (8·6-38·7)	24·7%
Spain	Leon	2001-2014	14	30·8 (14·6-53·2)	61·8%
Spain	Logrono	2002-2014	13	15·7 (2·4-37·8)	21·6%
Spain	Lleida	2001-2014	14	25·9 (8·0-47·7)	49·1%
Spain	Lugo	2006-2014	9	22·9 (13·6-33·9)	32·8%
Spain	Malaga	2001-2014	14	32·6 (20·7-46·5)	82·6%
Spain	Madrid	2001-2014	14	47·2 (23·8-76·9)	93·6%
Spain	Murcia	2005-2014	10	43·1 (31·4-57·0)	100·0%
Spain	Ourense	2007-2014	8	30·7 (9·3-57·5)	61·4%
Spain	Oviedo	2001-2014	14	31·7 (15·1-56·3)	65·1%
Spain	Palmas G. Canaria	2001-2014	14	24·7 (9·2-42·7)	45·8%
Spain	Palma Mallorca	2002-2014	13	27·3 (12·7-44·6)	55·9%
Spain	Palencia	2001-2014	14	29·2 (16·9-43·9)	67·8%
Spain	Pontevedra	2006-2014	9	22·3 (6·0-44·0)	34·5%
Spain	Segovia	2002-2014	13	30·4 (19·0-42·9)	77·5%
Spain	Salamanca	2001-2014	14	32·5 (20·1-48·9)	79·4%
Spain	San Sebastian	2001-2014	14	30·1 (13·1-51·9)	62·5%
Spain	Santander	2001-2014	14	27·7 (14·1-45·5)	58·4%
Spain	Soria	2004-2014	11	25·8 (9·5-46·7)	48·9%
Spain	Sevilla	2001-2014	14	33·5 (15·7-52·2)	75·8%
Spain	Teruel	2004-2014	11	15·4 (4·1-31·4)	13·5%
Spain	Tenerife	2004-2014	11	20·5 (7·7-40·4)	26·6%
Spain	Toledo	2001-2014	14	25·2 (15·7-37·4)	46·0%
Spain	Tarragona	2001-2014	14	25·7 (10·5-45·4)	47·3%
Spain	Vitoria	2001-2014	14	29·6 (12·8-52·5)	59·7%
Spain	Valladolid	2001-2014	14	29·5 (13·6-48·5)	63·6%
Spain	Valencia	2001-2014	14	40·7 (21·4-64·4)	88·7%
Spain	Zamora	2001-2014	14	29·1 (18·8-40·7)	72·3%
Spain	Zaragoza	2001-2014	14	42·8 (24·6-64·7)	94·2%
Switzerland	Basel	1995-2013	19	25·9 (6·5-51·9)	46·8%
Switzerland	Bern	1995-2013	19	48·9 (28·6-72·4)	97·8%
Switzerland	Geneve	1995-2013	19	38·0 (17·1-64·6)	80·9%
Switzerland	Lausanne	1995-2013	19	44·6 (22·1-67·2)	92·4%
Switzerland	Lugano	1995-2013	19	37·5 (14·2-67·0)	72·9%
Switzerland	Luzern	1995-2013	19	26·3 (11·6-48·0)	46·9%

Switzerland	St. Gallen	1995-2013	19	15·0 (5·0-33·7)	13·4%
Switzerland	Zürich	1995-2013	19	35·2 (15·7-61·7)	74·2%
Sweden	Stockholm	1995-2010	16	28·4 (11·9-48·5)	57·6%
Thailand	Bangkok	1999-2008	10	48·1 (27·5-83·4)	98·1%
Thailand	Chon Buri	1999-2008	10	24·6 (12·8-42·9)	39·1%
Thailand	Chiang Mai	1999-2008	10	20·7 (6·4-44·0)	27·6%
Thailand	Khon Kaen	1999-2008	10	38·3 (16·9-71·8)	76·0%
Thailand	Lampang	1999-2008	10	11·3 (4·1-24·3)	4·3%
Thailand	Nakhon Ratchasima	2001-2008	8	20·5 (7·1-41·7)	26·8%
Thailand	Nakhon Sawan	2001-2008	8	20·2 (10·3-38·6)	20·2%
Thailand	Nonthaburi	2000-2008	9	35·9 (17·4-62·9)	75·7%
Thailand	Pathum Thani	1999-2008	10	29·8 (4·2-55·7)	62·5%
Thailand	Ratchaburi	1999-2008	10	14·7 (4·0-33·4)	15·0%
Thailand	Rayong	1999-2008	10	17·9 (7·7-33·3)	16·8%
Thailand	Samutprakan	1999-2008	10	34·9 (16·1-70·9)	59·2%
Thailand	Samut Sakhon	1999-2008	10	33·9 (16·3-63·4)	66·6%
Thailand	Songkhla	2001-2008	8	16·0 (4·9-27·4)	9·5%
Thailand	Saraburi	2000-2008	9	27·9 (14·0-51·5)	50·6%
Thailand	Surat Thani	2000-2008	9	10·6 (2·5-20·6)	1·0%
Taiwan	Kaohsiung	1995-2014	20	43·2 (18·3-74·9)	81·8%
Taiwan	Taipei	1995-2014	20	48·0 (24·4-76·8)	94·6%
Taiwan	Taichung	1995-2014	20	39·5 (19·5-67·5)	83·9%
UK	Blackpool	2001-2016	16	18·3 (5·4-44·2)	22·6%
UK	Brighton and Hove	2005-2016	12	18·5 (5·6-39·5)	24·0%
UK	Barnsley/Dearne Valley	1999-2016	18	21·8 (7·0-45·8)	32·1%
UK	Birkenhead	2001-2016	16	21·2 (7·4-46·6)	29·8%
UK	Bournemouth/Poole	2001-2016	16	16·2 (4·6-37·4)	18·5%
UK	Bristol	1995-2016	22	34·8 (13·3-68·4)	66·0%
UK	Chesterfield	2008-2016	9	17·8 (4·9-39·3)	21·8%
UK	Cardiff	1995-2016	22	32·7 (14·4-57·5)	67·7%
UK	Crawley	2001-2016	16	30·5 (15·8-51·2)	64·7%
UK	Eastbourne	2004-2016	13	14·9 (3·3-35·9)	16·1%
UK	Kingston upon Hull	1995-2016	22	30·8 (9·7-57·0)	61·5%
UK	Leicester	1995-2016	22	34·5 (13·8-60·8)	71·2%
UK	London	1995-2016	22	40·1 (19·8-67·3)	84·8%
UK	Liverpool	1995-2016	22	37·2 (11·7-69·9)	70·3%
UK	Medway Towns	1997-2009	13	25·6 (7·9-52·1)	44·6%
UK	Manchester	1995-2016	22	36·9 (16·4-64·9)	77·8%
UK	Northampton	2002-2016	15	18·4 (5·6-40·9)	23·1%
UK	Norwich	1998-2016	19	20·0 (6·3-42·2)	27·5%
UK	Nottingham	1998-2016	19	36·2 (17·1-60·0)	78·2%
UK	Newport	2002-2016	15	20·8 (6·8-42·5)	29·7%
UK	Plymouth	1999-2016	18	25·0 (9·1-46·0)	44·5%
UK	Preston	2001-2016	16	24·6 (9·8-48·2)	41·2%

UK	Reading	1998-2016	19	28·0 (9·5-54·2)	51·5%
UK	Sheffield	1995-2016	22	35·7 (14·4-62·2)	74·7%
UK	South Hampshire	1995-2016	22	31·7 (14·9-55·4)	64·6%
UK	Southend-on-Sea	2001-2016	16	22·2 (7·8-45·9)	32·8%
UK	Stoke-on-Trent	1998-2016	19	30·4 (12·9-55·1)	61·1%
UK	Swansea	1995-2016	22	28·1 (10·3-51·2)	54·4%
UK	Thanet	2003-2009	7	22·4 (7·4-47·6)	35·1%
UK	Teesside	1998-2016	19	21·8 (6·1-44·3)	33·6%
UK	Tyneside	1995-2016	22	32·8 (14·7-56·7)	69·2%
UK	West Midlands	1995-2016	22	32·6 (12·5-59·3)	64·5%
UK	West Yorkshire	1995-2016	22	39·6 (18·4-66·0)	84·1%
USA	Albuquerque (NM)	1995-2006	12	31·9 (12·7-57·1)	63·9%
USA	Allentown (PA)	1995-2006	12	29·7 (11·0-56·9)	56·9%
USA	Anaheim (CA)	1995-2006	12	47·2 (17·3-90·9)	83·8%
USA	Annandale (VA)	1995-2006	12	31·4 (14·0-53·9)	65·5%
USA	Austin (TX)	1995-2006	12	13·0 (2·0-44·1)	14·6%
USA	Atlanta (GA)	1995-2006	12	33·3 (12·0-61·8)	67·2%
USA	Aztec (NM)	1997-2006	10	19·9 (8·0-39·2)	22·9%
USA	Buffalo (NY)	1995-2006	12	32·3 (13·9-57·2)	67·3%
USA	Bakersfield (CA)	1995-2006	12	28·6 (14·2-47·9)	59·4%
USA	Baltimore (MD)	1995-2006	12	39·1 (19·3-63·4)	85·2%
USA	Paterson (NJ)	1995-2006	12	43·6 (16·3-77·4)	82·5%
USA	Burlington (VT)	1995-2006	12	27·7 (11·8-47·7)	55·9%
USA	Boston (MA)	1995-2006	12	38·7 (17·0-65·0)	81·8%
USA	Baton rouge (LA)	1995-2006	12	23·4 (11·9-41·2)	34·9%
USA	Chicago (IL)	1995-2006	12	42·8 (21·3-67·0)	90·8%
USA	Charlotte (NC)	1995-2006	12	30·9 (12·9-53·5)	63·9%
USA	Charleston (SC)	1995-2006	12	12·9 (3·0-27·6)	8·1%
USA	Colorado springs (CO)	1995-2001	7	30·0 (11·6-53·1)	63·0%
USA	Cleveland (OH)	1995-2006	12	39·0 (18·1-65·8)	83·9%
USA	Cincinnati (OH)	1995-2006	12	42·2 (21·5-66·8)	90·4%
USA	Columbia (SC)	1995-2006	12	13·4 (4·2-27·4)	7·9%
USA	Layton (UT)	1995-2006	12	37·0 (13·1-78·0)	67·3%
USA	Dallas (TX)	1995-2006	12	29·5 (12·1-53·7)	57·2%
USA	Denver (CO)	1995-2006	12	37·4 (14·0-70·1)	72·7%
USA	Detroit (MI)	1995-2006	12	35·4 (14·0-62·3)	73·6%
USA	Davenport (IA)	2001-2006	6	11·3 (3·8-23·7)	4·2%
USA	El centro (CA)	1995-2006	12	25·1 (5·8-54·7)	41·9%
USA	El paso (TX)	1995-2006	12	35·2 (13·9-65·2)	69·6%
USA	Elizabeth (NJ)	1995-2006	12	67·4 (33·3-105·6)	98·9%
USA	Erie (PA)	1995-2006	12	24·6 (8·7-44·9)	43·4%
USA	Essex (MA)	1995-2006	12	17·5 (4·4-38·3)	20·2%
USA	Evansville (IN)	2000-2006	7	21·8 (9·6-39·2)	30·7%
USA	Fargo (ND)	1996-2006	11	12·2 (2·8-26·9)	7·0%

USA	Fresno (CA)	1995-2006	12	31·3 (13·8-55·3)	65·6%
USA	Fort lauderdale (FL)	1995-2006	12	16·6 (3·5-34·0)	17·3%
USA	Fort pierce (FL)	1999-2004	6	18·3 (7·0-33·9)	18·9%
USA	Fort worth (TX)	1995-2006	12	25·9 (8·8-49·5)	46·4%
USA	Gary (IN)	1995-2006	12	35·3 (13·5-60·5)	75·4%
USA	Greensburg (PA)	1998-2006	9	28·8 (12·5-49·0)	60·3%
USA	Greenville (SC)	1995-2006	12	27·8 (9·8-52·6)	52·0%
USA	Honolulu (HI)	1995-2006	12	7·0 (1·8-13·5)	0·0%
USA	Harrisburg (PA)	1995-2006	12	32·5 (12·5-60·3)	65·3%
USA	Hartford (CT)	1995-2006	12	31·8 (10·7-62·4)	60·6%
USA	Houston (TX)	1995-2006	12	29·6 (12·4-54·0)	59·0%
USA	Indianapolis (IN)	1995-2006	12	31·9 (14·4-53·5)	68·2%
USA	Jacksonville (FL)	1995-2006	12	27·1 (11·7-47·8)	52·0%
USA	Jersey city (NJ)	1995-2006	12	47·0 (19·6-79·1)	89·4%
USA	Kansas city (KS)	1995-2006	12	26·2 (12·2-45·6)	49·3%
USA	Lake charles (LA)	1995-2006	12	11·1 (3·7-22·2)	3·0%
USA	Lancaster (PA)	1995-2006	12	27·5 (10·9-50·0)	52·1%
USA	Louisville (KY)	1995-2006	12	32·0 (16·1-51·3)	72·2%
USA	Los angeles (CA)	1995-2006	12	57·0 (28·0-93·9)	97·2%
USA	Las vegas (NV)	1995-2006	12	26·6 (7·9-63·0)	40·7%
USA	Little rock (AR)	1995-2006	12	22·5 (9·2-42·2)	34·7%
USA	Middlesex (NJ)	1995-2006	12	33·8 (12·8-64·3)	66·0%
USA	Modesto (CA)	1995-2006	12	31·5 (14·5-54·4)	65·6%
USA	Miami (FL)	1995-2006	12	19·7 (7·6-40·9)	25·4%
USA	Milwaukee (WI)	1995-2006	12	33·6 (13·7-59·1)	70·7%
USA	Memphis (TN)	1995-2006	12	41·7 (5·5-75·4)	81·5%
USA	Minneapolis (MN)	1995-2002	8	38·0 (17·0-65·9)	80·7%
USA	Nashua (NH)	1995-2006	12	23·4 (4·7-50·1)	38·4%
USA	Melville (NY)	1995-2006	12	38·9 (15·9-68·5)	78·3%
USA	Norfolk (VA)	1995-2004	10	32·8 (13·8-55·9)	70·7%
USA	Nashville (TN)	1995-2006	12	28·3 (4·7-55·7)	55·8%
USA	New haven (CT)	1995-2006	12	41·4 (16·2-71·8)	82·3%
USA	New orleans (LA)	1995-2006	12	26·5 (10·7-47·1)	50·6%
USA	Newark (NJ)	1995-2006	12	40·9 (17·8-72·4)	81·7%
USA	New york (NY)	1995-2006	12	59·3 (34·1-90·8)	99·3%
USA	Oklahoma city (OK)	1995-2006	12	21·2 (8·3-41·6)	29·8%
USA	Oakland (CA)	1995-2006	12	27·9 (11·2-50·0)	54·0%
USA	Orlando (FL)	1995-2006	12	20·7 (7·2-40·6)	28·6%
USA	Philadelphia (PA)	1995-2006	12	42·3 (21·4-69·4)	89·6%
USA	Phoenix (AZ)	1995-2006	12	47·8 (21·0-79·8)	89·8%
USA	Palm beach (FL)	1995-2006	12	24·6 (9·9-40·9)	46·2%
USA	Pensacola (FL)	1999-2006	8	14·3 (4·2-29·8)	10·2%
USA	Provo (UT)	1995-2006	12	43·2 (20·5-71·6)	88·5%
USA	Port arthur (TX)	1995-2006	12	15·1 (2·8-31·5)	13·7%
USA	Portland (ME)	1995-2006	12	27·8 (5·5-53·8)	55·2%

USA	Providence (RI)	1995-2006	12	22·4 (6·3-43·8)	35·6%
USA	Pittsburgh (PA)	1995-2006	12	40·0 (16·2-67·6)	81·4%
USA	Richmond (VA)	1995-2006	12	35·8 (14·1-62·2)	75·3%
USA	Reading (PA)	1995-2005	11	37·1 (18·3-60·4)	83·6%
USA	Riverside (CA)	1995-2006	12	40·3 (19·6-64·2)	85·9%
USA	Sacramento (CA)	1995-2006	12	24·8 (10·6-45·3)	42·8%
USA	Scranton (PA)	1995-2006	12	26·8 (9·6-51·3)	49·2%
USA	San diego (CA)	1995-2006	12	35·5 (15·9-64·9)	72·7%
USA	San francisco (CA)	1995-2006	12	33·5 (11·9-63·6)	62·4%
USA	Salt lake city (UT)	1996-2006	11	45·9 (19·6-83·6)	87·8%
USA	San jose (CA)	1995-2006	12	42·8 (17·2-78·2)	82·7%
USA	San antonio (TX)	1997-2006	10	18·7 (7·4-37·2)	22·1%
USA	Springfield (MA)	1995-2006	12	28·4 (11·2-54·0)	53·4%
USA	Springfield (MO)	1995-2006	12	21·9 (7·0-41·6)	33·6%
USA	Sarasota (FL)	1999-2006	8	10·0 (2·3-22·6)	3·4%
USA	St. charles (MO)	1995-2006	12	17·0 (4·5-35·8)	19·3%
USA	Stockton (CA)	1995-2006	12	31·6 (13·8-54·4)	66·8%
USA	East st. louis (IL)	1995-2006	12	33·6 (18·3-51·2)	79·9%
USA	South bend (IN)	1995-2006	12	25·3 (9·9-44·6)	46·4%
USA	St. louis (MO)	1995-2006	12	33·3 (15·8-54·2)	74·1%
USA	Stamford (CT)	1995-2006	12	34·1 (12·0-64·0)	67·5%
USA	St. petersburg (FL)	1995-2006	12	20·7 (4·2-44·8)	31·7%
USA	Seattle (WA)	1995-2005	11	32·7 (12·3-56·3)	68·6%
USA	Tampa (FL)	1995-2006	12	15·9 (5·3-32·9)	13·3%
USA	Tucson (AZ)	1995-2006	12	30·8 (14·0-52·1)	62·5%
USA	Trenton (NJ)	1995-2006	12	29·5 (11·4-56·9)	56·2%
USA	Tulsa (OK)	1995-2006	12	20·4 (4·6-40·0)	30·3%
USA	Visalia (CA)	1995-2006	12	33·8 (16·8-57·0)	75·5%
USA	Ventura (CA)	1995-2006	12	22·4 (9·9-39·9)	33·0%
USA	Ogden (UT)	1995-2006	12	46·7 (20·7-78·9)	89·4%
USA	Wilmington (DE)	1995-2006	12	32·1 (9·1-59·6)	63·7%
USA	Winston-salem (NC)	1995-2006	12	27·9 (9·6-52·2)	53·0%
USA	Worcester (MA)	1995-2006	12	33·7 (13·2-60·5)	68·6%
USA	Washington (DC)	1995-2006	12	41·5 (21·3-67·8)	88·7%
USA	Washington (PA)	1995-2006	12	24·7 (10·9-43·8)	42·7%
USA	York (PA)	1995-2006	12	34·6 (13·8-60·4)	72·1%
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Canada	Abbotsford	2000-2011	12	13·0 (5·6-25·1)	0·0%
Canada	Calgary	2000-2011	12	23·4 (8·1-47·2)	6·1%
Canada	Edmonton	2000-2011	12	21·0 (5·6-47·9)	6·1%
Canada	Regina	2001-2011	11	23·6 (7·0-54·5)	9·2%
Canada	Victoria	2001-2011	11	14·0 (6·2-28·2)	1·3%
Canada	Vancouver	2000-2011	12	12·5 (6·1-22·1)	0·0%
Canada	Winnipeg	2000-2011	12	15·9 (4·5-39·4)	3·2%
China	Hong Kong	1996-2002	7	51·6 (21·5-98·4)	50·7%

