Environmental Research 286 (2025) 122780

Contents lists available at ScienceDirect

Environmental Research

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

Review article

# Systematic review and meta-analysis on short-term concentrations of ambient ultrafine particles and natural, cardiovascular and respiratory mortality

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ARTICLE INFO

*Keywords:*
Air pollution
Cardiovascular diseases
Mortality
Particulate matter
Respiratory diseases
Ultrafine particles

ABSTRACT

*Background:* Ambient ultrafine particles (UFP, <100 nm) are suspected to cause adverse health effects independent from larger particle fractions. Accordingly, there is increasing interest in their health effects. This paper describes a systematic review and meta-analysis of studies investigating the association of short-term concentrations of UFP with natural, cardiovascular, and respiratory mortality.
*Methods:* We systematically searched for epidemiological studies published between January 2011 and December 2024 in the databases PubMed and LUDOK and added studies from before 2011 from a previous review. We assessed heterogeneity and risk of bias and performed random-effects meta-analyses when at least four estimates were available.
*Results:* We identified 21 studies in total, with 17, 17, and 15 studies on natural, cardiovascular, and respiratory mortality, respectively. Meta-analytic summary estimates were 1.000 (95 % CI: 0.993, 1.007), 0.996 (0.990, 1.002) and 1.005 (0.979, 1.032) for natural, cardiovascular, and respiratory mortality, respectively, per 10,000 pt/cm$^3$ increase in UFP at lag 0, which had most available estimates. Overall, associations were non-significant and close to null across most lags. We found heterogeneity in UFP monitoring and lag reporting.
*Conclusion:* The number of studies on the association between short-term UFP concentrations and mortality has increased substantially in the last years. However, the current evidence does not clearly support an association between short-term concentrations of UFP and mortality. Future studies should improve and harmonize UFP monitoring to improve investigation of health effects and inform policymaking.

## 1. Introduction

Ambient air pollution is the leading environmental risk factor for death and disease worldwide, accounting for more than eight million deaths every year (Health Effects Institute, 2024; Brauer et al., 2024). While the adverse health effects of air pollution, particularly in the form of particulate matter (PM) < 2.5 μm in diameter ($PM_{2.5}$), are well-documented (United States Environmental Protection Agency (US EPA), 2019; European Environment Agency, 2020; World Health Organization, 2021), ultrafine particles (UFP) may be more relevant to health. Their small diameter of <0.1 μm allows them to penetrate deep into the lungs, enter the blood stream, and reach other organs including the brain (Schraufnagel, 2020). Furthermore, their increased toxicity is related to their large surface-area to mass ratio and increased surface reactivity, allowing them to carry large amounts of potentially toxic materials per unit mass (Kwon et al., 2020). They have been shown to

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https://doi.org/10.1016/j.envres.2025.122780
Received 9 May 2025; Received in revised form 31 July 2025; Accepted 5 September 2025
Available online 10 September 2025

cause systemic inflammation and oxidative stress, which in turn can cause cardiovascular and respiratory diseases (Schraufnagel, 2020; Leikauf et al., 2020). Unlike $PM_{2.5}$, which is routinely monitored and regulated, there are no specific ambient air quality standards or guidelines for UFP, and regulatory agencies do not commonly measure them. Furthermore, UFP vary highly in space and time, complicating exposure assessment. Particles in the ultrafine range contribute little to the mass of particles, but are the dominant contributors to particle number (Hofman et al., 2016); hence, total particle number concentration (PNC) is commonly used as a proxy for UFP. The number of epidemiological studies on the health effects of UFP is growing, yet it remains relatively limited. Recognizing this, the World Health Organization (WHO) provided a "Good Practice Statement" for UFP in their latest Air Quality Guidelines geared towards additional monitoring, mitigation, and epidemiological research (World Health Organization, 2021).

Three previous reviews have evaluated studies on the health effects of UFP. First, a 2013 narrative review by the Health Effects Institute (HEI) examined 75 studies published between 1997 and 2011 on short-term health effects of UFP and reported that the available evidence was too limited and inconsistent to confirm adverse health effects of UFP independent of $PM_{2.5}$ (HEI Review Panel on Ultrafine Particles, 2013). Second, a systematic review and meta-analysis by Atkinson et al., 2015) identified twelve studies on short-term UFP concentrations and mortality or hospital admissions published up to 2013 (Atkinson et al., 2015). Third, a systematic review by Ohlwein et al., 2019), which was a follow-up to the HEI 2013 review, found an additional 75 studies on short-term UFP concentrations and health that were published since the HEI review and corroborated earlier conclusions (Ohlwein et al., 2019). All reviews found large heterogeneity in exposure assessment methods regarding particles size ranges and instrumentation, as well as differences in the analysis of lagged exposures periods and co-pollutant adjustment (HEI Review Panel on Ultrafine Particles, 2013; Ohlwein et al., 2019). The only available meta-analysis on short-term UFP concentrations and mortality by Atkinson et al. (2015) grouped various exposure lags and size fractions and found positive, yet non-significant, associations for natural, cardiovascular, and respiratory mortality (Atkinson et al., 2015).

There has been an increase in the available evidence on the association between short-term UFP concentrations and health outcomes since the 2019 review. To update this, we conducted a systematic review and meta-analysis on the associations of short-term concentrations of UFP with natural, cardiovascular, and respiratory mortality, examining the effects of different exposure lags, size fractions, and adjustment for co-pollutants.