China	Taiyuan	2004-2008	5	132·1 (46·1-251·2)	95·3%
Colombia	Bogota	2002-2013	12	62·7 (34·1-97·6)	81·2%
Cyprus	Famagusta	2011-2016	6	37·0 (17·8-63·1)	14·4%
Cyprus	Larnaka	2005-2016	12	49·1 (25·1-82·2)	45·6%
Cyprus	Limassol	2005-2016	12	47·3 (23·5-82·4)	41·4%
Cyprus	Nicosia	2005-2016	12	48·7 (23·6-90·5)	43·2%
Cyprus	Pafos	2005-2016	12	38·7 (17·7-72·0)	21·4%
Czech Republic	Prague	1995-2009	15	34·3 (12·0-77·2)	21·2%
Estonia	Kohtla-Jarve linn	2003-2016	14	15·3 (4·1-36·7)	2·7%
Estonia	Narva linn	2009-2016	8	14·2 (4·6-30·1)	0·8%
Estonia	Tallinn	2005-2016	12	21·0 (5·0-50·0)	6·9%
Estonia	Tartu linn	2009-2016	8	17·5 (5·8-38·1)	2·9%
Finland	Helsinki	1995-2014	20	19·8 (4·7-52·0)	7·6%
France	Bordeaux	2007-2015	9	21·8 (10·3-42·8)	4·0%
France	Clermont-Ferrand	2007-2015	9	19·6 (7·2-42·6)	4·2%
France	Dijon	2007-2015	9	19·0 (7·1-40·2)	3·5%
France	Grenoble	2007-2015	9	25·2 (9·7-52·3)	8·7%
France	Le Havre	2007-2015	9	23·2 (9·0-50·7)	6·5%
France	Lille	2007-2015	9	27·6 (11·2-58·1)	12·0%
France	Lens-Douai	2007-2015	9	24·6 (9·5-54·5)	8·7%
France	Lyon	2007-2015	9	26·8 (10·7-55·9)	10·6%
France	Montpellier	2007-2015	9	21·4 (7·4-42·9)	3·8%
France	Marseille	2007-2015	9	31·0 (14·0-54·5)	13·3%
France	Nice	2007-2015	9	27·4 (14·0-43·0)	3·5%
France	Nancy	2007-2015	9	24·2 (8·9-48·1)	6·9%
France	Nantes	2007-2015	9	20·2 (9·0-41·2)	3·6%
France	Paris	2007-2015	9	25·3 (11·1-51·1)	8·0%
France	Rennes	2007-2015	9	19·8 (7·8-43·2)	4·3%
France	Rouen	2007-2015	9	24·5 (11·0-50·5)	7·4%
France	Strasbourg	2007-2015	9	24·2 (9·0-50·0)	7·3%
France	Toulouse	2007-2015	9	21·0 (9·0-39·9)	2·8%
Greece	Athens	2001-2010	10	43·9 (18·5-83·3)	38·5%
Iran	Tehran	2002-2015	14	87·5 (30·1-164·2)	86·1%
Japan	Akita	2012-2016	5	24·0 (10·5-51·8)	7·3%
Japan	Chiba	2011-2016	6	29·5 (11·0-60·2)	15·0%
Japan	Fukushima	2011-2016	6	24·2 (9·1-47·5)	6·2%
Japan	Fukuoka	1995-2016	22	33·4 (13·3-65·5)	20·2%
Japan	Fukui	2011-2016	6	29·3 (8·6-61·7)	15·2%
Japan	Gifu	2011-2016	6	21·8 (5·5-47·5)	6·1%
Japan	Hiroshima	2012-2016	5	38·0 (15·8-71·6)	27·7%
Japan	Kagoshima	2011-2016	6	36·8 (15·1-69·9)	26·6%
Japan	Kumamoto	2011-2016	6	36·2 (11·4-72·3)	26·7%
Japan	Kanazawa	2011-2016	6	23·8 (7·1-53·0)	8·4%
Japan	Kochi	2011-2016	6	24·7 (7·7-54·4)	9·5%
Japan	Kofu	2011-2016	6	30·3 (10·3-60·2)	15·2%

Japan	Kitakyushu	1995-2008	14	31·0 (11·5-62·0)	17·6%
Japan	Matsue	2011-2016	6	20·8 (5·1-46·9)	5·8%
Japan	Maebashi	2011-2016	6	24·7 (5·7-55·1)	10·2%
Japan	Mito	2011-2016	6	25·2 (7·7-52·7)	9·1%
Japan	Morioka	2011-2016	6	18·7 (3·8-42·6)	4·3%
Japan	Matsuyama	2011-2016	6	33·6 (12·0-67·5)	20·8%
Japan	Nagano	2011-2016	6	22·6 (6·9-46·3)	5·6%
Japan	Nagoya	1995-2016	22	38·5 (12·8-76·8)	30·8%
Japan	Nara	2011-2016	6	25·3 (8·7-52·0)	8·0%
Japan	Nagasaki	2011-2016	6	31·3 (11·8-59·4)	16·8%
Japan	Niigata	2011-2016	6	24·7 (10·7-49·7)	7·1%
Japan	Oita	2011-2016	6	28·0 (10·5-57·0)	12·0%
Japan	Okayama	2011-2016	6	32·4 (10·3-67·2)	20·6%
Japan	Osaka	1995-2016	22	36·1 (12·8-72·6)	26·1%
Japan	Saga	2011-2016	6	32·3 (10·2-62·9)	18·7%
Japan	Saitama	2011-2016	6	30·9 (11·2-61·2)	16·2%
Japan	Sendai	1995-2016	22	24·2 (8·5-52·0)	8·8%
Japan	Shimonoseki	2012-2016	5	35·1 (11·5-70·2)	24·2%
Japan	Sapporo	1995-2016	22	15·9 (6·3-33·2)	1·5%
Japan	Takamatsu	2011-2016	6	35·3 (11·1-74·3)	25·7%
Japan	Tokushima	2011-2016	6	29·2 (9·3-64·3)	13·5%
Japan	Tokyo	1995-2016	22	36·8 (12·4-78·1)	26·1%
Japan	Toyama	2011-2016	6	22·0 (5·5-51·5)	7·4%
Japan	Tsu	2011-2016	6	33·6 (11·9-66·8)	19·2%
Japan	Utsunomiya	2011-2016	6	28·8 (11·0-59·0)	12·9%
Japan	Wakayama	2011-2016	6	31·9 (13·0-62·8)	15·9%
Japan	Yokohama	2011-2016	6	35·1 (14·6-66·6)	21·4%
Japan	Yamagata	2011-2016	6	25·4 (9·0-52·2)	8·9%
South Korea	Busan	1999-2015	17	54·2 (25·7-99·2)	55·7%
South Korea	Daegu	1999-2015	17	53·8 (22·4-100·9)	55·5%
South Korea	Daejeon	1999-2015	17	46·4 (16·4-92·5)	42·3%
South Korea	Gwangju	1999-2015	17	47·4 (17·6-97·1)	42·6%
South Korea	Incheon	1999-2015	17	56·6 (22·2-111·0)	58·3%
South Korea	Seoul	1999-2015	17	57·9 (18·1-121·6)	57·8%
South Korea	Ulsan	1999-2015	17	49·2 (23·4-89·8)	47·1%
Kuwait	Kuwait	2010-2016	7	191·0 (60·7-539·5)	98·3%
Mexico	Guadalajara	2000-2012	13	49·1 (20·9-84·7)	53·6%
Mexico	Leon	2006-2012	7	59·5 (23·9-110·8)	66·3%
Mexico	Monterrey	2000-2012	13	78·2 (38·0-130·9)	90·1%
Mexico	Puebla-Tlaxcala	2001-2011	11	40·1 (18·1-82·5)	30·0%
Mexico	Toluca de Lerdo	2000-2012	13	66·7 (22·4-132·1)	67·3%
Mexico	Valley of Mexico	2000-2012	13	51·7 (23·7-88·2)	57·3%
Norway	Oslo	2000-2016	17	22·1 (8·3-45·9)	5·6%
Portugal	Beja	2005-2016	12	20·7 (8·2-45·2)	5·1%
Portugal	Coimbra	2003-2016	14	22·2 (7·1-48·6)	6·5%

Portugal	Castelo Branco	2004-2016	13	14·1 (4·0-32·4)	2·0%
Portugal	Lisboa	2000-2016	17	26·3 (9·8-56·0)	10·5%
Portugal	Porto	1999-2016	18	32·2 (9·5-75·1)	21·4%
South Africa	City of Johannesburg	2004-2013	10	56·8 (23·4-106·5)	58·9%
South Africa	Sedibeng	2007-2013	7	66·5 (26·2-127·4)	68·5%
Spain	A Coruna	2008-2014	7	26·7 (13·7-45·6)	5·6%
Spain	Albacete	2001-2013	13	41·8 (19·2-73·3)	36·8%
Spain	Avila	2001-2014	14	23·5 (14·4-35·1)	0·6%
Spain	Bilbao	2003-2014	12	36·6 (24·2-52·3)	15·5%
Spain	Barcelona	2004-2014	11	32·8 (12·8-65·0)	19·2%
Spain	Burgos	2001-2014	14	27·0 (15·2-42·2)	2·9%
Spain	Ciudad Real	2008-2013	6	21·2 (7·2-43·2)	4·0%
Spain	Cordoba	2001-2008	8	44·8 (28·9-64·5)	45·5%
Spain	Guadalajara	2001-2013	13	26·8 (8·5-58·0)	11·3%
Spain	Granada	2001-2008	8	37·8 (17·1-68·0)	27·0%
Spain	Leon	2001-2014	14	26·4 (11·8-48·6)	6·9%
Spain	Logrono	2002-2014	13	27·0 (11·3-51·7)	9·4%
Spain	Lugo	2009-2014	6	20·5 (8·5-33·4)	1·5%
Spain	Malaga	2001-2008	8	27·3 (16·5-42·4)	3·2%
Spain	Madrid	2001-2014	14	29·3 (11·5-59·6)	14·1%
Spain	Murcia	2003-2014	12	21·3 (11·7-33·1)	0·5%
Spain	Ourense	2008-2014	7	16·8 (6·7-34·8)	1·9%
Spain	Oviedo	2003-2014	12	35·0 (15·4-78·2)	20·2%
Spain	Palmas G. Canaria	2001-2014	14	28·8 (12·6-54·5)	10·3%
Spain	Palma Mallorca	2002-2014	13	23·2 (11·5-40·4)	3·0%
Spain	Palencia	2004-2014	11	27·2 (18·8-38·2)	1·4%
Spain	Pontevedra	2009-2014	6	20·3 (8·5-38·0)	1·8%
Spain	Segovia	2002-2014	13	23·1 (11·8-37·0)	1·2%
Spain	Salamanca	2004-2014	11	21·9 (10·6-38·8)	2·0%
Spain	San Sebastian	2001-2014	14	25·7 (12·3-45·6)	5·6%
Spain	Santander	2001-2014	14	29·1 (14·4-52·3)	10·6%
Spain	Soria	2004-2014	11	23·9 (7·3-45·3)	5·2%
Spain	Sevilla	2001-2008	8	40·7 (22·0-62·8)	33·4%
Spain	Tenerife	2006-2014	9	21·5 (8·4-44·8)	4·9%
Spain	Toledo	2001-2014	14	35·5 (23·0-52·1)	12·8%
Spain	Vitoria	2001-2014	14	24·4 (9·0-51·2)	8·6%
Spain	Valencia	2009-2013	5	25·8 (11·3-44·0)	4·1%
Spain	Zamora	2001-2014	14	23·6 (16·2-34·0)	0·3%
Spain	Zaragoza	2001-2014	14	30·8 (11·5-61·6)	17·4%
Switzerland	Basel	1995-2013	19	22·1 (6·0-50·0)	7·1%
Switzerland	Bern	1995-2013	19	33·5 (13·1-68·9)	19·3%
Switzerland	Geneve	1998-2013	16	23·5 (7·6-51·7)	8·1%
Switzerland	Lausanne	1995-2013	19	27·5 (9·4-60·9)	13·1%
Switzerland	Lugano	1995-2013	19	29·4 (7·2-68·5)	16·6%

Switzerland	Luzern	2001-2013	13	22·0 (6·3-48·8)	6·7%
Switzerland	St. Gallen	1995-2013	19	19·3 (5·1-46·4)	5·4%
Switzerland	Zürich	1995-2013	19	23·7 (7·2-52·6)	8·2%
Sweden	Stockholm	1995-2010	16	14·9 (6·0-32·1)	1·0%
Thailand	Bangkok	1999-2008	10	58·8 (35·7-100·6)	73·8%
Thailand	Chon Buri	1999-2008	10	43·9 (19·6-81·6)	38·3%
Thailand	Chiang Mai	1999-2008	10	53·3 (19·7-128·5)	45·0%
Thailand	Khon Kaen	1999-2008	10	39·7 (13·4-87·0)	31·2%
Thailand	Lampang	1999-2008	10	53·0 (19·8-139·4)	40·7%
Thailand	Nakhon Ratchasima	2001-2008	8	58·3 (21·5-127·4)	56·3%
Thailand	Nakhon Sawan	2001-2008	8	50·5 (22·9-98·5)	46·9%
Thailand	Nonthaburi	1999-2008	10	48·7 (24·4-95·5)	43·1%
Thailand	Pathum Thani	2001-2008	8	47·8 (21·7-95·6)	43·9%
Thailand	Ratchaburi	1999-2008	10	48·4 (18·9-108·3)	40·1%
Thailand	Rayong	1999-2008	10	42·4 (18·3-85·0)	35·3%
Thailand	Samutprakan	1999-2008	10	94·9 (43·2-183·3)	94·1%
Thailand	Samut Sakhon	1999-2008	10	48·5 (22·3-95·4)	44·0%
Thailand	Songkhla	2000-2008	9	37·2 (19·1-63·2)	21·9%
Thailand	Saraburi	1999-2008	10	62·6 (25·7-125·8)	66·3%
Thailand	Surat Thani	2000-2008	9	30·2 (15·4-54·5)	11·7%
Taiwan	Kaohsiung	1995-2014	20	78·6 (28·6-145·4)	73·9%
Taiwan	Taipei	1995-2014	20	50·0 (21·8-94·8)	50·1%
Taiwan	Taichung	1995-2014	20	60·0 (25·4-115·0)	62·8%
UK	Blackpool	2001-2008	8	23·6 (9·4-43·6)	4·1%
UK	Birkenhead	2001-2008	8	19·2 (7·2-37·9)	2·3%
UK	Bristol	1995-2016	22	23·2 (9·0-48·4)	6·7%
UK	Chesterfield	2008-2016	9	17·8 (7·5-39·1)	3·0%
UK	Cardiff	1995-2015	21	25·8 (10·5-50·2)	7·7%
UK	Crawley	2001-2016	16	20·4 (9·9-40·1)	2·9%
UK	Eastbourne	2001-2016	16	21·9 (9·4-42·1)	4·0%
UK	Kingston upon Hull	1995-2014	20	23·3 (7·4-47·7)	6·1%
UK	Leicester	1995-2013	19	21·2 (9·1-42·4)	3·9%
UK	London	1995-2016	22	23·8 (11·1-48·2)	6·5%
UK	Liverpool	1995-2016	22	21·4 (6·3-48·8)	6·6%
UK	Medway Towns	1997-2009	13	20·0 (8·2-41·9)	3·8%
UK	Manchester	1996-2016	21	21·7 (9·0-43·8)	4·4%
UK	Norwich	1998-2016	19	18·8 (7·8-37·4)	2·0%
UK	Nottingham	1997-2016	20	23·2 (10·4-45·5)	5·2%
UK	Newport	2002-2016	15	18·2 (6·6-35·7)	2·0%
UK	Plymouth	1998-2016	19	19·3 (7·7-38·4)	2·4%
UK	Preston	2001-2008	8	19·6 (8·9-37·0)	2·3%
UK	Reading	1998-2016	19	18·9 (6·6-39·3)	2·6%
UK	Sheffield	1996-2016	21	22·5 (8·5-48·2)	6·4%
UK	South Hampshire	1995-2016	22	23·4 (11·0-44·2)	4·7%
UK	Southend-on-Sea	2001-2008	8	20·6 (9·3-41·0)	3·5%

UK	Stoke-on-Trent	1998-2014	17	21·9 (9·6-42·3)	3·9%
UK	Swansea	1995-2016	22	24·8 (9·6-49·7)	7·5%
UK	Teesside	1998-2016	19	20·9 (7·5-42·8)	3·9%
UK	Tyneside	1995-2016	22	18·8 (6·5-41·3)	3·7%
UK	Warrington	2009-2016	8	17·8 (7·9-39·0)	2·9%
UK	West Midlands	1995-2016	22	21·2 (7·2-44·7)	4·8%
UK	West Yorkshire	1995-2016	22	25·4 (10·4-52·6)	8·3%
UK	York	2008-2016	9	16·4 (7·0-36·0)	2·0%
USA	Akron (OH)	2000-2004	5	21·1 (8·2-41·2)	3·3%
USA	Albuquerque (NM)	1995-2006	12	28·7 (9·4-55·4)	12·4%
USA	Allentown (PA)	2001-2006	6	23·1 (7·2-50·1)	7·9%
USA	Atlanta (GA)	2000-2006	7	25·8 (10·1-47·0)	6·2%
USA	Birmingham (AL)	2000-2006	7	30·7 (8·8-63·5)	18·5%
USA	Brownsville (TX)	2001-2006	6	26·2 (7·3-53·4)	9·9%
USA	Chicago (IL)	1995-2006	12	28·8 (10·1-57·3)	12·8%
USA	Charleston (SC)	2000-2006	7	18·8 (8·4-31·7)	0·7%
USA	Columbus (OH)	2000-2006	7	27·9 (11·3-57·0)	11·9%
USA	Cleveland (OH)	1995-2006	12	28·6 (8·7-58·3)	15·1%
USA	Cincinnati (OH)	1995-2006	12	27·3 (11·4-53·3)	9·5%
USA	Columbia (SC)	2000-2006	7	25·2 (4·7-53·1)	10·1%
USA	Denver (CO)	1995-2006	12	24·9 (7·1-48·4)	7·0%
USA	Des moines (IA)	2000-2005	6	26·6 (9·7-54·3)	10·5%
USA	Detroit (MI)	1995-2006	12	31·9 (8·6-67·4)	20·1%
USA	Davenport (IA)	1996-2006	11	29·3 (6·6-64·0)	17·4%
USA	Daytona beach (FL)	2000-2006	7	20·3 (9·8-35·4)	1·9%
USA	El paso (TX)	1995-2006	12	34·7 (9·5-74·7)	23·5%
USA	Erie (PA)	2001-2006	6	17·0 (6·3-36·9)	2·3%
USA	Fort myers (FL)	2001-2006	6	19·4 (11·0-30·9)	0·6%
USA	Gary (IN)	1995-2006	12	23·3 (7·1-51·2)	7·5%
USA	Greensburg (PA)	2001-2006	6	25·2 (11·0-48·0)	7·1%
USA	Grand junction (CO)	2000-2006	7	25·3 (10·8-47·2)	5·7%
USA	Greenville (SC)	2001-2006	6	22·6 (8·0-41·1)	2·6%
USA	Harrisburg (PA)	2001-2006	6	20·9 (7·7-42·2)	3·4%
USA	Lakeland (FL)	2000-2006	7	21·3 (11·2-35·6)	1·7%
USA	Lancaster (PA)	2001-2006	6	20·8 (7·2-41·5)	3·1%
USA	Los angeles (CA)	2000-2006	7	32·7 (13·3-53·2)	13·7%
USA	Las vegas (NV)	1995-2006	12	32·8 (13·0-58·5)	15·5%
USA	Madison (IL)	1995-2006	12	35·1 (10·2-71·9)	28·5%
USA	Minneapolis (MN)	1995-2006	12	24·9 (10·0-47·8)	6·7%
USA	New haven (CT)	1995-2004	10	24·4 (6·7-51·1)	7·8%
USA	Orlando (FL)	2001-2006	6	19·2 (10·6-30·5)	1·1%
USA	Ottawa (IL)	1995-2006	12	26·4 (9·0-58·7)	11·7%
USA	Philadelphia (PA)	2001-2006	6	24·3 (11·5-45·6)	5·4%
USA	Phoenix (AZ)	2000-2006	7	44·0 (14·0-84·2)	42·4%
USA	Provo (UT)	1995-2006	12	28·0 (6·9-60·2)	13·2%