## 2. METHODS

This study is part of a comprehensive systematic review on the effects of both long-term and short-term concentrations of UFP and $PM_1$ ($PM < 1$ μm) on various pre-clinical, morbidity and mortality outcomes. We conducted our systematic review in line with a PROSPERO protocol (CRD42022348060), which is accessible online and was amended to extend the inclusion period to December 2024. In this paper, we focused only on the association of short-term concentrations of UFP and natural, cardiovascular, and respiratory mortality. Other outcomes and long-term exposures will be reported in separate manuscripts.

### *2.1. Studies from a previous report*

Besides the studies included in the current systematic review and meta-analysis, which covered the years 2011–2024, we additionally included the studies identified in a previous review by the HEI in 2013 (HEI Review Panel on Ultrafine Particles, 2013). The HEI review's authors searched PubMed and Web of Science for studies published through December 2011. It was planned a priori to combine studies from their and our review. We therefore harmonized our search strategy with the HEI search strategy, inclusion and exclusion criteria, and harmonized the information extracted from each study. For the current review, we selected all studies from the HEI review that focused on short-term concentrations and natural, cardiovascular, or respiratory mortality. Duplicate studies from the overlapping search period were removed.

### *2.2. Development of PECOS question*

We developed the following PECOS (Population, Exposure, Comparator, Outcome and Study) (Higgins et al., 2024) question to form the basis of our literature search: "In the general population or in population subgroups, including pre-diseased or diseased subjects (P), what is the increase in risk of health effects (O) per unit increase (C) of short- or long-term exposure to UFP (E), observed in epidemiological studies (S)?" Inclusion and exclusion criteria for each PECOS domain are presented in Table S1.

### *2.3. Search strategy*

We systematically searched the databases PubMed and LUDOK (the Swiss literature database on air pollution and health) (Kutlar and Probst-Hensch, 2023) for epidemiological studies investigating the health effects of UFP published between January 01, 2011 and December 31, 2024. We did not include other databases such as the Web of Science (WoS) since LUDOK covers the WoS journals relevant to our search. Additionally, a 2017 search on WoS yielded no information beyond what was found through PubMed.

The search consisted of three different concepts, operationalized with multiple synonyms and combined with the operators "AND" and "OR": 1) ambient air pollution, 2) ultrafine particles, 3a) health and epidemiology, and 3b) specific disease-related keywords (clinical and pre-clinical). The final combination was a combination of the three concepts (see Supplementary Material for further details).

Results are reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Page et al., 2021).

### *2.4. Study eligibility criteria*

Studies for the comprehensive review were eligible if they met the following criteria: 1) original epidemiological study adopting a cohort, cross-sectional, case-control, time-series, panel, case-crossover, crossover or scripted exposure design; 2) reported on the general population or on sub-populations, including pre-diseased or diseased subjects, of all ages, with no geographical restrictions; 3) assessed one of the following proxies of UFP: PNC or size-fractioned PNC for particles $<100$ nm, nucleation-mode particles, and Aitken-mode particles, or containing at least one quasi-UFP effect measure: PNC $<3000$ nm, $PM_{0.25}$, $PM_{0.1}$, lung deposited surface-area concentration (LDSA), $PM_1$, or accumulation mode particles; 4) defined health outcomes as morbidity or mortality of ICD-coded diseases (e.g., data from emergency/hospital admissions or visits) as well as pre-clinical conditions (e.g., blood pressure, lung function, or inflammation markers data); 5) quantifiable measures of association between exposure-outcome pair (odds ratio, risk ratio, relative risk, hazard ratio, or β-estimates of percent change); 6) written in English or German.

We applied the following exclusion criteria, eliminating studies reporting on: 1) exposure to industrially engineered nanoparticles, exclusively indoor environments, occupational settings or restricted to diesel particles, black carbon (BC) or elemental carbon (EC) only; 2) distance measures in substitution of exposure measurements; 3) health outcomes of unclear clinical health relevance, (e.g., epigenetics, metabolomics, methylation); 4) non-human studies (in vivo, in vitro), toxicological and controlled exposure studies, and 5) methodological papers.

### 2.5. Screening and data extraction

We imported all articles into EndNote 20 (Philadelphia, PA), removed duplicates and screened the abstracts and titles. We organized the articles into 'included' and 'excluded' using different bins: reviews, occupational, industrial or other sources of UFP, no appropriate UFP measures, unclear clinical outcomes, non-human or animal studies, toxicological, methodological, ecological studies, or other studies. The initial screening was conducted by PH and HJ, who divided the articles between themselves and simultaneously checked 10 % of the articles screened by their counterpart. A third study author (BH) was consulted to resolve any differences in the two screeners' assessments. A second screening involved full-text screening and separating studies into short-term (i.e., one day to several days) versus long-term (i.e., months to years) exposures. In a Microsoft Access questionnaire and database, information on study design, population, exposure and outcome assessment, and effect estimates was extracted for each study. In the last step, for the current study, we selected those studies focusing on natural (i.e., all natural causes of death, excluding accidental deaths and suicides; ICD-10 codes A00-R99), cardiovascular (ICD-10: I00-I99), or respiratory (ICD-10: J00-J99) mortality.