USA	Portage (IN)	1995-2006	12	18·7 (6·0-39·4)	2·9%
USA	Pittsburgh (PA)	1995-2006	12	26·0 (7·6-57·8)	12·9%
USA	Raleigh (NC)	2000-2006	7	20·7 (8·1-37·9)	1·8%
USA	Riverside (CA)	2000-2006	7	34·8 (13·4-55·5)	17·9%
USA	Sacramento (CA)	2000-2006	7	23·2 (9·6-42·6)	3·6%
USA	Scranton (PA)	2001-2006	6	18·6 (6·5-39·0)	2·6%
USA	Salt lake city (UT)	1995-2006	12	30·2 (8·7-64·0)	17·1%
USA	Spokane (WA)	1995-2006	12	23·0 (5·4-50·2)	8·0%
USA	St. louis (MO)	2000-2006	7	31·1 (4·1-76·4)	22·0%
USA	Tampa (FL)	2000-2006	7	24·6 (12·8-40·1)	2·5%
USA	Tucson (AZ)	1995-2006	12	25·5 (10·0-46·9)	6·2%
USA	Toledo (OH)	2000-2006	7	22·3 (8·7-46·3)	6·1%
USA	Wichita (KS)	2000-2006	7	22·8 (9·5-41·9)	2·7%
USA	Ogden (UT)	1995-2006	12	26·2 (7·0-53·0)	9·9%
USA	Winston-salem (NC)	2000-2006	7	22·1 (9·1-39·6)	1·7%
USA	Washington (PA)	2001-2006	6	20·6 (6·7-44·4)	4·6%
USA	York (PA)	2001-2006	6	23·2 (8·4-46·1)	5·6%
				$PM_{2·5}$	
Canada	Abbotsford	1997-2015	19	5·8 (1·8-12·3)	2·2%
Canada	Calgary	1998-2015	18	9·8 (3·0-20·6)	14·8%
Canada	Edmonton	1998-2015	18	10·0 (2·8-23·3)	16·3%
Canada	Halifax	2006-2015	10	6·2 (1·8-13·2)	2·9%
Canada	Hamilton	1998-2015	18	10·8 (2·8-25·1)	21·0%
Canada	Kingston	2003-2013	11	8·4 (2·2-20·9)	12·4%
Canada	Kitchener-Waterloo	1998-2015	18	9·2 (1·9-23·4)	16·6%
Canada	London Ontario	2001-2015	15	9·6 (2·4-22·3)	15·8%
Canada	Montreal	1998-2015	18	10·8 (2·9-25·6)	19·7%
Canada	Oakville	2004-2015	12	8·5 (2·1-20·1)	12·0%
Canada	Oshawa	1997-2015	19	8·9 (2·0-22·6)	14·8%
Canada	Ottawa	1998-2015	18	7·6 (1·6-18·9)	10·2%
Canada	Regina	2001-2013	13	7·2 (2·2-15·4)	5·5%
Canada	Sarnia	2000-2015	16	12·6 (3·7-28·2)	29·0%
Canada	Sudbury	2005-2015	11	5·3 (1·2-12·9)	3·2%
Canada	Saint John NB	1997-2015	19	6·9 (1·9-15·7)	5·7%
Canada	St. John's NFL	1998-2015	18	5·3 (1·5-11·1)	1·0%
Canada	Sault Ste. Marie	2000-2015	16	6·9 (1·2-18·9)	8·0%
Canada	Saskatoon	2004-2015	12	6·7 (1·7-14·6)	4·4%
Canada	Thunder Bay	2002-2015	14	6·1 (1·4-14·1)	4·0%
Canada	Toronto	1997-2015	19	9·7 (2·7-23·3)	16·8%
Canada	Victoria	1998-2015	18	7·0 (2·3-14·9)	5·0%
Canada	Vancouver	1999-2015	17	6·1 (2·3-12·7)	2·6%
Canada	Windsor	1999-2015	17	10·9 (3·0-24·9)	21·1%
Canada	Winnipeg	1998-2015	18	7·0 (2·0-14·8)	4·7%
Cyprus	Famagusta	2010-2016	7	18·4 (8·0-30·6)	58·4%
Cyprus	Nicosia	2011-2016	6	21·7 (10·0-38·3)	73·7%

Estonia	Kohtla-Jarve linn	2011-2016	6	6·1 (0·7-15·0)	5·0%
Estonia	Narva linn	2009-2016	8	8·0 (1·6-18·2)	9·9%
Estonia	Tartu linn	2009-2016	8	9·0 (1·2-23·1)	15·9%
Finland	Helsinki	1995-2014	20	16·8 (3·9-43·5)	41·5%
France	Bordeaux	2007-2015	9	15·5 (5·7-37·0)	35·7%
France	Clermont-Ferrand	2007-2015	9	13·5 (3·5-36·1)	29·4%
France	Dijon	2009-2015	7	13·5 (4·6-31·2)	29·7%
France	Grenoble	2007-2015	9	18·8 (5·9-44·4)	50·7%
France	Le Havre	2007-2015	9	15·1 (4·0-39·0)	33·2%
France	Lille	2009-2015	7	18·0 (5·5-45·3)	44·4%
France	Lyon	2007-2015	9	19·7 (6·0-46·0)	54·3%
France	Montpellier	2008-2015	8	14·9 (4·6-30·1)	42·4%
France	Marseille	2008-2015	8	16·4 (5·0-34·0)	45·7%
France	Nancy	2009-2015	7	16·0 (4·2-39·1)	40·3%
France	Nantes	2009-2015	7	14·9 (5·8-35·0)	33·7%
France	Paris	2007-2015	9	16·7 (5·5-40·3)	41·9%
France	Rouen	2007-2015	9	17·3 (6·0-40·5)	43·2%
France	Strasbourg	2007-2015	9	18·7 (5·8-42·0)	50·9%
France	Toulouse	2007-2015	9	15·2 (5·5-32·6)	39·1%
Japan	Chiba	2011-2016	6	12·5 (3·8-27·3)	28·6%
Japan	Fukuoka	2011-2016	6	18·1 (6·5-36·1)	54·8%
Japan	Fukui	2011-2016	6	14·6 (4·6-30·6)	39·0%
Japan	Gifu	2011-2016	6	14·1 (4·4-29·1)	37·7%
Japan	Hiroshima	2012-2016	5	16·6 (6·3-32·9)	50·4%
Japan	Kagoshima	2011-2016	6	18·6 (8·3-34·2)	58·9%
Japan	Kobe	2012-2016	5	14·7 (5·7-29·9)	39·0%
Japan	Kofu	2011-2016	6	12·6 (3·5-26·0)	30·7%
Japan	Kyoto	2012-2016	5	13·6 (4·8-27·6)	34·4%
Japan	Matsue	2011-2016	6	13·6 (4·1-27·2)	35·8%
Japan	Maebashi	2011-2016	6	14·3 (2·5-30·7)	41·3%
Japan	Morioka	2011-2016	6	12·9 (4·3-25·2)	31·7%
Japan	Matsuyama	2011-2016	6	17·1 (6·4-32·5)	53·1%
Japan	Nagano	2011-2016	6	11·4 (3·0-23·5)	25·3%
Japan	Nagoya	2011-2016	6	15·5 (4·9-31·7)	44·3%
Japan	Oita	2011-2016	6	16·2 (5·1-33·0)	47·1%
Japan	Osaka	2011-2016	6	16·7 (5·8-33·5)	50·8%
Japan	Saitama	2012-2016	5	12·9 (3·4-26·2)	32·6%
Japan	Sendai	2011-2016	6	12·3 (3·3-26·1)	29·0%
Japan	Shizuoka	2011-2016	6	11·8 (3·9-25·2)	24·7%
Japan	Sapporo	2011-2016	6	10·0 (2·7-21·4)	16·9%
Japan	Tokushima	2011-2016	6	14·0 (4·3-29·2)	35·1%
Japan	Tokyo	2001-2016	16	18·8 (7·0-39·0)	54·8%
Japan	Tsu	2011-2016	6	15·2 (5·1-31·8)	42·1%
Japan	Wakayama	2011-2016	6	16·7 (5·3-34·2)	50·1%
Japan	Yokohama	2011-2016	6	16·3 (5·3-32·3)	48·3%

Mexico	Monterrey	2004-2012	9	28·0 (13·4-48·5)	90·8%
Mexico	Valley of Mexico	2004-2012	9	25·8 (10·5-44·6)	84·0%
Norway	Oslo	2000-2016	17	10·8 (4·6-21·8)	16·5%
Portugal	Beja	2005-2016	12	10·8 (4·3-21·5)	18·6%
Portugal	Castelo Branco	2005-2016	12	6·8 (1·3-16·8)	7·2%
Portugal	Lisboa	2004-2016	13	12·8 (4·0-29·2)	29·3%
South Africa	Sedibeng	2007-2013	7	36·0 (14·6-71·0)	94·2%
Spain	Barcelona	2004-2014	11	20·8 (7·8-41·4)	66·5%
Spain	Madrid	2009-2013	5	11·7 (6·1-20·5)	20·1%
Switzerland	Basel	1998-2009	12	16·9 (4·2-40·7)	45·2%
Switzerland	Bern	1998-2009	12	20·7 (8·5-41·5)	66·0%
Switzerland	Lugano	1999-2007	9	24·1 (5·3-58·7)	66·5%
Switzerland	Zürich	1998-2009	12	17·2 (5·7-39·0)	46·3%
Sweden	Stockholm	2001-2010	10	8·2 (3·1-19·4)	9·2%
Taiwan	Kaohsiung	2007-2014	8	42·3 (14·8-77·5)	94·6%
Taiwan	Taipei	2007-2014	8	27·3 (10·2-52·7)	82·9%
Taiwan	Taichung	2007-2014	8	33·6 (13·0-65·2)	90·6%
UK	Birkenhead	2010-2016	7	9·1 (2·0-27·6)	16·6%
UK	Bristol	2010-2016	7	12·9 (3·9-33·1)	27·0%
UK	Chesterfield	2009-2016	8	12·2 (4·1-31·4)	23·7%
UK	Cardiff	2009-2016	8	11·9 (4·3-29·1)	23·0%
UK	Eastbourne	2010-2016	7	14·0 (5·1-34·1)	30·1%
UK	Kingston upon Hull	2010-2016	7	11·4 (3·8-29·0)	20·3%
UK	Leicester	2010-2016	7	13·2 (5·4-31·2)	27·5%
UK	London	1998-2016	19	13·6 (6·1-29·0)	28·6%
UK	Liverpool	2010-2016	7	10·8 (3·6-29·4)	19·8%
UK	Manchester	2009-2016	8	12·9 (4·4-31·2)	27·5%
UK	Norwich	2010-2016	7	12·8 (4·6-31·1)	25·4%
UK	Nottingham	2009-2016	8	12·8 (4·0-32·0)	26·9%
UK	Newport	2009-2016	8	11·5 (4·0-26·5)	22·4%
UK	Plymouth	2010-2016	7	11·3 (3·6-26·6)	20·8%
UK	Preston	2010-2016	7	11·0 (3·9-28·5)	19·7%
UK	Reading	2009-2016	8	11·0 (2·2-30·4)	21·9%
UK	Sheffield	2009-2016	8	12·9 (3·2-32·5)	26·2%
UK	Sunderland	2010-2016	7	10·0 (2·5-25·3)	16·2%
UK	South Hampshire	2009-2016	8	13·2 (5·1-31·9)	27·4%
UK	Southend-on-Sea	2009-2016	8	11·9 (3·8-30·3)	23·2%
UK	Stoke-on-Trent	2009-2016	8	14·1 (5·8-32·6)	31·5%
UK	Swansea	2007-2016	10	12·3 (4·1-28·8)	23·6%
UK	Teesside	2010-2016	7	10·7 (3·1-28·4)	18·8%
UK	Tyneside	2010-2016	7	10·2 (3·6-25·7)	16·7%
UK	Warrington	2010-2016	7	12·4 (4·5-31·6)	24·5%
UK	West Midlands	2009-2016	8	13·1 (4·0-32·2)	28·6%
UK	West Yorkshire	2009-2016	8	14·2 (5·2-34·1)	31·0%
UK	York	2009-2016	8	12·5 (4·6-31·0)	24·3%

USA	Akron (OH)	1999-2004	6	16·0 (5·5-33·1)	47·0%
USA	Albuquerque (NM)	2000-2006	7	6·8 (3·0-13·9)	3·7%
USA	Allentown (PA)	2000-2006	7	14·0 (4·1-31·0)	37·2%
USA	Anaheim (CA)	2000-2006	7	14·8 (4·4-34·9)	35·3%
USA	Annandale (VA)	2000-2006	7	13·8 (4·9-28·3)	35·0%
USA	Atlanta (GA)	1999-2006	8	17·3 (7·2-32·3)	55·8%
USA	Bath (NY)	2000-2006	7	9·4 (2·6-22·6)	15·9%
USA	Bakersfield (CA)	1999-2006	8	17·3 (4·1-48·3)	40·0%
USA	Baltimore (MD)	2000-2006	7	15·4 (5·3-32·8)	42·0%
USA	Birmingham (AL)	1999-2006	8	16·4 (5·8-32·8)	47·2%
USA	Boston (MA)	2000-2006	7	11·9 (4·4-25·3)	26·4%
USA	Baton rouge (LA)	1999-2006	8	13·4 (6·0-24·8)	31·8%
USA	Cedar rapids (IA)	2000-2005	6	11·0 (3·3-25·2)	23·2%
USA	Chicago (IL)	2000-2006	7	15·2 (5·4-31·4)	43·4%
USA	Charlotte (NC)	1999-2006	8	15·2 (5·7-28·5)	45·2%
USA	Charleston (SC)	1999-2006	8	12·1 (4·7-22·7)	25·9%
USA	Columbus (OH)	1999-2004	6	16·2 (5·8-32·4)	49·0%
USA	Cleveland (OH)	1999-2004	6	15·5 (4·4-32·5)	44·4%
USA	Cincinnati (OH)	1999-2004	6	17·1 (6·6-33·3)	52·4%
USA	Carlisle (PA)	2000-2006	7	14·8 (4·0-32·3)	40·3%
USA	Dallas (TX)	2000-2006	7	12·5 (5·3-23·1)	28·0%
USA	Denver (CO)	2000-2006	7	10·3 (4·7-20·0)	12·6%
USA	Durham (NC)	2000-2006	7	14·2 (5·5-26·5)	40·1%
USA	Des moines (IA)	2000-2006	7	10·3 (3·3-23·2)	18·8%
USA	Detroit (MI)	1999-2006	8	15·4 (4·8-32·2)	43·0%
USA	Davenport (IA)	2000-2006	7	12·2 (3·9-26·1)	28·6%
USA	Elizabeth (NJ)	2000-2006	7	14·4 (4·2-31·2)	38·5%
USA	Eugene (OR)	1999-2004	6	9·3 (1·3-26·9)	16·2%
USA	Fresno (CA)	1999-2006	8	19·2 (5·2-52·9)	42·8%
USA	Fort lauderdale (FL)	1999-2006	8	8·4 (3·8-15·7)	6·2%
USA	Fort worth (TX)	2000-2006	7	12·0 (5·0-23·0)	24·4%
USA	Grand rapids (MI)	1999-2005	7	13·6 (4·0-30·0)	35·0%
USA	Greensboro (NC)	2000-2005	6	14·1 (5·2-27·3)	38·5%
USA	Greenville (SC)	2000-2006	7	15·0 (5·3-27·7)	44·8%
USA	Gettysburg (PA)	1999-2006	8	13·2 (3·7-29·5)	32·5%
USA	Harrisburg (PA)	1999-2006	8	15·3 (4·5-32·6)	43·0%
USA	Hartford (CT)	2000-2006	7	11·5 (3·6-26·0)	24·7%
USA	Houston (TX)	2000-2006	7	12·8 (5·7-23·0)	28·8%
USA	Indianapolis (IN)	1999-2006	8	16·1 (5·9-31·6)	47·9%
USA	Jacksonville (FL)	2000-2006	7	10·4 (3·9-20·2)	16·2%
USA	Kansas city (KS)	1999-2006	8	12·0 (4·5-23·5)	25·7%
USA	Knoxville (TN)	2001-2006	6	15·3 (5·7-28·2)	46·1%
USA	Louisville (KY)	1999-2006	8	15·6 (5·8-30·7)	44·7%
USA	Los angeles (CA)	2000-2006	7	17·8 (5·7-38·2)	53·0%
USA	Las vegas (NV)	1999-2006	8	7·5 (2·0-17·1)	7·4%

USA	Little rock (AR)	2000-2006	7	13·9 (5·4-27·0)	35·7%
USA	Mercer (PA)	2001-2006	6	13·7 (4·4-28·7)	34·1%
USA	Norfolk (VA)	1999-2006	8	12·7 (4·5-25·5)	29·6%
USA	New haven (CT)	2000-2006	7	13·4 (4·3-29·9)	32·9%
USA	New orleans (LA)	1999-2006	8	12·7 (5·7-24·2)	28·0%
USA	New york (NY)	2000-2006	7	14·5 (5·2-30·6)	37·4%
USA	Omaha (NE)	2000-2006	7	10·3 (3·6-22·5)	17·8%
USA	Orlando (FL)	1999-2006	8	10·0 (4·0-18·7)	13·5%
USA	Philadelphia (PA)	1999-2006	8	14·1 (4·7-30·2)	36·4%
USA	Palm beach (FL)	1999-2006	8	8·0 (3·4-15·1)	5·2%
USA	Provo (UT)	1999-2006	8	9·4 (3·0-25·9)	13·8%
USA	Providence (RI)	1999-2006	8	11·0 (4·0-24·1)	21·5%
USA	Pittsburgh (PA)	1999-2006	8	15·6 (3·9-35·7)	42·2%
USA	Richmond (VA)	1999-2006	8	13·8 (5·1-28·2)	35·5%
USA	Raleigh (NC)	2000-2006	7	14·1 (5·6-26·5)	38·6%
USA	Riverside (CA)	2000-2006	7	17·5 (3·5-39·7)	49·9%
USA	Sacramento (CA)	1999-2006	8	12·7 (3·4-36·1)	23·7%
USA	Scranton (PA)	1999-2006	8	12·0 (3·1-26·8)	28·5%
USA	San diego (CA)	1999-2006	8	13·1 (4·1-27·7)	29·8%
USA	Salt lake city (UT)	1999-2006	8	11·3 (3·4-35·3)	17·8%
USA	Spartanburg (SC)	1999-2006	8	14·3 (5·2-27·8)	39·4%
USA	St. louis (MO)	1999-2006	8	14·2 (5·1-27·9)	37·7%
USA	St. petersburg (FL)	1999-2006	8	10·3 (4·5-19·5)	14·6%
USA	State college (PA)	2001-2006	6	12·9 (3·5-28·9)	30·3%
USA	Seattle (WA)	1999-2005	7	9·4 (3·2-20·8)	14·1%
USA	Tampa (FL)	1999-2006	8	11·6 (5·4-20·7)	21·1%
USA	Tucson (AZ)	1999-2006	8	6·5 (3·3-12·0)	2·0%
USA	Wilmington (DE)	2000-2006	7	14·9 (4·9-31·4)	40·3%
USA	Winston-salem (NC)	1999-2006	8	14·6 (4·8-29·0)	41·0%
USA	Washington (DC)	1999-2006	8	14·9 (5·2-31·6)	41·6%
USA	Washington (PA)	1999-2006	8	14·6 (5·5-29·8)	38·0%
USA	Youngstown (OH)	1999-2004	6	15·4 (5·7-31·0)	42·1%

N: Number of years included; NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm; WHO: World Health Organization; 24-hour limit according to WHO air quality guideline[8]: 25 µg/m³ (NO_2), 45 µg/m³ (PM_{10}), 15 µg/m³ ($PM_{2·5}$); Air pollutants measured in µg/m³.

Table S5: Spearman correlation coefficients (r_S) of air pollutants over the entire study period and stratified by individual periods.

Variable	+NO_2	+PM_{10}	+$PM_{2·5}$
NO_2			
Total period	-	0·39	0·44
1995-2001	-	0·44	0·49
2002-2008	-	0·42	0·48
2009-2016	-	0·38	0·44
PM_{10}			
Total period	0·41	-	**0·77**
1995-2001	0·48	-	0·69
2002-2008	0·45	-	**0·75**
2009-2016	0·37	-	**0·82**
$PM_{2·5}$			
Total period	0·47	**0·79**	-
1995-2001	0·49	**0·73**	-
2002-2008	0·48	**0·76**	-
2009-2016	0·48	**0·85**	-

Numbers in bold indicate high correlations ($r_S \geq 0·7$); NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm; Air pollutants measured in µg/m^3.