### 2.6. Meta-analysis

We conducted a meta-analysis of studies identified in our systematic review when at least four estimates were available for a specific exposure (lag)-outcome pair. We applied further selection criteria adapted from a previous meta-analysis on UFP and respiratory morbidity (Samoli et al., 2020). First, we only included studies that presented associations for particles covering at least the 20–100 nm size range. If multiple size ranges were reported, we selected the one closest to 10–100 nm. Second, if the same city was included in several studies reporting the same lags, we chose the one with the longest study period, to assure independent study populations necessary for meta-analysis. If two study periods in the same city overlapped by no more than one year, we included both studies. In the case of multi-city studies, we used the available single-city estimates (or contacted the corresponding authors to obtain them) rather than summary estimates. For comparability of estimates, we converted all estimates to beta-estimates associated with a one-unit increase (one particle (pt)/$cm^3$) in exposure. Odds ratios were considered equivalent to relative risks (RRs) due to the rarity of the outcome. Next, we conducted a random-effects meta-analysis on single-pollutant, city-specific estimates using the restricted maximum likelihood (REML) method. Summary and individual study estimates were presented in forest plots as RRs per 10,000 pt/$cm^3$ increase in exposure. Statistical heterogeneity was assessed through prediction intervals and $I^2$-statistics. For interpretation of the $I^2$-statistics, we classified values below 50 % as indicating low heterogeneity, 50–75 % as moderate heterogeneity, and above 75 % as high heterogeneity. Results were presented as RR and corresponding 95 % confidence intervals (CI) of natural, cardiovascular, and respiratory mortality associated with each 10,000 pt/$cm^3$ increase in UFP.

We explored several subset analyses to investigate potential sources of heterogeneity. Related to particle size, these included: 1) restricting our analyses to studies with an upper size limit ≤100 nm, to include only particle counts in the formal ultrafine range; 2) restricting our analyses to studies with a lower size limit ≤15 nm, as the lower limit is particularly critical in UFP measurements; 3) analysing different size ranges of UFP (10–30, 30–50, or 50–100 nm) broadly representing different sources (Ma and Birmili, 2015). Additionally, to account for the variety in presented cumulative exposure lags (moving averages), we performed a meta-analysis of studies grouped by comparable cumulative lags. Specifically, we identified 'shorter' (averaging periods of a maximum of two days directly before the outcome), 'medium' (averaging periods of three to four days before the outcome), and 'longer' (averaging periods of a minimum of five days before the outcome) cumulative lags. Furthermore, we stratified studies based on the mean exposure level in a city during their respective study periods, defined as below and above 10,000 particles (pt)/$cm^3$, which is a typical level observed in urban background locations (World Health Organization, 2021). Next, we assessed the available estimates for effect modification by season (warm versus cold months). Lastly, we assessed the available estimates from selected multi-pollutant models (specifically $PM_{2.5}$ and $NO_2$) and compared those to the estimates from single-pollutant models.

Sensitivity analyses involved excluding city-specific estimates that contributed most of the weight. Furthermore, in addition to our main analysis, where we used only one estimate for each city, we conducted an analysis where we included all studies with available estimates for a specific exposure-outcome pair, including multiple studies from the same city, and added 'city' as a random effect to the model.

One individual study presented separate results for urban background and traffic-site UFP (Schwarz et al., 2023). Here, we used urban background estimates, as these were more comparable to the other studies. As this study provided within-city results using two urban background stations for Leipzig (Germany), we applied a fixed-effects meta-analysis first to obtain a single city-specific estimate, which was then included in the meta-analysis.

Publication bias was assessed by means of funnel plots and Egger's regression tests. Statistical analyses were done in R (version 4.3.3) (R Core Team, 2024) using the '*metafor*' package (Viechtbauer, 2010).

### 2.7. Risk of bias assessment

Four authors (PH, HJ, RK, and MB) conducted a risk of bias assessment independently, using the Quality Assessment Tool for Observational Cohort, Cross-sectional Studies and Case-control studies (National Heart et al., 2021), adapted as in Ohlwein et al., 2019) (Ohlwein et al., 2019). This critical appraisal tool evaluates the potential for selection bias, information bias, or confounding (see Supplementary Material for further details). Each reviewer checked 10 % of the articles assessed by their counterpart. Another study author (BH) was consulted to resolve any differences in two authors' assessments.

### 2.8. Assessment of the confidence in the body of evidence

We applied the Office of Health Assessment and Translation (OHAT) method to rate the confidence of the association by considering the strengths and weaknesses in the body of evidence (Office of Health Assessment and Translation, 2019), adapted as in a 2022 HEI review (Health Effects Institute, 2022). Two authors (MB and BH) conducted this assessment, rating the body of evidence as 'very low', 'low', 'moderate', or 'high'.

## 3. Results

### 3.1. Description of included studies

We identified 152 studies on short-term exposure to UFP and any health outcomes, meeting our inclusion and exclusion criteria, published between January 01, 2011 and December 31, 2024 (Fig. S1), adding to 75 studies from the previous HEI review. Focusing on mortality, we included a final number of 21 studies (13 from the current review and 8 from the HEI review), and specifically 17 on natural, 17 on cardiovascular, and 15 on respiratory mortality.