Supplementary figures:

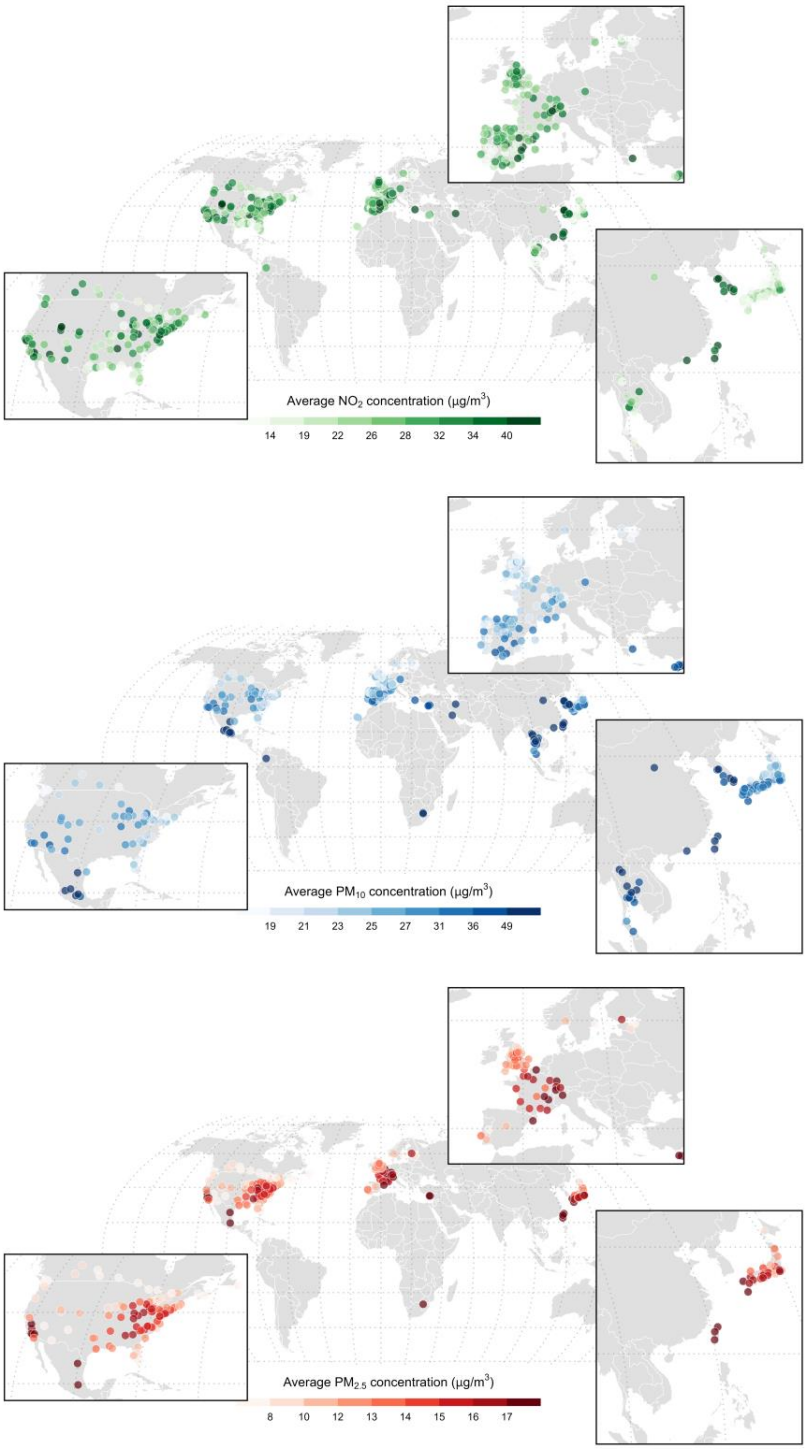

Figure S1: Geographical distribution and average concentrations (in µg/m³) of NO_2 (top panel), PM_{10} (middle panel), and $PM_{2.5}$ (bottom panel).

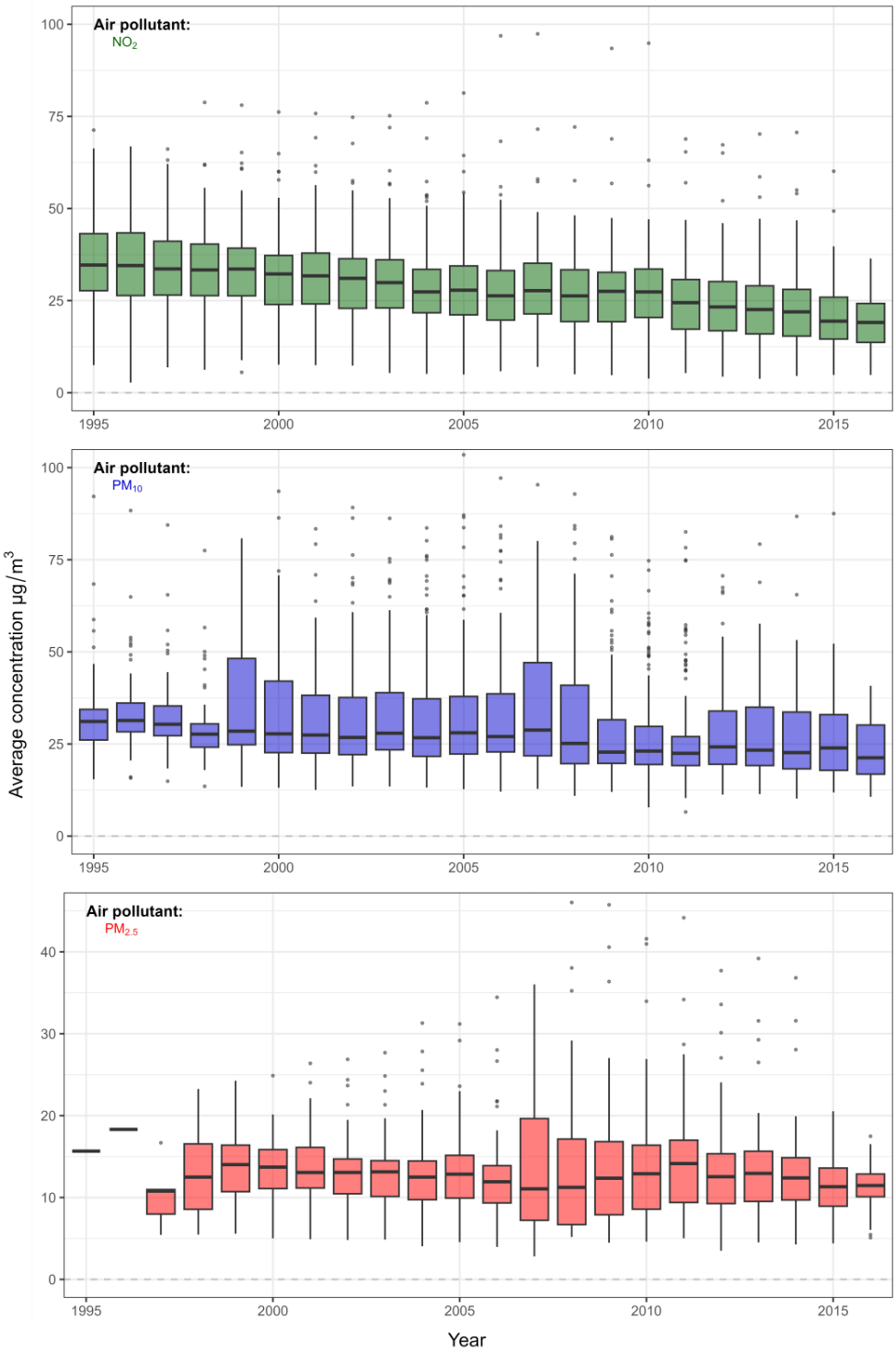

Figure S2: Yearly boxplots of 24-hour average concentrations (in µg/m³) of NO_2 (top panel), PM_{10} (middle panel), and $PM_{2.5}$ (bottom panel).

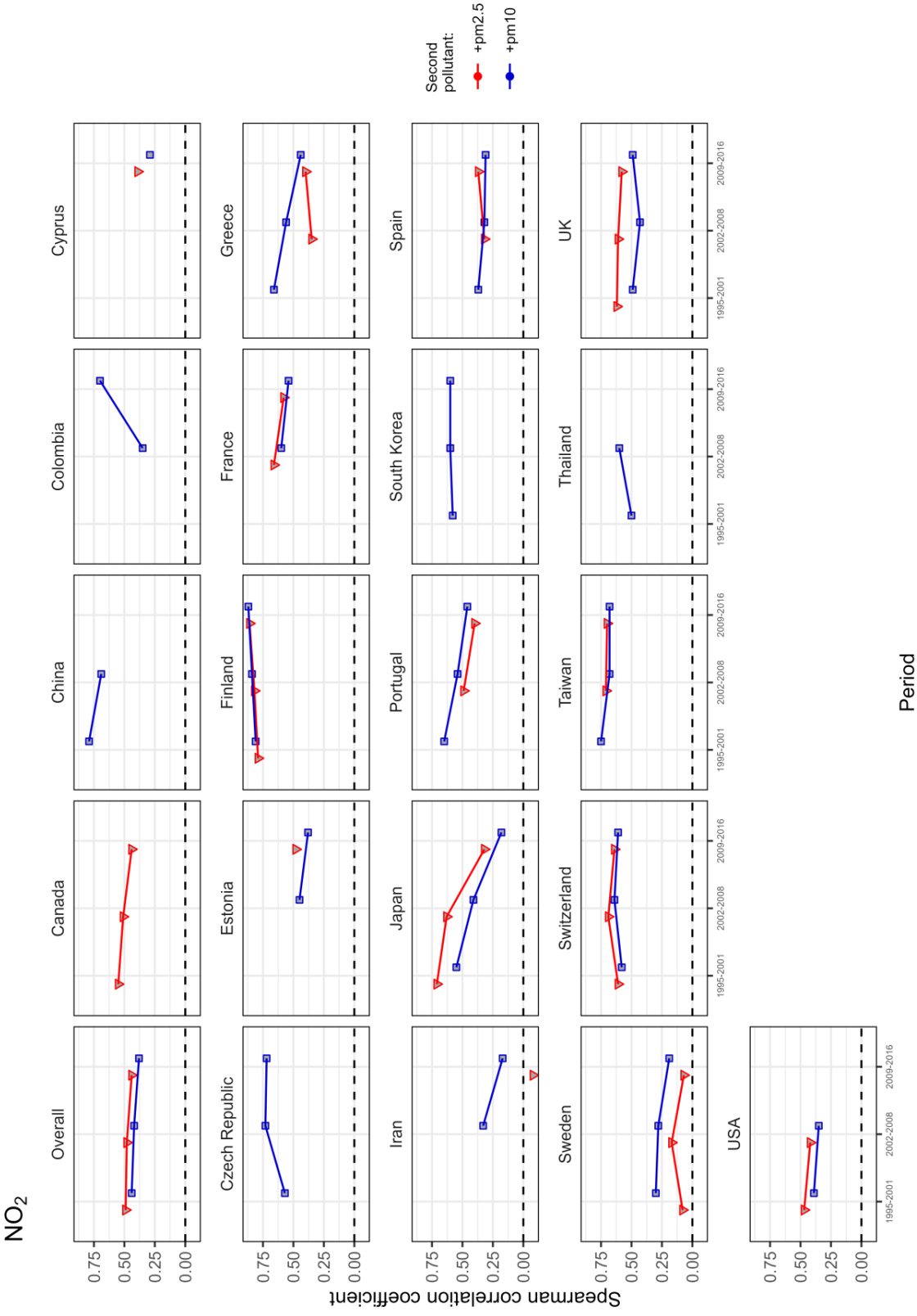

Figure S3: Spearman correlation coefficients of NO_2 and other air pollutants by individual periods and countries.

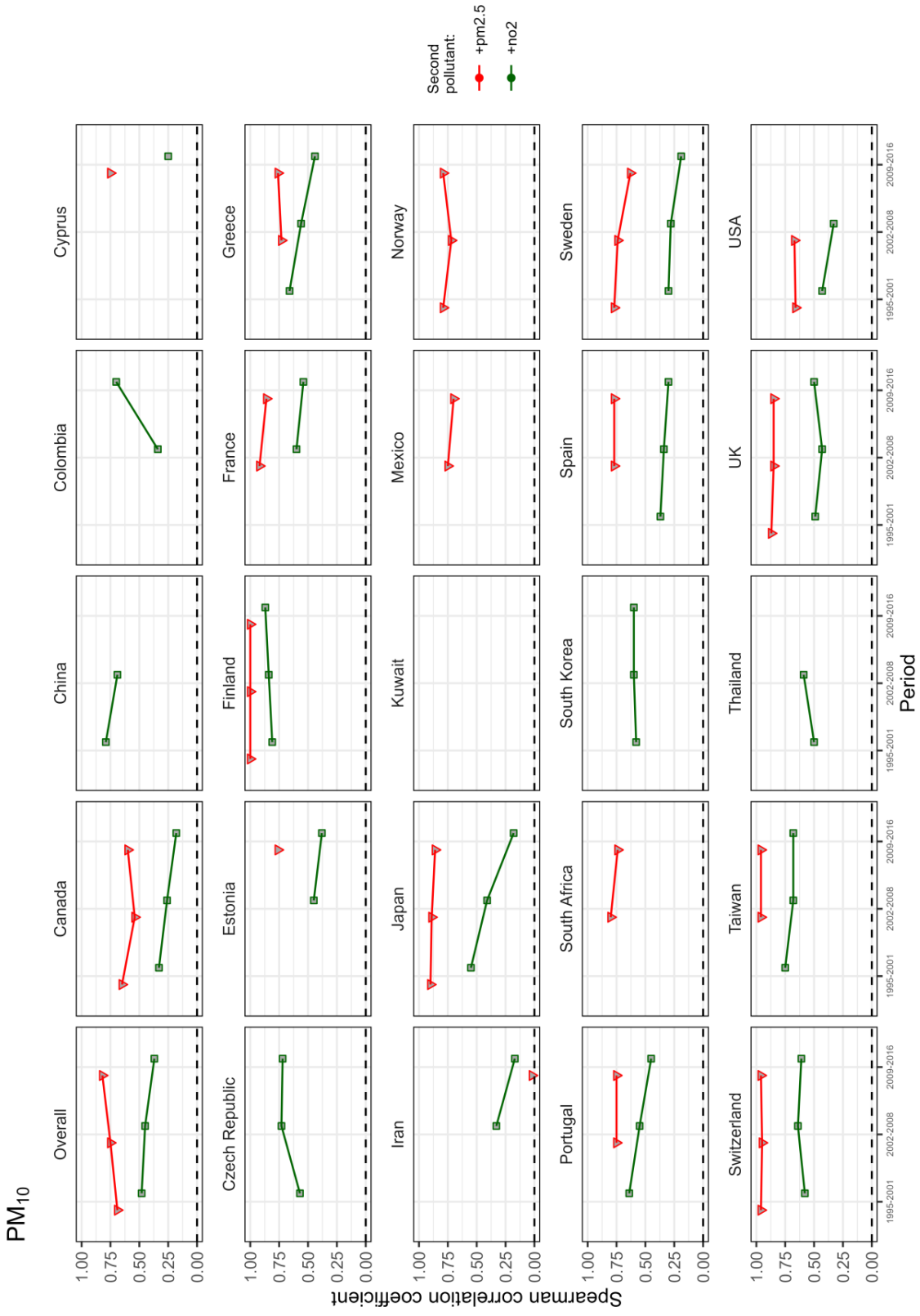

Figure S4: Spearman correlation coefficients of PM_{10} and other air pollutants by individual periods and countries.

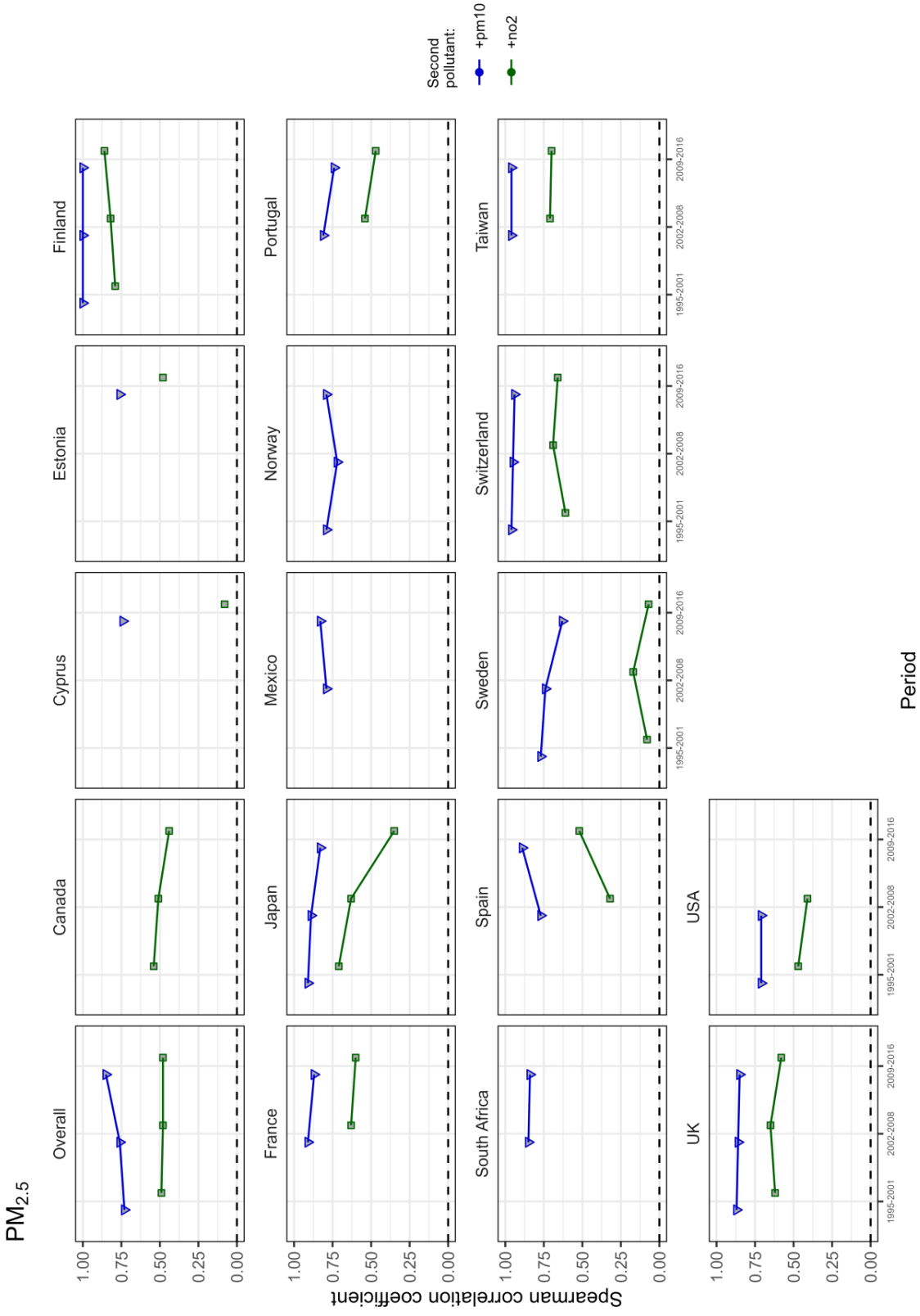

Figure S5: Spearman correlation coefficients of $PM_{2.5}$ and other air pollutants by individual periods and countries.

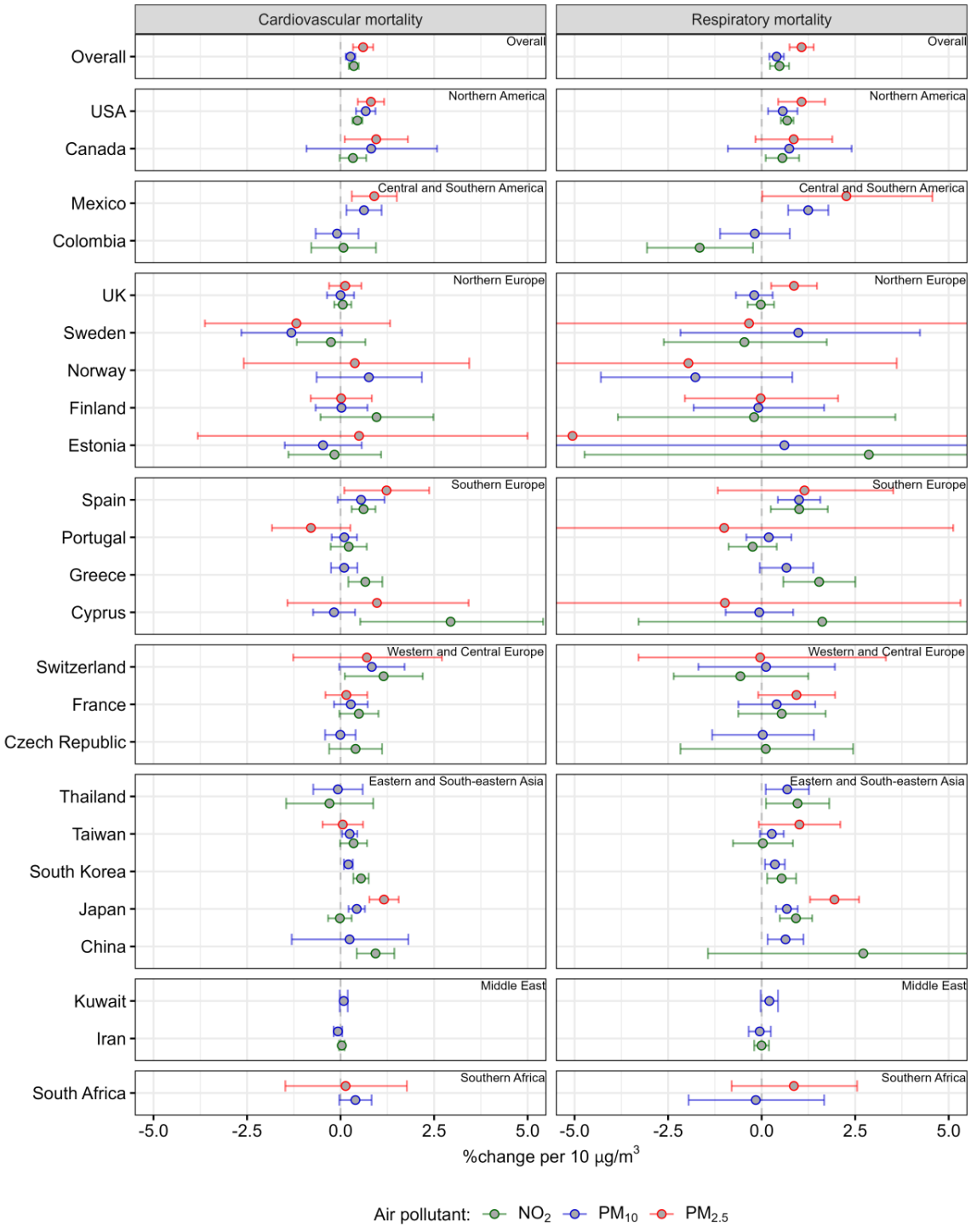

Figure S6: Percent change in daily mortality and 95% CI per 10 µg/m^3 increase in air pollutants. Estimates represent the global (top panel) and country-specific (lower panels) pooled analysis using multilevel random-effects models and were adjusted for main model covariates without assessment of temporal variation. NO_2 analyses were conducted using lag1, PM fractions lag01 of the respective pollutant.

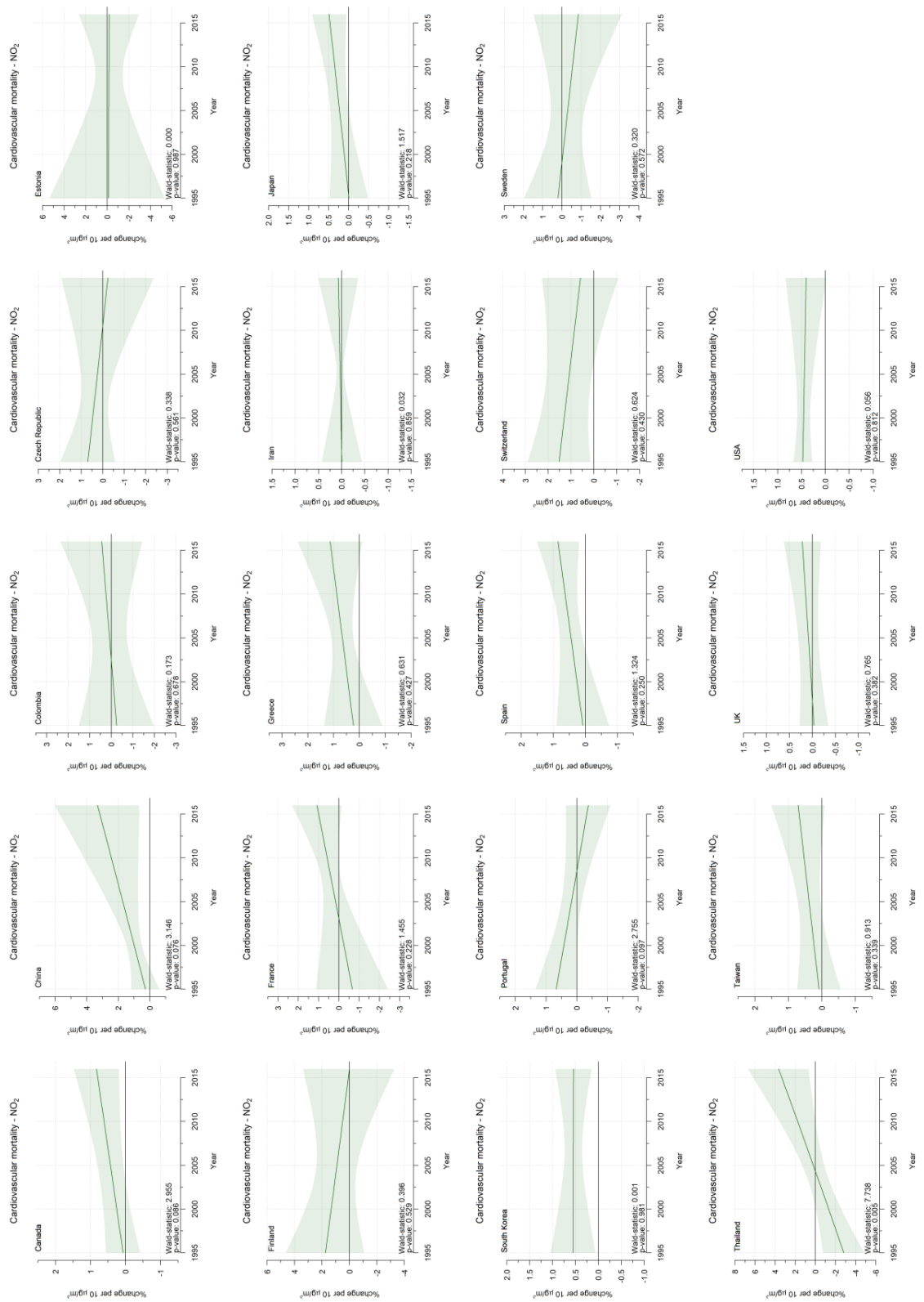

Figure S7: Percent change in daily cardiovascular mortality and 95% CI (shaded area) per 10 µg/m³ increase in NO_2 (at lag1) over the study period 1995-2016, stratified by country. The graph represents the result of the pooled longitudinal meta-regression using time as a linear term. Note: NO_2: Nitrogen dioxide.

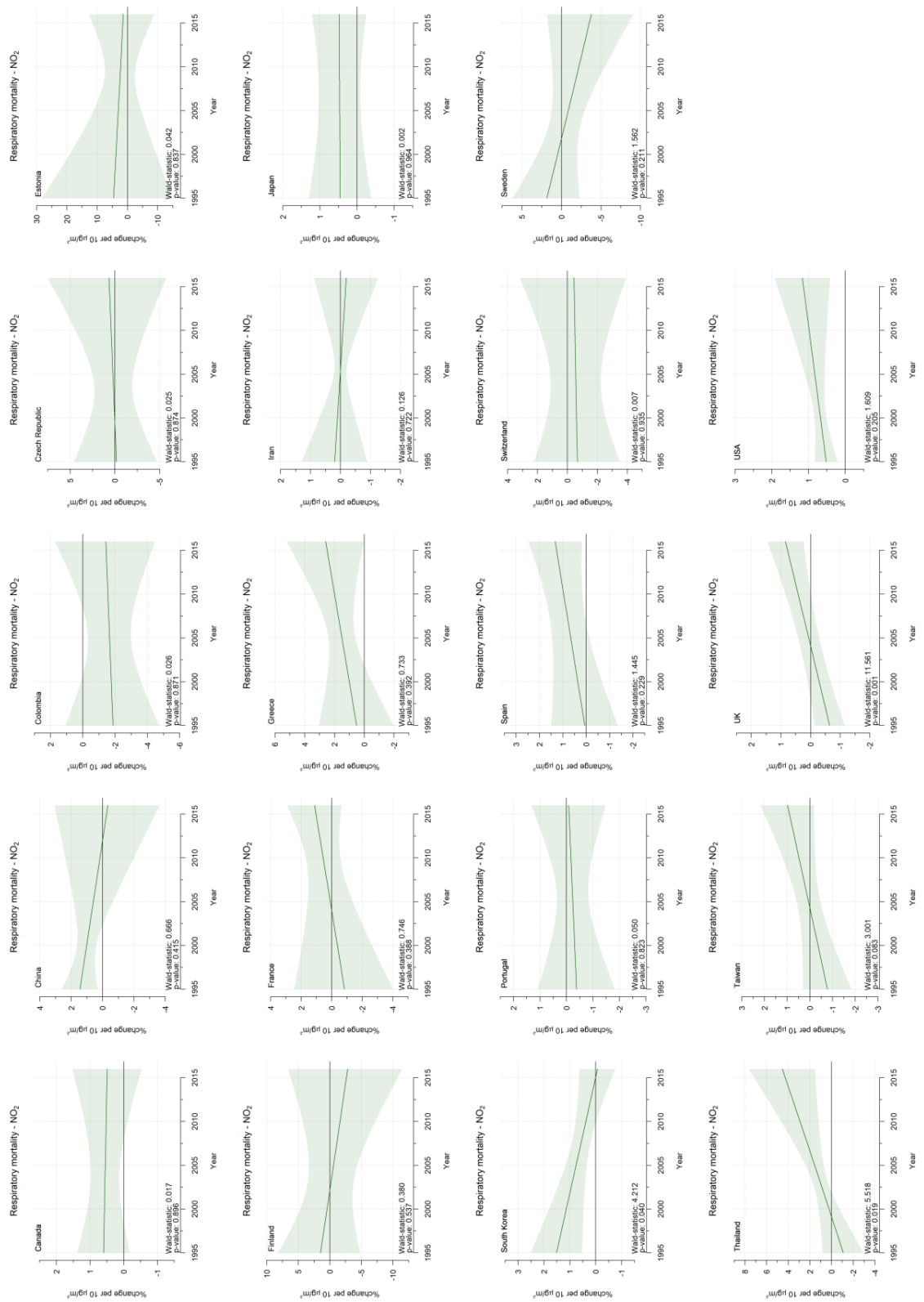

Figure S8: Percent change in daily respiratory mortality and 95% CI (shaded area) per 10 µg/m³ increase in NO_2 (at lag1) over the study period 1995-2016, stratified by country. The graph represents the result of the pooled longitudinal meta-regression using time as a linear term. Note: NO_2: Nitrogen dioxide.

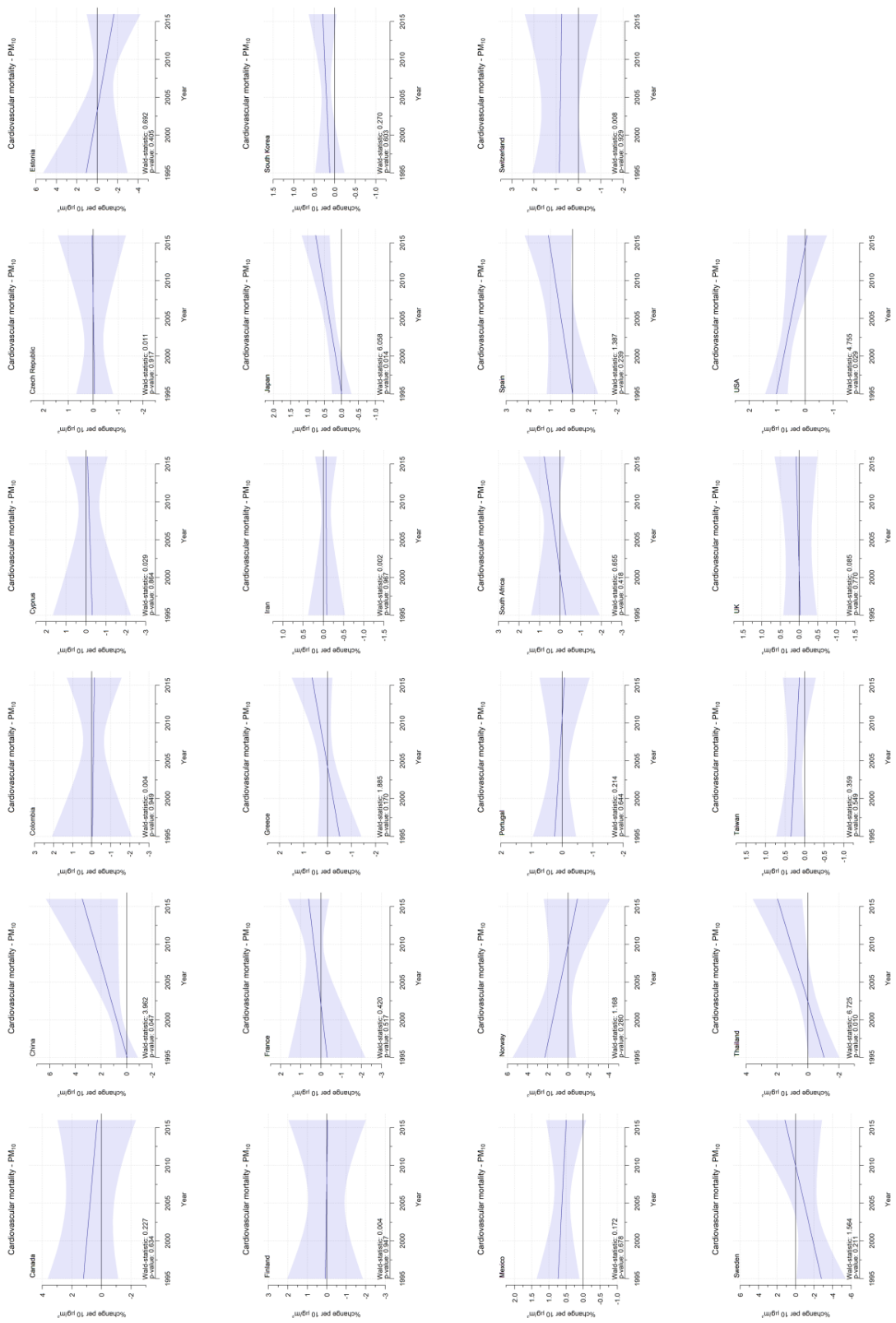

Figure S9: Percent change in daily cardiovascular mortality and 95% CI (shaded area) per 10 µg/m³ increase in PM_{10} (at lag01) over the study period 1995-2016, stratified by country. The plot represents the result of the pooled longitudinal meta-regression using time as a linear term. Note: PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm.

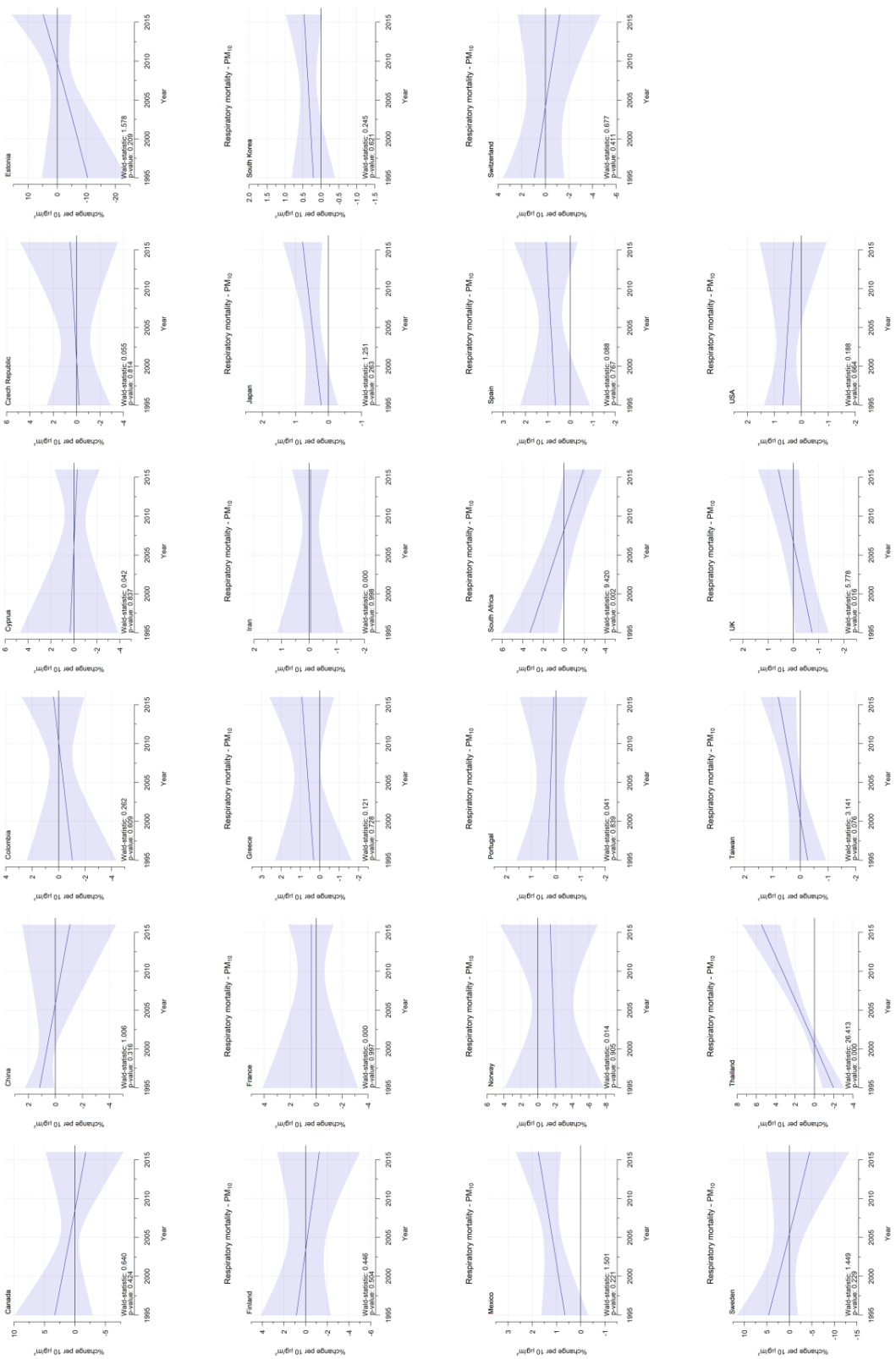

Figure S10: Percent change in daily respiratory mortality and 95% CI (shaded area) per 10 µg/m³ increase in PM_{10} (at lag01) over the study period 1995-2016, stratified by country. The plot represents the result of the pooled longitudinal meta-regression using time as a linear term. Note: PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm.