Table 1 presents the included studies and their characteristics (see Table S2 for a summary of study characteristics). Of the 21 included studies, the majority were from Western/Southern Europe (n = 15), five were from Asia, and one from Eastern Europe. Most studies applied a time series design, and a single study applied a case-crossover design. Three studies included selected age groups, while the remaining studies included the general population. No studies in patient populations were included. All studies assigned their exposure as PNC, based on central

**Table 1**
Description of the 21 included studies on short-term exposure to UFP and natural, cardiovascular and respiratory mortality.

| Reference | Location | Mortality outcomes | Study design | Study population | Study period | Particle size range (nm)[a] | Exposure assignment | Monitoring instrument | Station height (m) | UFP concentration mean ± SD[b] (pt/cm$^3$) | Pollutants in multi-pollutant models | Analysis of lag days[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atkinson et al., 2010 | London, UK | Natural, Cvd, Rsp | Time series | General | 2000–2005 | **>10** | Central (urban background) | TSI 3022A CPC | 5 | Median: 18,769 (IQR: 10,456) | $PM_{2.5}$ | **0, 1, 2, 3, 4, 5** |
| Bergmann et al., 2023 | Copenhagen, Denmark | Natural, Cvd, Rsp | Case-crossover | >30 | 2002–2018 | **11–110**, 11-700 | Central (urban background) | DMPS | 20 | 5021 ± 2600 | $PM_{2.5}$, $NO_2$ | **0, 1, 2, 3, 4, 5, 6, 0–1, 0–2, 0–3, 0–4, 0–5, 0–6** |
| Braniš et al., 2010) | Prague, Czech Republic | Natural, Cvd, Rsp | Time series | General | 2006 | **15–487,** 15–50, 50-200 | Central (urban background) | TSI 3936L25 SMPS | 25 | 9697 (IQR: 5603) | / | **0, 1, 2, 0–3, 0–6** |
| Breitner et al., 2009 | Erfurt, Germany | Natural | Time series | General | 1995–2002 | **10–100,** 10–30, 30–50, 50-100 | Central (urban background) | MAS | 4 | 12,910 ± 8685 | CO, $NO_2$, $PM_{2.5}$, $PM_{10}$ | **0–5, 0–14** |
| Breitner et al., 2011 | Beijing, China | Cvd | Time series | General | 2004–2005 | 3-30, 30–100, **3–800** | Central (urban background) | Twin DMPS | 20 | Median: 33,500 (IQR: 13,790) | Selected PNC size fractions | **0, 1, 2, 3, 0–4** |
| Halonen et al., 2009 | Helsinki, Finland | Cvd, Rsp | Time series | >65 | 1998–2004 | **30–100**, 8–30, 100-290 | Central (urban background) | DMPS | 30 | Median: 3628 (IQR: 2467) | / | 0, 1, 2, 0-4 |
| Hennig et al., 2018 | Ruhr area, Germany | Natural, Cvd, Rsp | Time series | General | 2009–2014 | **13–100,** 13–30, 30–50, 50–100, 100–250, 250–500, 500-750 | Central (urban background) | SMPS | 4 | Median: 9871 ± 4900 | $NO_2$, $PM_{10}$, $O_3$ | **0, 1, 2, 3, 4, 5, 6, 7, 0–1,** 2–3, 4-7 |
| Lanzinger et al., 2016 | Augsburg and Dresden, Germany; Prague, Czech Republic; Ljubljana, Slovenia; Chernivtsi, Ukraine | Natural, Cvd, Rsp | Time series | General | Augsburg, Dresden: 2011–2012, Ljubljana, Prague: 2012–2013, Chernivtsi: 2013–2014 | **20–100**, 20-800 | Central (sub-/urban background) | DMPS/SMPS | N/A | Augsburg: 5880 ± 3,016, Dresden: 4286 ± 2,338, Prague: 4197 ± 2,010, Ljubljana:4693 ± 1,896, Chernivtsi: 5511 ± 2614 | $PM_{2.5}$, $NO_2$ | **0, 1, 2,** 3, 4, 5, **0–1, 0–5, 2–5** |
| Leitte et al., 2012 | Beijing, China | Rsp | Time series | >20 | 2004–2005 | Total PNC, 3–10, **3–100**, 10–30, 30–50, 50–100, 100–300, 300-1000 | Central (urban background) | Twin DMPS | 20 | 27,000 ± 10,000 | $SO_2$, $NO_2$, $PM_{10}$ | **0, 1, 2, 3, 0–3, 0–4** |
| Meng et al., 2013 | Chenyang, China | Natural, Cvd, Rsp | Time series | General | 2006–2008 | 250–1000 | Central (urban background) | Ambient Dust Monitor 365 | 10 | 11,000 ± 400 | $NO_2$, $PM_{2.5}$, $PM_{10}$, $SO_2$ | 0–1 |
| Olstrup et al., 2019 | Stockholm, Sweden | Natural | Time series | General | 2000–2016 | **>4** | Central (urban background) | TSI 3752/3022 CPC | 20 | 9177 (IQR: 5354) | $PM_{2.5}$, BC, $NO_2$, $O_3$ | **1, 2** |
| Park et al., 2022 | Seoul, South Korea | Natural, Cvd, Rsp | Time series | General | 2013–2016 | 10-30, 30–50, 50–100, 100–200, 200–300, 300-478 | Central (urban residential) | SMPS | N/A | 50–100 nm: 1558 (IQR: 1194) | / | 0, 1, 2, 3, 4, 5, 0–1, 0-5 |
| Peters et al., 2009 | Erfurt, Germany | Natural, Cvd | Time series | General | 1995–2002 | **10–100**, 10–30, 30–50, 50-100 | Central (urban background) | MAS | 4 | 12,910 ± 8685 | $NO_2$, CO, $O_3$ | **0, 1, 2, 3, 4, 5** |
| Rivas et al., 2021 | Barcelona, Spain; Helsinki, | Natural, Cvd, Rsp | Time series | General | Barcelona: 2013–2016, | Barcelona: **11–478**, Helsinki: **6–700**, | Central (urban background) | DMPS/SMPS | N/A | Barcelona: 11,371 ± 4,049, Helsinki: | $NO_2$, $O_3$ | **0, 1, 2,** 3, 4, 5 |

(*continued on next page*)

**Table 1** (*continued*)

| Reference | Location | Mortality outcomes | Study design | Study population | Study period | Particle size range (nm)[a] | Exposure assignment | Monitoring instrument | Station height (m) | UFP concentration mean ± SD[b] (pt/cm$^3$) | Pollutants in multi-pollutant models | Analysis of lag days[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Finland; London, UK; Zurich, Switzerland | | | | Helsinki: 2009–2016, London: 2010–2016, Zurich: 2011–2014 | London: **17–649**, Zurich: **10–487** | | | | 7006 ± 3,689, London: 5562 ± 2,409, Zurich: 9491 ± 4054 | | |
| Samoli et al., 2016 | London, UK | Natural, Cvd, Rsp | Time series | General | 2011–2012 | **10–600** | Central (urban background) | TSI 3022 CPC | 5 | Median: 12,124 (IQR: 5180) | PNC sources: urban background, nucleation, secondary, traffic | 1 (natural and cvd), 2 (rsp) |
| Schwarz et al., 2023 | Dresden, Leipzig, Augsburg, Germany | Natural, Cvd, Rsp | Time series | General | 2010–2017 | 10-800, **10–100,** 10–30, 30–100, 100-800 | Central (urban background and traffic) | MPSS | N/A | Median (IQR)[d]: Dresden: 4791 (3156), Leipzig: 4520/4838 (3003/3154), Augsburg: 5655 (3514) | $NO_2$, $NO_x$, $PM_{2.5}$, BC | **0–1, 0–7, 2–4, 5–7** |
| Stafoggia et al., 2017 | Helsinki, Finland; Stockholm, Sweden; Copenhagen, Denmark; Ruhr area, Germany; Augsburg, Germany; Rome, Italy; Barcelona, Spain; Athens, Greece | Natural, Cvd, Rsp | Time series | General | Helsinki, Stockholm, Copenhagen, Rome: 2001–2010, Ruhr area: 2009–2014, Augsburg: 1999–2009, Barcelona: 2005–2010, Athens: 2008–2010 | Athens, Copenhagen, Helsinki: **0–100**, Barcelona: **5–1000**, Ruhr Area: **14–750**, Rome, Augsburg: **7–3000/10–2000**, Stockholm: **4–3000/7–3000** | Central (urban background, traffic in Rome) | SMPS/CPC/Twin DMPS/Water-based CPC/DMPS | Helsinki: 4/18, Stockholm: 20/24, Copenhagen: 20, Ruhr area: 4, Augsburg: 2/4, Rome: 2, Barcelona: 2/10, Athens: 10 | Helsinki: 7951 ± 4,912, Stockholm: 9128 ± 4,320, Copenhagen: 5105 ± 2,563, Ruhr area: 10,303 ± 3,902, Augsburg: 11,158 ± 5,617, Rome: 34,046 ± 20,164, Barcelona: 19,554 ± 8,044, Athens: 6917 ± 4878 | $PM_{2.5}$, $PM_{10}$, $NO_2$ | **0, 1, 2, 3, 4, 5, 6,** 7, 8, 9, 10 |
| Stölzel et al., 2007 | Erfurt, Germany | Natural, Cvd-Rsp (combined) | Time series | General | 1995–2001 | **10–100,** 10–30, 30–50, 50-100 | Central (urban background) | MAS | 4 | Median: 8203 (IQR: 5760) | NO, $NO_2$, CO | 0, 1, 2, 3, 4, 5 |
| Su et al., 2015 | Beijing, China | Cvd | Time series | General | 2008 | 3-10, 10–30, 30–50, 50–100, **3–100** | Central (urban background) | Twin DMPS | 20 | 14,331 ± 5611 | $PM_{2.5}$, $NO_2$ | **0, 1,** 2, 3, 4, **0–4** |
| Tobías et al., 2018 | Barcelona, Huelva, Santa Cruz de Tenerife, Spain | Natural | Time series | General | Barcelona: 2009–2014, Huelva: 2008–2010, Santa Cruz: 2008–2012 | Barcelona:**5–1000**, Huelva and Santa Cruz: **2.5–1000** | Central (Barcelona and Santa Cruz: urban background, Huelva: urban industrial) | Water-based CPC 3785/CPC 3776 | Barcelona: N/A, Huelva: 10, Santa Cruz: 45 | Barcelona: 12,608 ± 5,089, Huelva: 16,752 ± 12,787, Santa Cruz: 14,151 ± 9131 | / | **0, 1, 2** |
| Wichmann et al., 2000 | Erfurt, Germany | Natural, Cvd, Rsp | Time series | General | 1995–1998 | **10–100,** 10–30, 30–50, 50–100, 100-250 | Central (urban background) | MAS | 4 | 15,773 ± 10,321 | CO, $NO_2$, $SO_2$, $PM_{2.5}$ | 4, **0–4** |

Abbreviations: CO, carbon monoxide; CPC, Condensation Particle Counter; Cvd, cardiovascular; DMPS, Differential Mobility Particle Sizer; MAS, Mobile Aerosol Spectrometer; MPSS, Mobility Particle Size Spectrometer; $NO_2$, nitrogen dioxide, $O_3$, ozone; $PM_{2.5}$, particulate matter $<2.5$ μm; $PM_{10}$, particulate matter $<10$ μm; PNC, particle number concentration; pt/cm$^3$, particles per square centimeter; Rsp, respiratory; SD, standard deviation; SMPS, Scanning Mobility Particle Sizer; $SO_2$, sulphur dioxide.