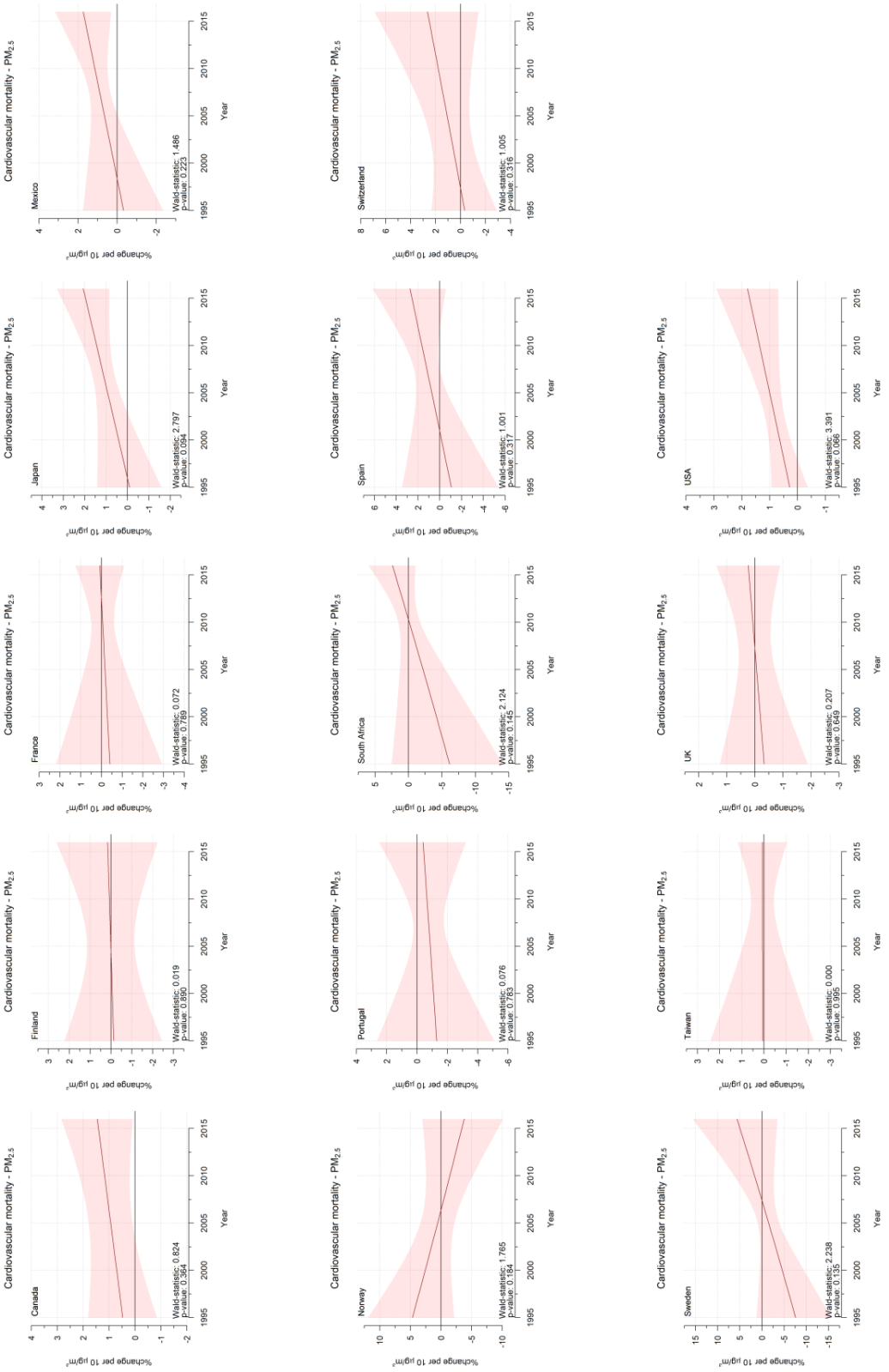

Figure S11: Percent change in cardiovascular mortality and 95% CI (shaded area) per 10 µg/m³ increase in $PM_{2·5}$ (at lag01) over the study period 1995-2016, stratified by country. The plot represents the result of the pooled longitudinal meta-regression using time as a linear term. Note: $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm.

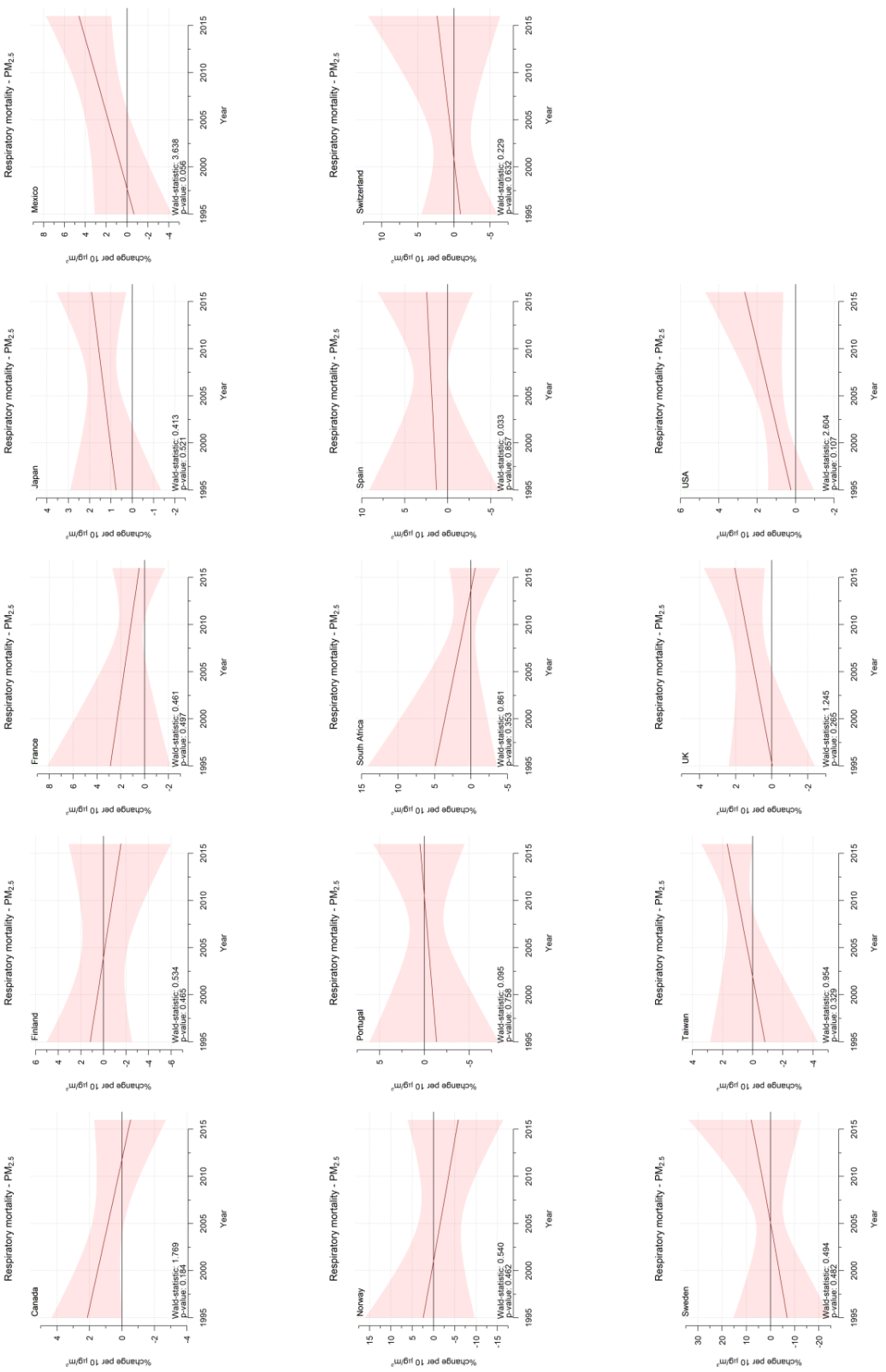

Figure S12: Percent change in daily respiratory mortality and 95% CI (shaded area) per 10 µg/m³ increase in $PM_{2.5}$ (at lag01) over the study period 1995-2016, stratified by country. The plot represents the result of the pooled longitudinal meta-regression using time as a linear term. Note: $PM_{2.5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm.

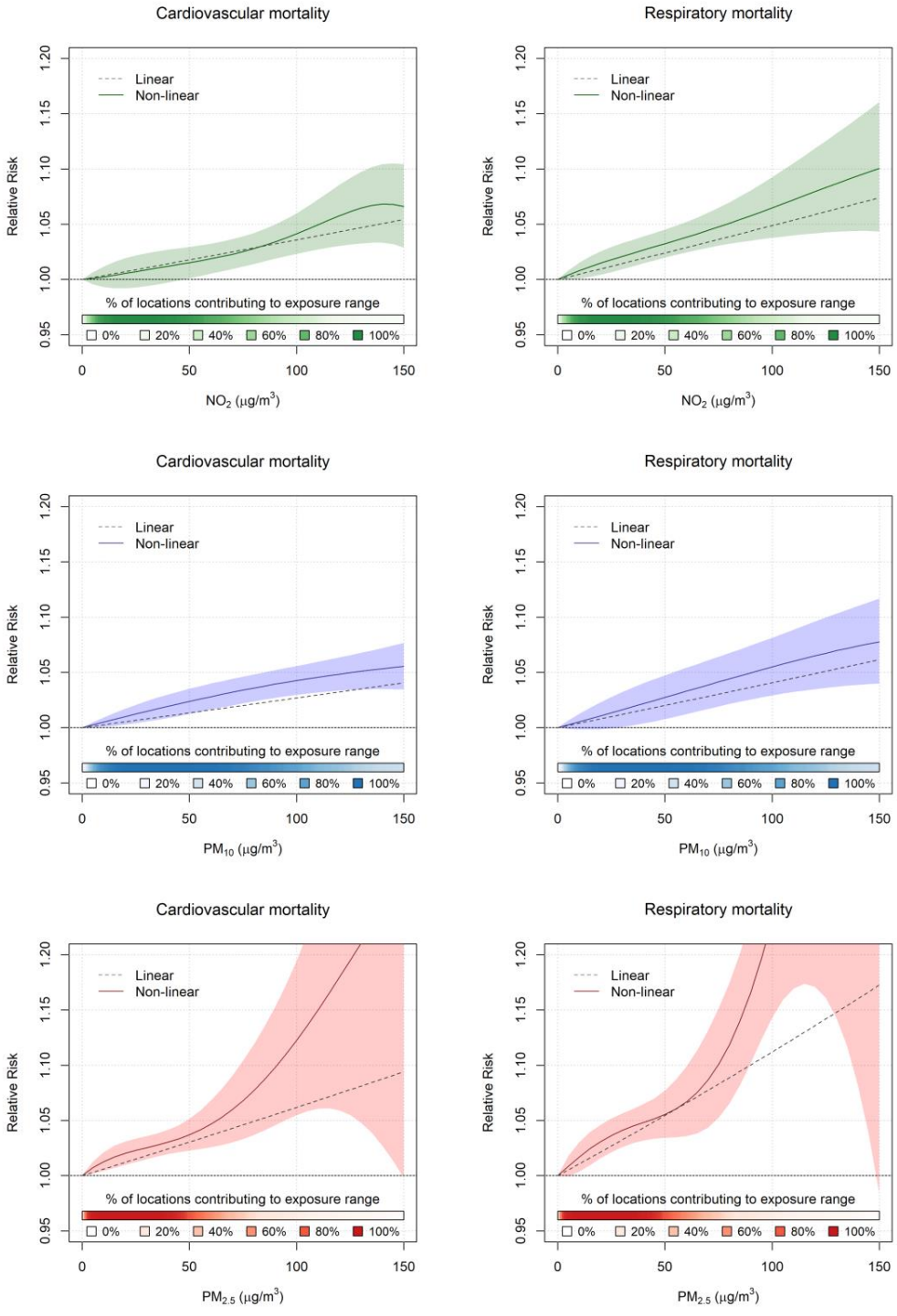

Figure S13: Pooled exposure-response functions for daily cardiovascular (left column) and respiratory (right column) mortality and NO_2 (top panel, at lag1), PM_{10} (middle panel, at lag01), and $PM_{2.5}$ (bottom panel, at lag01) over the study period 1995-2016. The plot displays the linear (dashed lines) and non-linear (quintic polynomial, continuous lines with 95% CI's, shaded areas) functions. The bar represents the percentage of locations that contribute to a specific exposure range. Note: A substantial reduction in available data at very high exposure concentrations (especially for $PM_{2.5}$ over 100 µg/m³) affected the non-linear functions and the 95% CI's

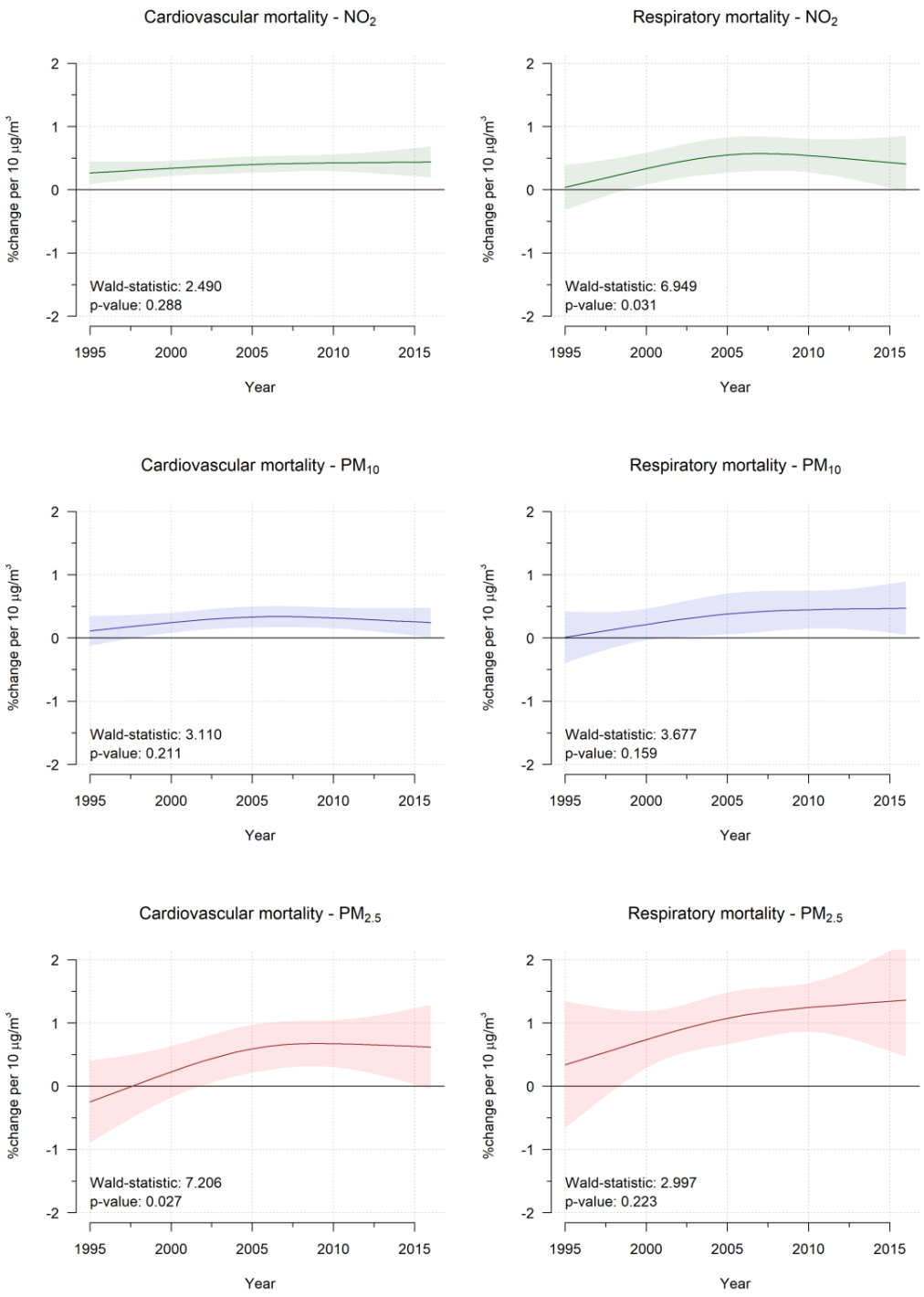

Figure S14: Percent change in daily cardiovascular (left column) and respiratory (right column) mortality and 95% CI (shaded area) per 10 µg/m³ increase in NO_2 (top panel, at lag1), PM_{10} (middle panel, at lag01), and $PM_{2·5}$ (bottom panel, at lag01) over the study period 1995-2016. The plot represents the result of the pooled longitudinal meta-regression using time as a nonlinear term. Note: NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm; The p-value of the related Wald-Test indicate a significant difference of the model with the nonlinear term for time.

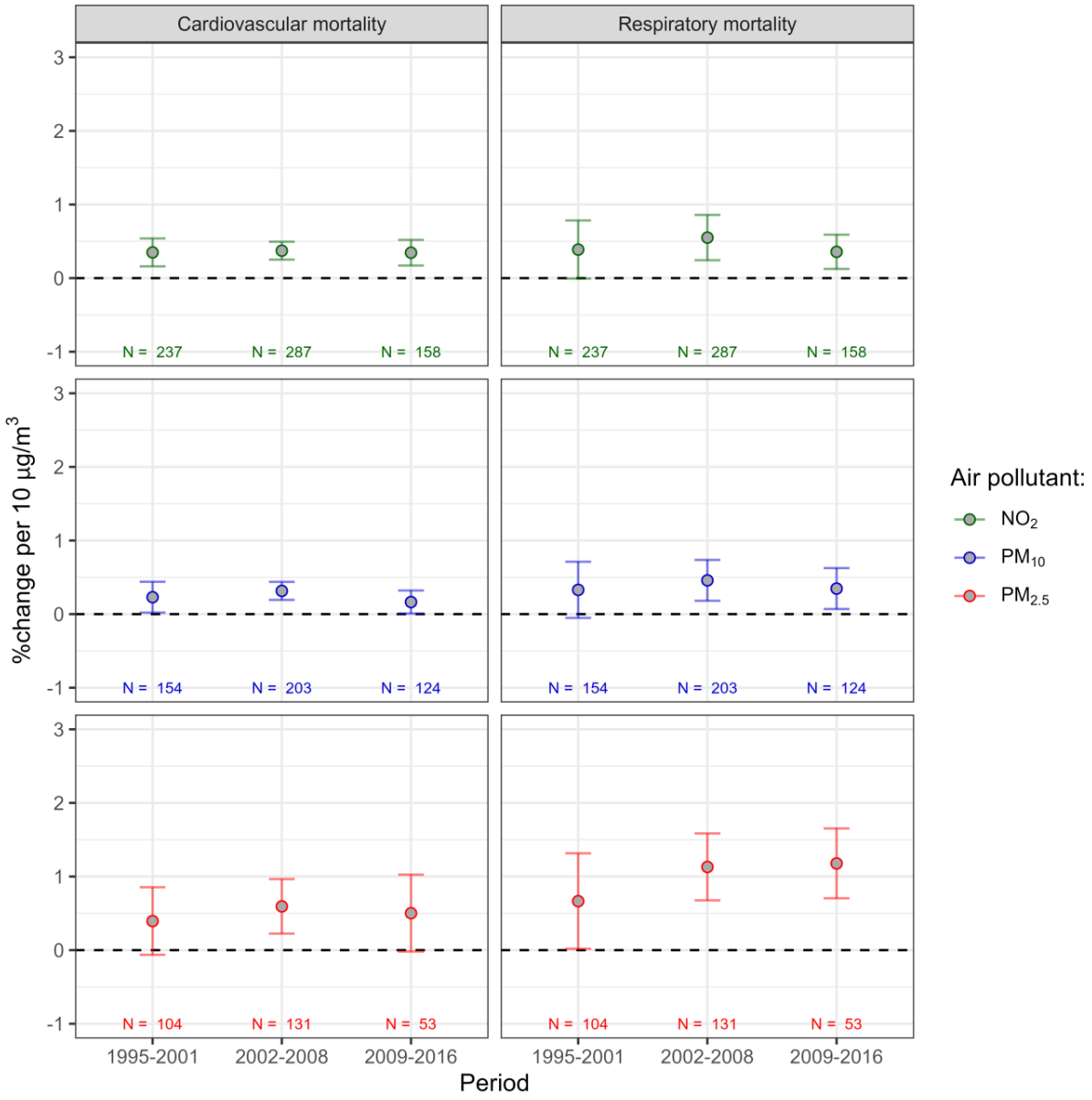

Figure S15: Percent change in daily cardiovascular (left column) and respiratory (right column) mortality and 95% CI (shaded area) per 10 µg/m³ increase in NO_2 (top panel, at lag1), PM_{10} (middle panel, at lag01), and $PM_{2·5}$ (bottom panel, at lag01) for each sub-period of the analysis. The plot represents the result of the pooled city-specific interactions between air pollution concentrations and time (defined as period). Note: NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm; N: number of cities that contributed to the respective period.