[a] The bolded metric is the one closest to the definition used in our meta-analysis.

[b] Indicating the daily mean particle number concentration of the bolded particle fraction, presented as particles per cm$^3$.

[c] Only bolded lags were presented in study results/obtained for our main meta-analysis.

[d] Urban background concentrations are presented here.

monitoring reflecting urban background concentrations. Two studies additionally considered street-level concentrations. Of these, one study conducted their analysis for Rome (Italy) based on a monitoring site close to traffic (Stafoggia et al., 2017), and the other study analysed multiple sites per city (street-level and background) separately (Schwarz et al., 2023). Mean exposure levels of PNC were lower than 10,000 pt/cm$^3$ in 23 cities and higher in 16 cities and respective study periods. The higher exposures were mostly observed in locations in Southern Europe, in Beijing (China), London (UK), and in earlier studies prior to 2010 (Table 1). The covered particle size fractions ranged from lower cut-offs of 3–250 nm, 79 % of which were below 15 nm, to upper cut-offs around 100 nm (n = 13) or to higher upper cut-offs >400 nm (n = 12). Some studies presented results for multiple size fractions, including particles in the size ranges 10–30 nm or 30/50–100 nm. Heterogeneity was observed in the instruments used for UFP exposure assessment (see Table S3 for an overview of instruments and size ranges) and in the height of monitoring stations, which ranged between 4 and 45 m above ground level. More than half of the studies adjusted their results for either $PM_{2.5}$ or $NO_2$ (some for both), and some adjusted for other pollutants. Most studies reported results for same-day UFP (lag 0) or single lags of one or two days (lag 1 or lag 2), and fewer studies applied single lags between three or six days or cumulative lags of two days (lag 0–1) or more (Table 1).

### 3.2. Main meta-analysis results

Of the 21 studies, 16 studies entered the main meta-analyses. We included 5 to 16 estimates in the main meta-analyses depending on the outcome and time lag (Table 2). A few studies (n = 5) were not included in the main meta-analysis, as they used particle size fractions outside our defined range of ≤20 nm to ≥100 nm (Park et al., 2022; Halonen et al., 2009; Meng et al., 2013) or as the same city was included in other studies with longer study periods that were overlapping (assessed for each lag-outcome pair separately) (Samoli et al., 2016; Stölzel et al., 2007). Five studies combined results from multiple cities, where we retrieved the estimated single-city estimates and used them in the main analysis, if those cities were not used in other studies with the same lags and longer periods (Schwarz et al., 2023; Stafoggia et al., 2017; Lanzinger et al., 2016; Rivas et al., 2021; Tobías et al., 2018). For one study, single-city estimates were only available for selected exposure-outcome pairs (Lanzinger et al., 2016).

Fig. 1 shows a forest plot of the main random-effects meta-analysis for the association between 10,000 pt/cm$^3$ increases in UFP (lag 0) and mortality. We chose to present these for lag 0, as this had the most available estimates, while other lag results are presented in Table 2 and Fig. 2. Summary estimates of relative risks at lag 0 were 1.000 (95 % CI: 0.993, 1.007) for natural mortality, 0.996 (95 % CI: 0.990, 1.002) for cardiovascular mortality, and 1.005 (95 % CI: 0.979, 1.032) for respiratory mortality based on 14, 16, and 15 estimates, respectively. At a lag of six days, we found a small increase in natural mortality associated with a 10,000 pt/cm$^3$ increase in UFP (RR: 1.004 [95 % CI: 1.000, 1.008]) based on seven estimates (Table 2 and Fig. 2). Similarly, at lag 6, we found an elevated, but non-significant, point estimate for respiratory mortality (RR: 1.020 [95 % CI: 0.988, 1.052]) based on eight estimates. For all other single day lag-outcome combinations, results were close to null and non-significant. At lag 0, there was low to moderate heterogeneity between studies ($I^2$ of 43 %, 0 %, and 64 % for natural, cardiovascular, and respiratory mortality, respectively). Similar $I^2$-values were observed for the other exposure-outcome pairs expect for a moderate $I^2$ of 69 % for natural mortality at lag 4 and $I^2$ of 64 % for respiratory mortality at lag 3 (Table 2). An analysis of funnel plots (Fig. S2) and Egger's test showed no indication of publication bias.

### 3.3. Assessment of the risk of bias

Overall, risk of bias was very low or low for the majority of the studies (Table 3). Four studies (Stafoggia et al., 2017; Lanzinger et al., 2016; Rivas et al., 2021; Tobías et al., 2018) ranked as medium risk of bias due to the inclusion of study populations from different populations and different study periods, owing to the multi-city design they all used. Seven studies were ranked as medium risk of bias because their sample was not representative of the general population, mainly due to the focus on selected age groups (Stafoggia et al., 2017; Park et al., 2022; Halonen et al., 2009; Rivas et al., 2021; Bergmann et al., 2023; Hennig et al., 2018; Olstrup et al., 2019). Four studies (Stafoggia et al., 2017; Halonen et al., 2009; Lanzinger et al., 2016; Hennig et al., 2018) were rated as having a medium risk of bias due potential issues with exposure assessment arising from the use of traffic stations, change of station location during the study period, or the use of one station for several cities. Two studies (Meng et al., 2013; Olstrup et al., 2019) ranked medium in adequate confounder adjustment, as they did not adjust for public holidays.