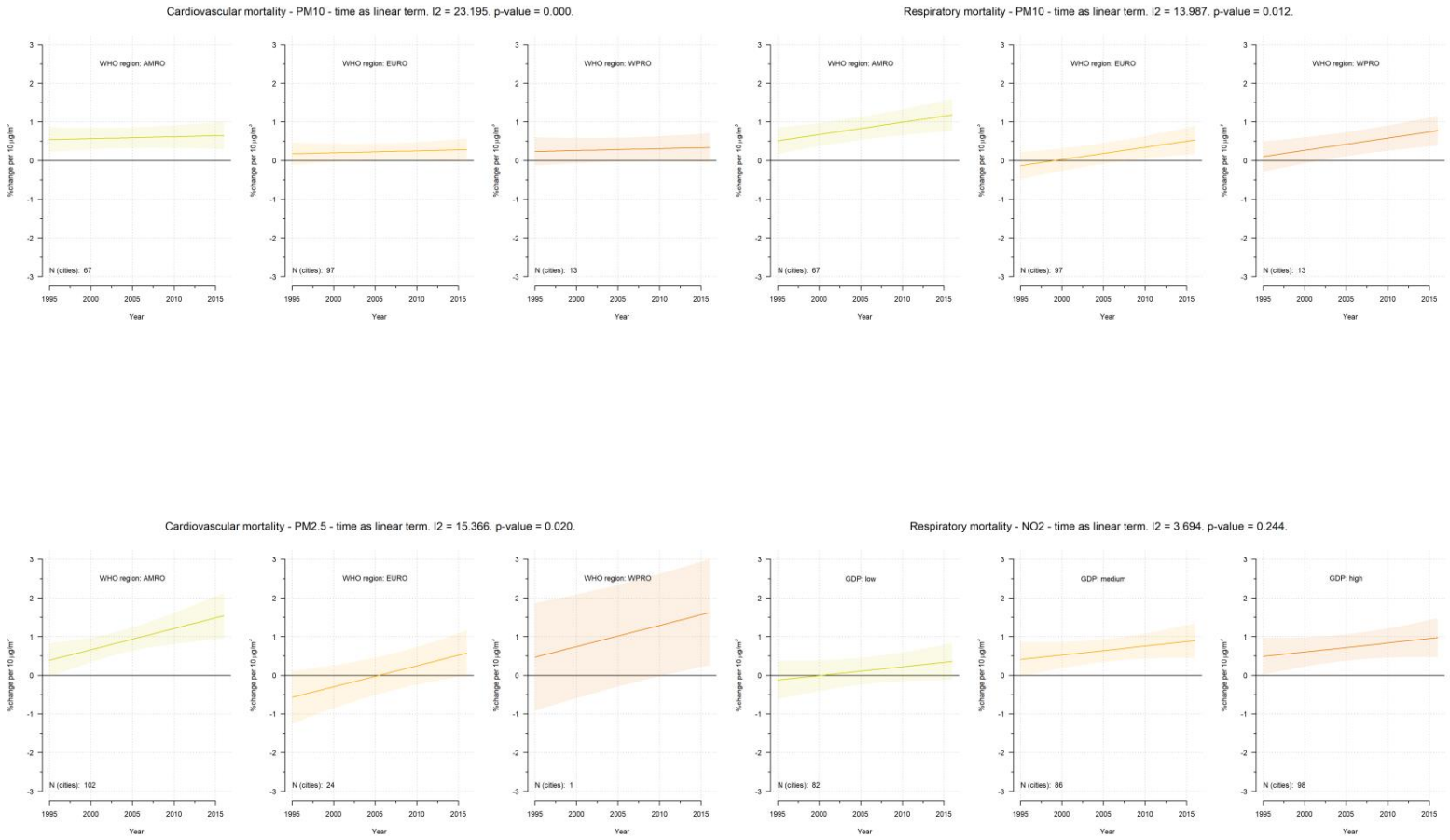

Figure S16: Percent change in daily cardiovascular (left column) and respiratory (right column) mortality and 95% CI (shaded area) per 10 µg/m^3 increase in NO_2 (bottom right, at lag1), PM_{10} (top, at lag01), and $PM_{2·5}$ (bottom left, at lag 01) over the study period 1995-2016. The plot represents the result of the pooled longitudinal meta-regression using time as a linear term, stratified by the levels of the significant meta-predictors (WHO region and gross domestic product (GDP)). Note: NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm. AMRO: Region of the Americas; EURO: Europe; WPRO: Western Pacific Region. N: number of cities that contributed to the respective stratum.

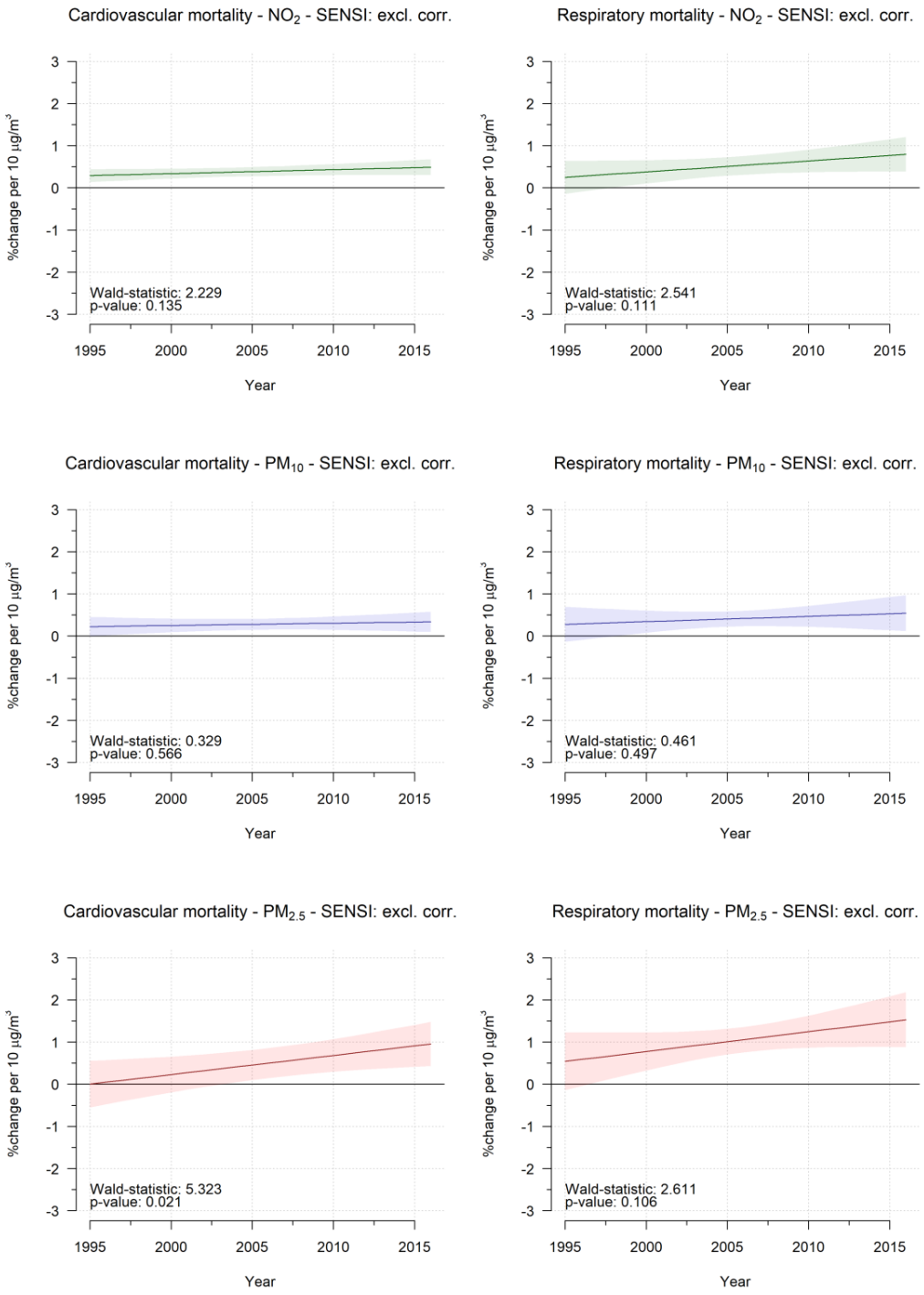

Figure S17: Percent change in cardiovascular (left column) and respiratory (right column) daily mortality and 95% CI (shaded area) per 10 µg/m³ increase in NO_2 (top panel, at lag1), PM_{10} (middle panel, at lag01), and $PM_{2·5}$ (bottom panel, at lag01) over the study period 1995-2016. The plot represents the result of the pooled longitudinal meta-regression sensitivity analysis (exclusion of cities with high correlations between model variables) using time as a linear term. Note: NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm; The p-value of the related Wald-Test indicate a significant difference of the model with the linear term for time.

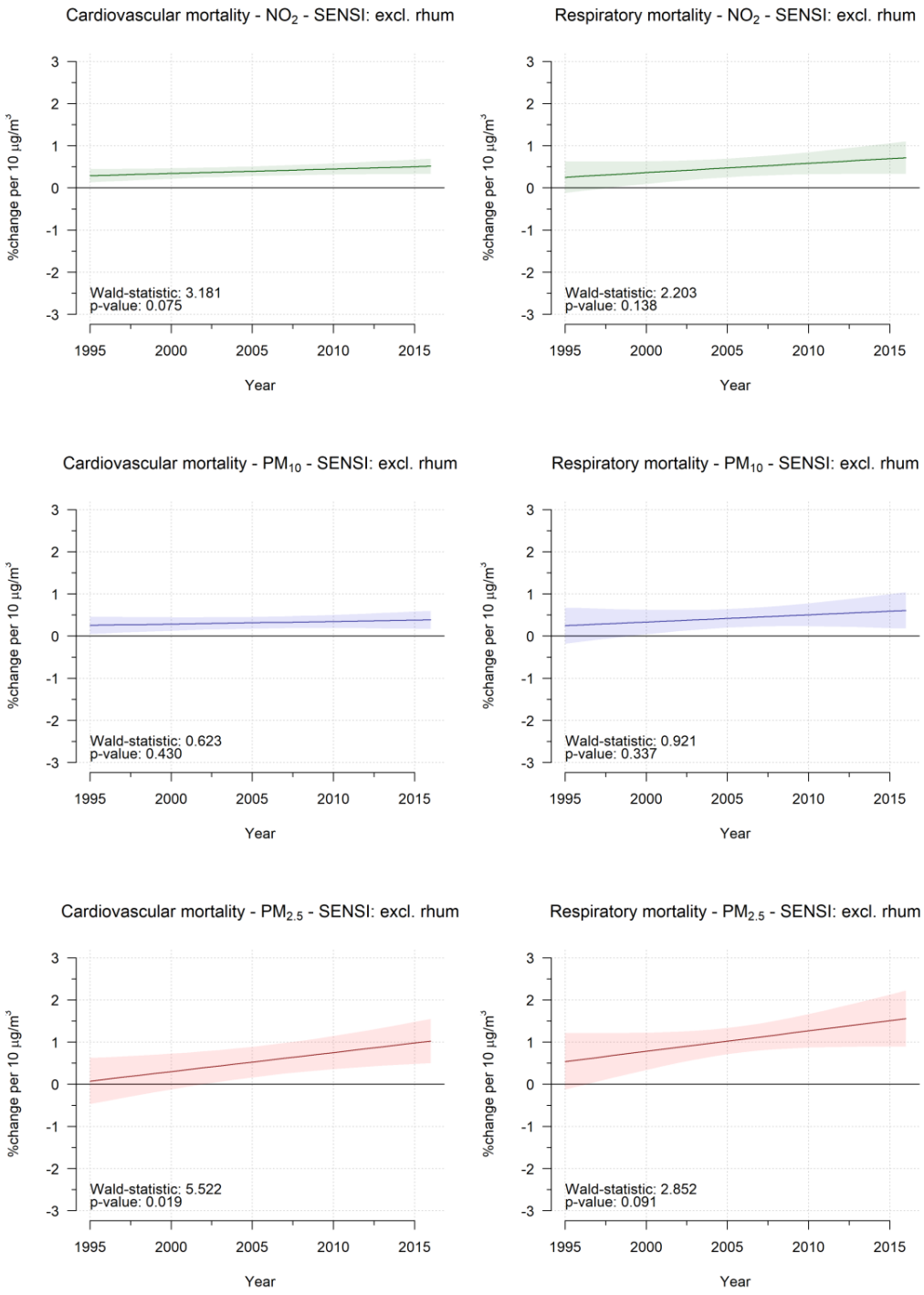

Figure S18: Percent change in cardiovascular (left column) and respiratory (right column) daily mortality and 95% CI (shaded area) per 10 µg/m³ increase in NO_2 (top panel, at lag1), PM_{10} (middle panel, at lag01), and $PM_{2·5}$ (bottom panel, at lag01) over the study period 1995-2016. The plot represents the result of the pooled longitudinal meta-regression sensitivity analysis (exclusion of relative humidity from the model) using time as a linear term. Note: NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm; The p-value of the related Wald-Test indicate a significant difference of the model with the linear term for time.

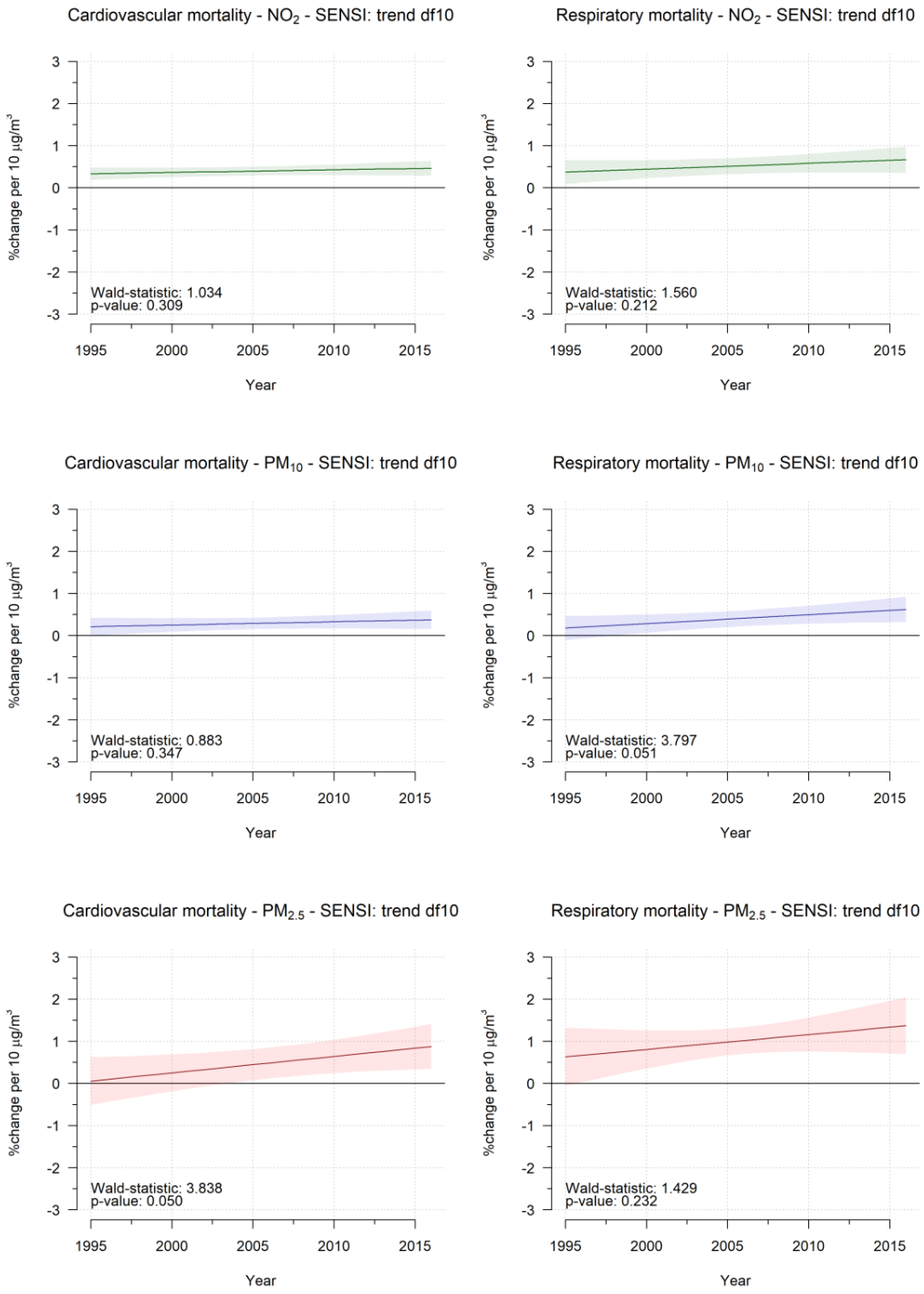

Figure S19: Percent change in cardiovascular (left column) and respiratory (right column) daily mortality and 95% CI (shaded area) per 10 µg/m³ increase in NO_2 (top panel, at lag1), PM_{10} (middle panel, at lag01), and $PM_{2·5}$ (bottom panel, at lag01) over the study period 1995-2016. The plot represents the result of the pooled longitudinal meta-regression sensitivity analysis (increasing the degrees of freedom for time trend from seven per year to ten per year) using time as a linear term. Note: NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm; The p-value of the related Wald-Test indicate a significant difference of the model with the linear term for time.

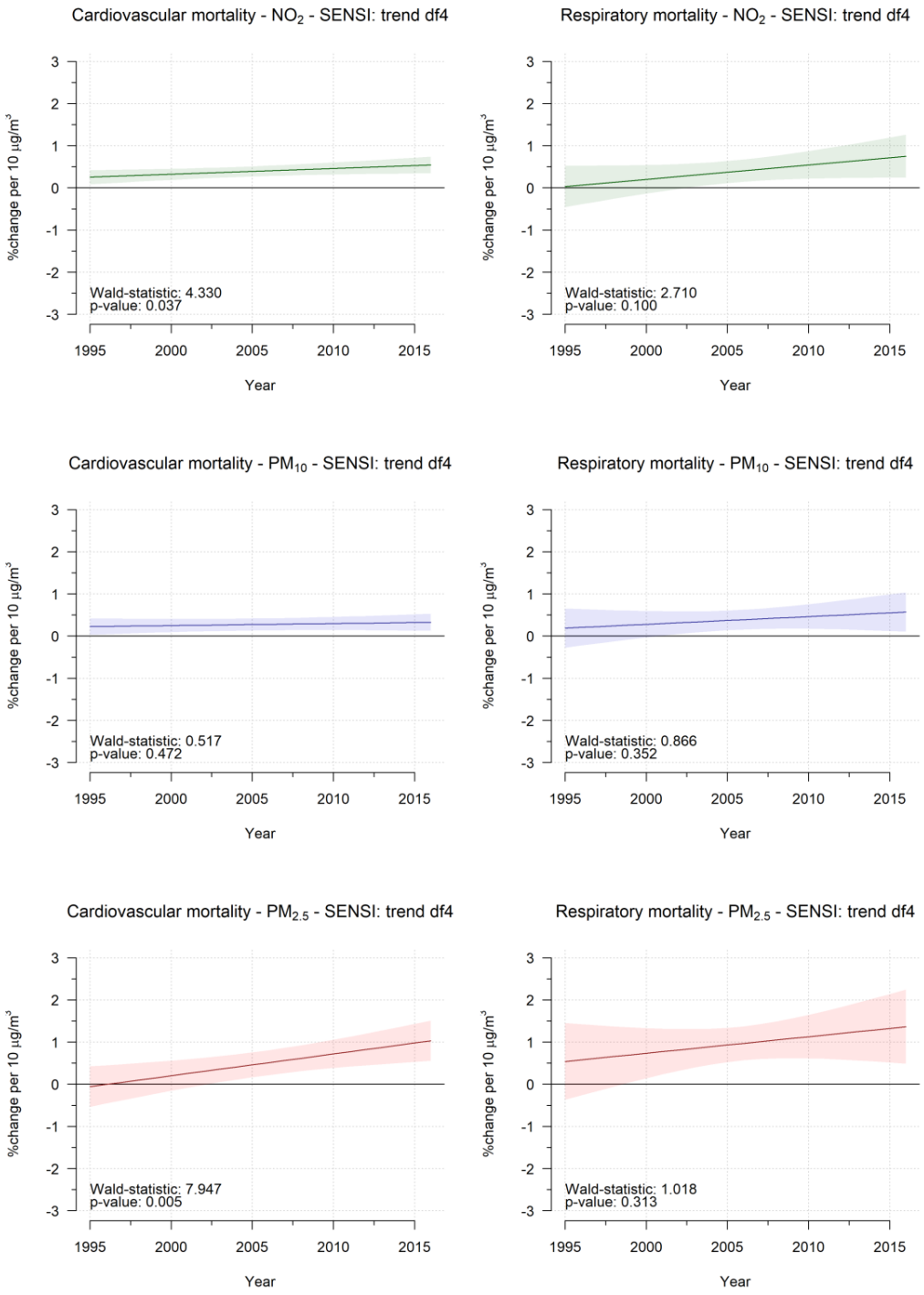

Figure S20: Percent change in cardiovascular (left column) and respiratory (right column) daily mortality and 95% CI (shaded area) per 10 µg/m³ increase in NO_2 (top panel, at lag1), PM_{10} (middle panel, at lag01), and $PM_{2·5}$ (bottom panel, at lag01) over the study period 1995-2016. The plot represents the result of the pooled longitudinal meta-regression sensitivity analysis (reducing the degrees of freedom for time trend from seven per year to four per year) using time as a linear term. Note: NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm; The p-value of the related Wald-Test indicate a significant difference of the model with the linear term for time.

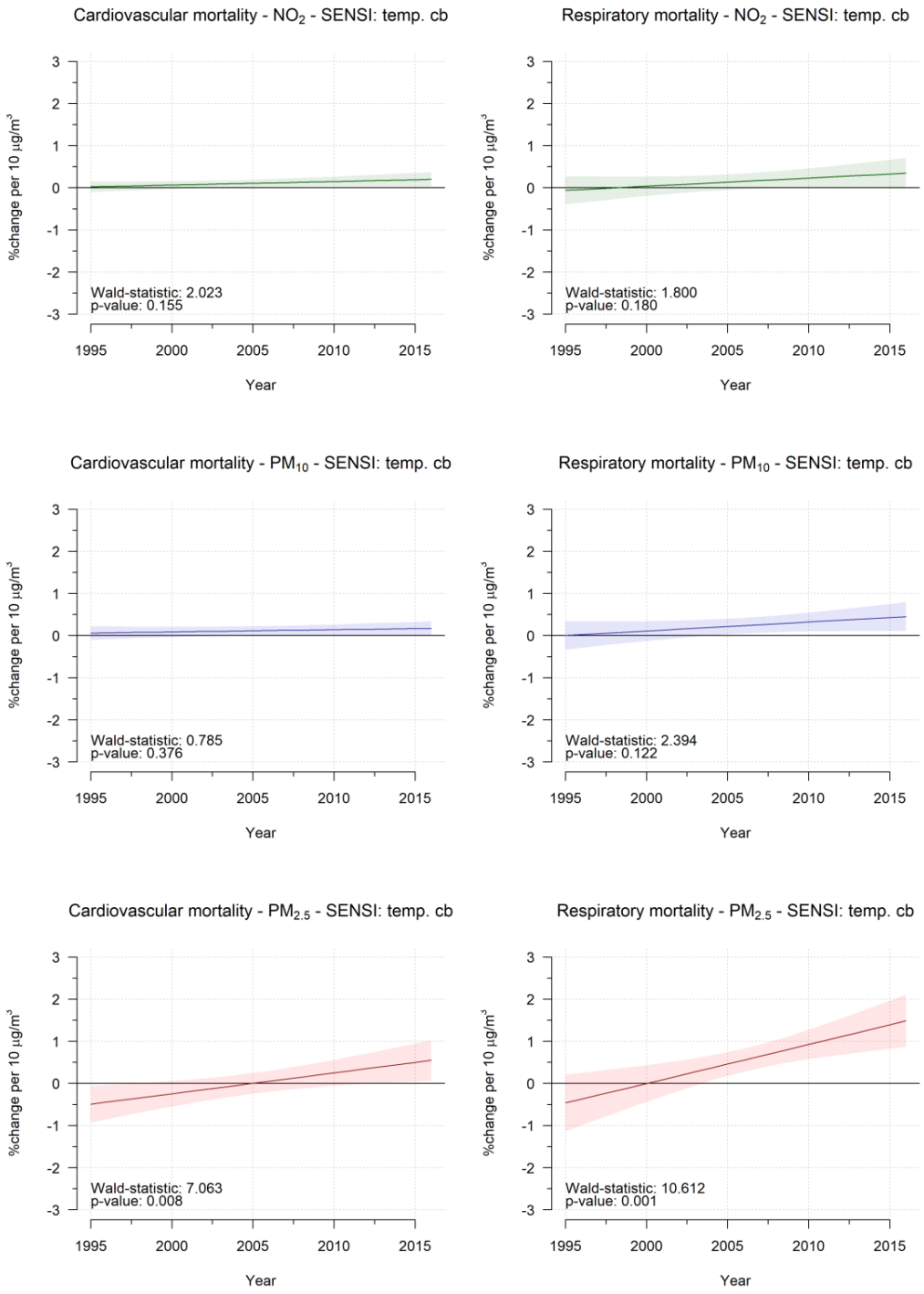

Figure S21: Percent change in cardiovascular (left column) and respiratory (right column) daily mortality and 95% CI (shaded area) per 10 µg/m³ increase in NO_2 (top panel, at lag1), PM_{10} (middle panel, at lag01), and $PM_{2·5}$ (bottom panel, at lag01) over the study period 1995-2016. The plot represents the result of the pooled longitudinal meta-regression sensitivity analysis (using a distributed lag non-linear term to control for temperature) using time as a linear term. Note: NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm; The p-value of the related Wald-Test indicate a significant difference of the model with the linear term for time.

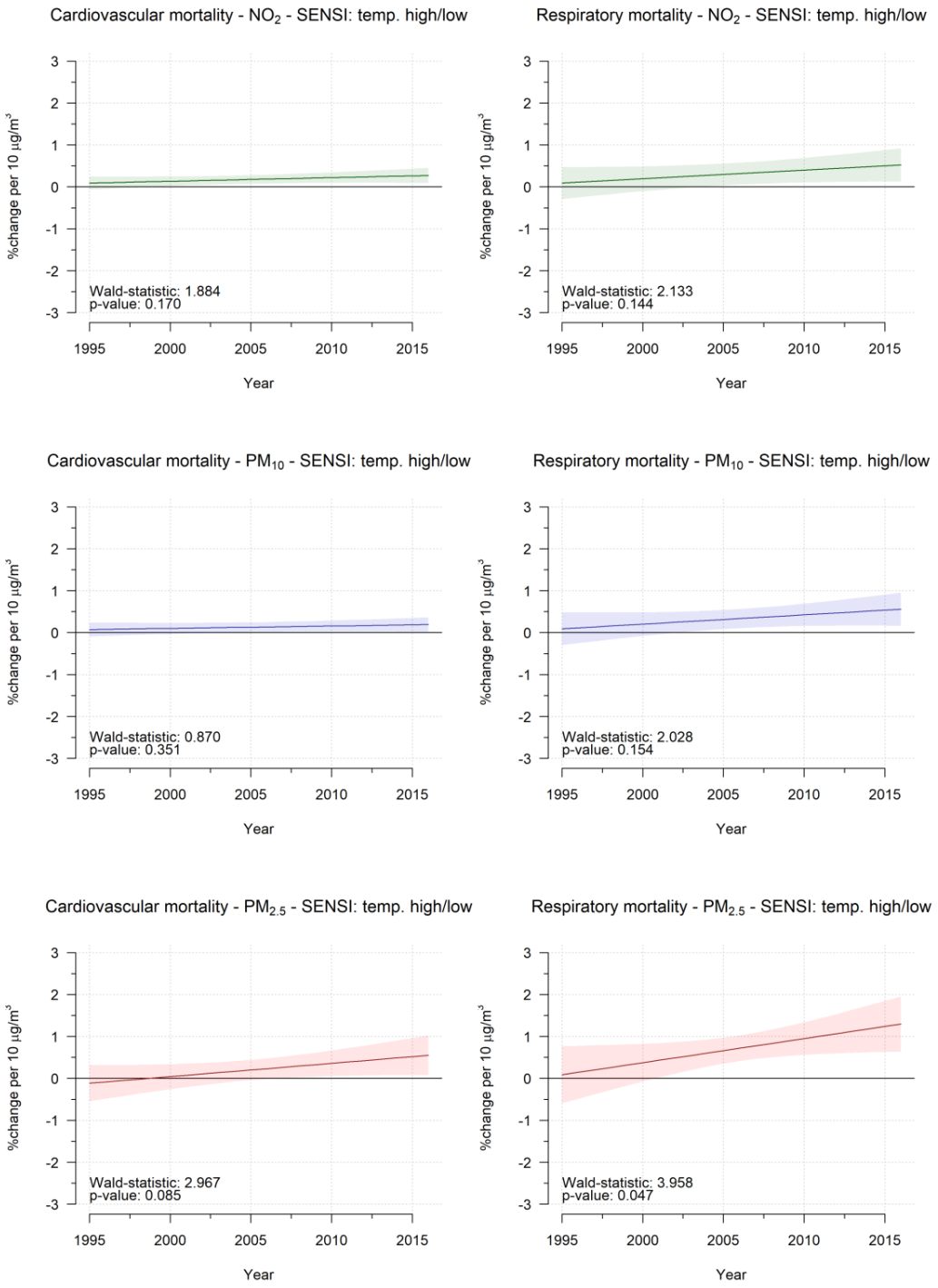

Figure S22: Percent change in cardiovascular (left column) and respiratory (right column) daily mortality and 95% CI (shaded area) per 10 µg/m³ increase in NO_2 (top panel, at lag1), PM_{10} (middle panel, at lag01), and $PM_{2·5}$ (bottom panel, at lag01) over the study period 1995-2016. The plot represents the result of the pooled longitudinal meta-regression sensitivity analysis (separate adjustment for high and low temperatures) using time as a linear term. Note: NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm; The p-value of the related Wald-Test indicate a significant difference of the model with the linear term for time.

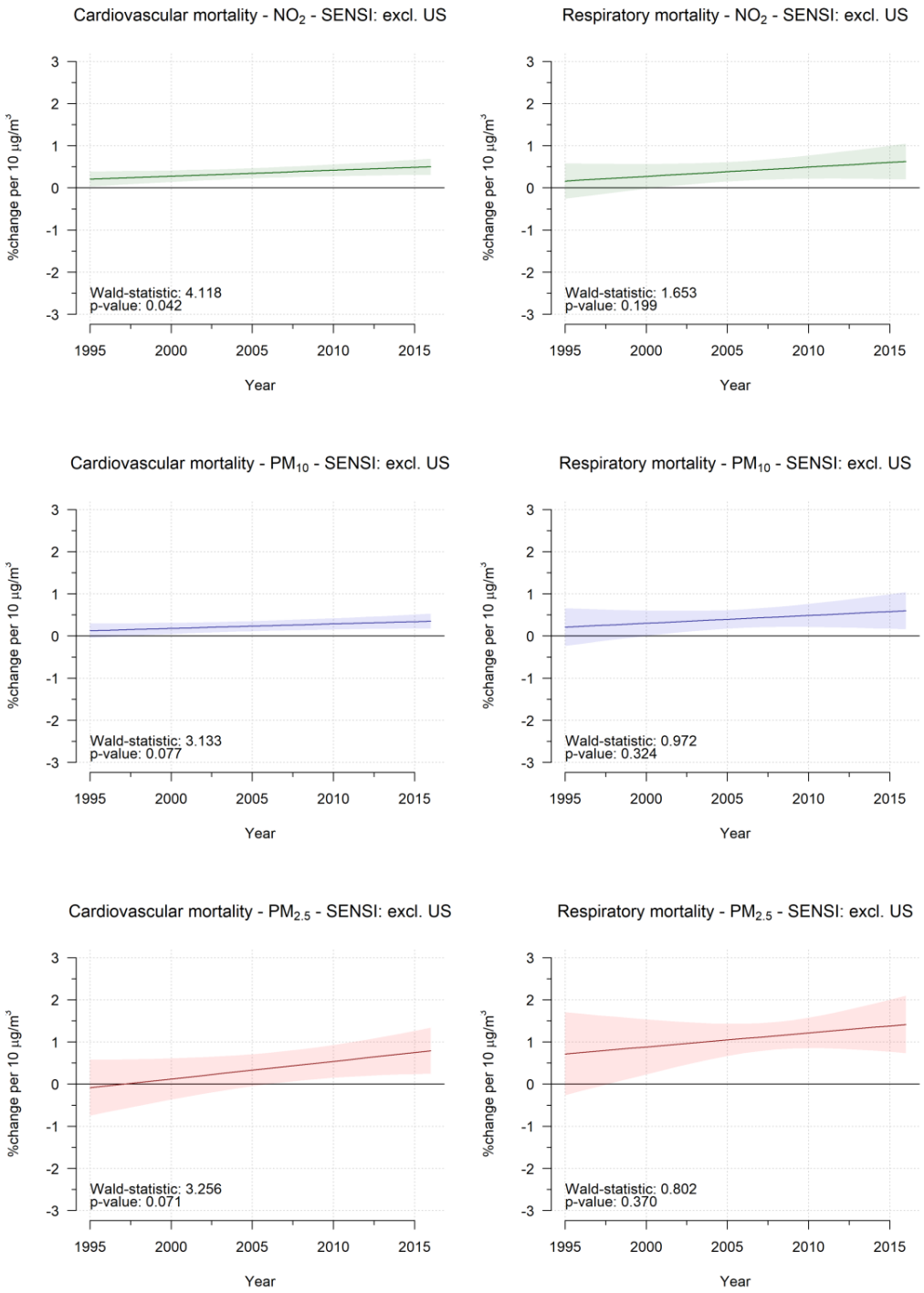

Figure S23: Percent change cardiovascular (left column) and respiratory (right column) daily mortality and 95% CI (shaded area) per 10 µg/m³ increase in NO_2 (top panel, at lag1), PM_{10} (middle panel, at lag01), and $PM_{2·5}$ (bottom panel, at lag01) over the study period 1995-2016. The plot represents the result of the pooled longitudinal meta-regression sensitivity analysis using time as a linear term (exclusion of US cities from the dataset). Note: NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with an aerodynamic diameter ≤ 10µm; $PM_{2·5}$: Particulate matter with an aerodynamic diameter ≤ 2·5µm; The p-value of the related Wald-Test indicate a significant difference of the model with the linear term for time.

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Acknowledgements

First, I would like to express my gratitude to Prof. Dr. Annette Peters, Director of the Institute of Epidemiology at Helmholtz Munich, for her dedicated and professional supervision and the opportunity to learn from her experience and expertise, as well as the possibility to pursue a doctoral degree at her institute.

I also want to thank Prof. Dr. Dennis Nowak, Prof. Dr. Michael Ingrisch, and Prof. Dr. Barbara Hoffmann for their support and advice as my Thesis Advisory Committee as well as for the very productive meetings, which challenged our research questions and improved the work a lot.

Furthermore, I would particularly like to thank my direct supervisors, Dr. Alexandra Schneider and Dr. Susanne Breitner-Busch, for their willingness to supervise my work and for their continuous and tireless support, not only in scientific topics, but also in my professional and personal development, which goes in hand with this dissertation. Thank you for your trust and patience, for the numerous opportunities to learn from you, and for the possibility to follow this path with all the doors that have opened for me over the past years.

Many thanks to Dr. Susanne Bastian and all the contributors and collaborators in our studies for their support and commitment, as well as to Karen Meyer for her efforts in times when some things turned out to be more difficult than originally thought due to global a pandemic.

In addition, I would like to express my gratitude to Dr. Kathrin Wolf, who supervised my initial internship and master's thesis at Helmholtz Munich and inspired my enthusiasm for environmental epidemiology, without which I wouldn't have considered pursuing a doctoral degree. I also thank Dr. Regina Pickford for her substantial contributions to my decision to stay in academia.

I owe my scientific and personal development not only to the people mentioned above, but also to my colleagues at the Institute of Epidemiology for the good cooperation, fun company trips as well as the very good working atmosphere. I highly appreciated the great people and the spirit in our PhD office, where colleagues became friends. It was always a pleasure, and I will always remember our ‘lunch meetings’.

Finally, none of this would have been possible without the selfless and tremendous support of my family! I would like to express my deepest gratitude to my parents Claudia and Mathias and my sister Lisa, who have always supported me unconditionally and stood by my side with advice and action, as well as to my friends and everyone who has been a part of this journey.

Vielen vielen Dank Euch und Ihnen!

List of publications

Publications included in this cumulative thesis:

Schwarz M, Schneider A, Cyrys J, Bastian S, Breitner S, Peters A. Impact of Ambient Ultrafine Particles on Cause-Specific Mortality in Three German Cities. Am J Respir Crit Care Med. 2023.

Schwarz M, Schneider A, Cyrys J, Bastian S, Breitner S, Peters A. Impact of ultrafine particles and total particle number concentration on five cause-specific hospital admission endpoints in three German cities. Environment International. 2023;178:108032.

Conference presentations (content is related to this thesis):

Schwarz M, Schneider A, Cyrys J, Bastian S, Peters A, Breitner S. Impact of ultrafine particles and total particle number concentration on natural-, cardiovascular, and respiratory mortality in three German cities. 34th Annual Conference of The International Society for Environmental Epidemiology; 2022 September 18-21; Athens, Greece: Environ Health Perspect.

Submitted manuscript included in this cumulative thesis (appendix):

Schwarz M, Peters A, Stafoggia M, De'Donato F, Sera F, Bell ML, Guo Y, Honda Y, Huber V, Jaakkola JJK, Urban A, Vicedo-Cabrera AM, Masselot P, Lavigne E, Kan H, Osorio S, Achilleos S, Kyselý J, Orru H, Indermitte E, Maasikmets M, Ryti N, Pascal M, Katsouyanni K, Analitis A, Samoli E, Entezari A, Mayvaneh F, Hashizume M, Kim Y, Ng CFS, Alahmad B, Diaz MH, Arellano EEF, Rao S, Palomares AD-L, Silva SdNPd, Madureira J, Scovronick N, Acquaotta F, Garland RM, Kim H, Lee W, Tobias A, Íñiguez C, Forsberg B, Ragettli MS, Guo YL, Pan S-C, Li S, Armstrong B, Zanobetti A, Schwartz J, Gasparrini A, Schneider A, Breitner S. Temporal Variations in the Short-Term Effects of Ambient Air Pollution on Cardiovascular and Respiratory Mortality in 380 Urban Areas during a 22-Year Period. The Lancet Planetary Health. 2024. Manuscript submitted for publication.

Other publication:

Schwarz M, Wolf K, Schneider A, Schramm KW, Bongaerts B, Henkelmann B, Herder C, Roden M, Peters A, Ziegler D, Rathmann W. Association of persistent organic pollutants with sensorimotor neuropathy in participants with and without diabetes or prediabetes: Results from the population-based KORA FF4 study. Int J Hyg Environ Health. 2021;235:113752.

Affidavit

Eidesstattliche Versicherung

Schwarz, Maximilian Arthur

Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema

Ambient Air Pollution and its Effects on Mortality and Hospital Admissions: A Comprehensive Analysis of Ultrafine Particles, Various Particle Sizes, and Temporal Patterns

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