### 3.4. Assessment of the confidence in the body of evidence

We rated the initial confidence in the body of evidence as low (Table 4). For risk of bias, inconsistency, or publication bias, no downgrade was applied. For imprecision, a sample size criterion of at least 100,000 mortality cases in the pooled analysis (Orellano et al., 2020) was met, the CIs were wide and overlapped unity, and a downgrade of one was applied. Among the upgrading factors, exposure-response functions were assessed in only four studies (Schwarz et al., 2023; Bergmann et al., 2023; Peters et al., 2009; Wichmann et al., 2000), with inconclusive findings, so no upgrade was applied. Regarding residual confounding, most estimates were close to the null either above or below one, with wide confidence intervals. It is unlikely that residual confounders acted in a way to systematically bias the estimates to the null in most of the studies. Therefore, no upgrade was applied. The results were consistent across several mortality outcomes and exposure periods and we applied an upgrade for consistency. The final confidence assessment yielded a rating of low confidence in the body of evidence, which means that the true effect may be different from the apparent relationship. Given the fact that the meta-analysis did not yield positive associations and that the level of confidence in the body of evidence is low, we conclude that currently there is insufficient evidence available to assess if short-term exposure to UFP is associated with mortality.

### 3.5. Additional meta-analyses

In our additional analyses related to particle size, we found similar results when only including those studies that used a UFP definition of particles below 100 nm (Table S4). Furthermore, results were similar when restricting to those studies with a lower size cut-off below 15 nm (Table S4). Too few studies reported results for smaller particle size fractions, such as 10–30 nm, 30–50 nm, or 50–100 nm, precluding a meta-analysis on specific size fractions.

When studies were grouped based on cumulative lag periods, summary estimates of RR were lowest at the shorter lags for all three outcomes. Highest associations were found at longer lags for natural (RR: 1.023 [95 % CI: 0.994, 1.052]) and respiratory mortality (RR: 1.091 [95 % CI: 0.914, 1.303]), and at medium lags for cardiovascular mortality (RR: 1.037 [95 % CI: 1.004, 1.072]) (Table S5 and Fig. S3). Significant associations were also detected for respiratory mortality at medium lags (RR: 1.061 [95 % CI: 1.011, 1.113]).

Further subset analyses included grouping studies below and above 10,000 particles/cm$^3$ mean UFP, which revealed slightly higher associations with natural and cardiovascular mortality in higher-exposure settings (RR: 1.008 [95 % CI: 1.000, 1.016] and 1.015 [0.995, 1.035], respectively) than in low-exposure settings (RR: 0.992 [95 % CI: 0.983, 1.002] and 0.988 [0.973, 1.004], respectively) at lag 1 (Table S6 and Fig. S4). Lastly, some studies assessed effect modification by season. A meta-analysis of these was not possible due to small numbers, and

**Table 2**
Random-effects meta-analysis of natural, cardiovascular, and respiratory mortality associated with each 10,000 pt/cm$^3$ increase in UFP at different lag days for particle diameters ranging from ≤20 nm to ≥100 nm.

| Outcome | Lag | RR (95 % CI) | p | Number of studies | Number of estimates | $I^2$ (%) | Q-test p |
|---|---|---|---|---|---|---|---|
| Natural | 0 | 1.000 (0.993, 1.007) | 0.969 | 8 | 14 | 43 | 0.16 |
| | 1 | 1.003 (0.998, 1.008) | 0.290 | 9 | 15 | 21 | 0.27 |
| | 2 | 1.001 (0.998, 1.005) | 0.489 | 9 | 15 | 2 | 0.41 |
| | 3 | 1.003 (0.999, 1.007) | 0.112 | 5 | 9 | 0 | 0.39 |
| | 4 | 1.004 (0.994, 1.014) | 0.432 | 5 | 9 | 69 | 0.19 |
| | 5 | 1.002 (0.996, 1.008) | 0.590 | 5 | 9 | 31 | 0.53 |
| | 6 | 1.004 (1.000, 1.008) | 0.090 | 3 | 7 | 0 | 0.65 |
| | 0–1 | 0.986 (0.965, 1.008) | 0.200 | 3 | 5 | 0 | 0.90 |
| Cardiovascular | 0 | 0.996 (0.990, 1.002) | 0.149 | 10 | 16 | 0 | 0.46 |
| | 1 | 1.003 (0.992, 1.014) | 0.584 | 9 | 15 | 43 | 0.02 |
| | 2 | 1.002 (0.995, 1.009) | 0.594 | 8 | 14 | 9 | 0.10 |
| | 3 | 1.002 (0.994, 1.009) | 0.695 | 5 | 10 | 16 | 0.32 |
| | 4 | 1.003 (0.994, 1.012) | 0.553 | 6 | 11 | 25 | 0.27 |
| | 5 | 0.998 (0.989, 1.007) | 0.621 | 4 | 9 | 23 | 0.57 |
| | 6 | 1.002 (0.996, 1.008) | 0.452 | 3 | 8 | 0 | 0.92 |
| | 0–1 | 0.984 (0.939, 1.032) | 0.510 | 4 | 5 | 36 | 0.21 |
| Respiratory | 0 | 1.005 (0.979, 1.032) | 0.706 | 8 | 15 | 64 | 0.04 |
| | 1 | 1.006 (0.986, 1.013) | 0.531 | 7 | 14 | 38 | 0.38 |
| | 2 | 1.001 (0.989, 1.013) | 0.898 | 7 | 14 | 0 | 0.50 |
| | 3 | 0.993 (0.966, 1.021) | 0.614 | 5 | 10 | 64 | 0.07 |
| | 4 | 1.001 (0.989, 1.014) | 0.851 | 5 | 10 | 0 | 0.81 |
| | 5 | 0.998 (0.986, 1.011) | 0.784 | 4 | 9 | 0 | 0.62 |
| | 6 | 1.020 (0.988, 1.052) | 0.228 | 3 | 8 | 49 | 0.15 |
| | 0–1 | 1.030 (0.953, 1.114) | 0.456 | 3 | 5 | 0 | 0.43 |

Abbreviations: CI, confidence interval; $I^2$, result of $I^2$ test for heterogeneity; p, p-value; Q-test p, p-value of Q-test; RR, relative risk.

among the few studies that assessed the effects of season, we saw a mixed picture with four studies finding stronger associations in the warm season, two in the cold season, and two studies finding no differences between seasons.

Furthermore, we assessed multi-pollutant models, focusing on the effects of $PM_{2.5}$ and $NO_2$-adjustment. The number of studies per exposure-outcome pair was not sufficient to conduct meta-analysis. Instead, a qualitative description of the effects of co-pollutant adjustment is presented in Table S7, showing that most studies' results were robust to adjustment for $PM_{2.5}$ or $NO_2$, as far as adjusted estimates were presented.

In sensitivity analyses, we included all available studies, allowing for multiple studies per city, and included the study location as a random effect indicator in the meta-analysis. Results were similar to our main analysis, with no significant associations, but with a small increase in natural mortality associated with a 10,000 pt/cm$^3$ increase in UFP at lag 6 (RR: 1.004 [95 % CI: 1.000, 1.008]) based on ten studies (Table S8).

The main results were influenced by the Rome estimate (Stafoggia et al., 2017), as indicated by the weights in the forest plots. Specifically, the positive association with natural mortality at lag 6 attenuated when the estimate from Rome was excluded (RR: 1.001 [95 % CI: 0.992, 1.011]); the association with respiratory mortality at lag 6 became somewhat larger (RR: 1.024 [95 % CI: 0.984, 1.067]) (Table S9).

## 4. Discussion

We identified 21 studies on the association between short-term concentrations of UFP and natural, cardiovascular, or respiratory mortality, published up to December 2024. These studies showed heterogeneity in designs related to the included particle size fractions and the analysis of lagged exposure periods. Similarities were found in the statistical methods (time series), exposure assignment (central monitoring), and in geographical locations (mostly Europe). In our meta-analysis, we found non-significant associations close to null across most single day lags and mortality types. In subset analyses of grouped cumulative lag exposures, we observed stronger albeit non-significantly increased associations with natural and respiratory mortality at longer lags (i.e., averages of more than five days before outcome) and significant associations with cardiovascular and respiratory mortality at medium lags (i.e., averages of three to four days). We were not able to meta-analyse different size fractions or estimates from multi-pollutant models due to the limited number of studies reporting these. However, the results from the few multi-pollutant analyses remained largely unchanged upon inclusion of $PM_{2.5}$ or $NO_2$ in the models. Overall, we rated the confidence in the body of evidence as low, suggesting that the true effect may be different from the apparent relationship.

Our study is the first to find enough studies to conduct a meta-analysis on the association between short-term exposure to UFP and mortality, grouping estimates by exposure lags. Our findings confirm previous reviews' findings (HEI Review Panel on Ultrafine Particles, 2013; Ohlwein et al., 2019), concluding that the available evidence is still insufficient and heterogeneous.

The lack of clear and consistent associations between short-term exposure to UFP and mortality could be explained by several factors. First, it is possible that short-term UFP exposure truly has no effect on mortality. However, this contradicts toxicological and sub-clinical studies that suggest UFP are harmful to human health, potentially more so than larger particles, in their ability to cause oxidative stress and systemic inflammation (Schraufnagel, 2020; Clifford et al., 2018; Habre et al., 2018; Bliss et al., 2018). Beyond that, there are several methodological considerations that might explain our null findings. First, exposure misclassification resulting from the use of a single monitoring station in all but one study (Schwarz et al., 2023), to assign exposure to a whole population is an important limitation in studies on short-term exposure to UFP and mortality. Spatial variation is substantial for UFP, as concentrations closest to UFP sources can be magnitudes higher than background concentrations (Morawska et al., 2019). However, in the case of time series studies, the use of a single monitor has been suggested to be adequate for capturing day-to-day variation in UFP concentrations across an urban area. To support this, several studies have found moderate to high correlation of temporal patterns at different locations within the same city, such as in Amsterdam (the Netherlands), Antwerp (Belgium), and Leicester (UK) (Hofman et al., 2016), Augsburg (Germany) (Cyrys et al., 2008), Copenhagen (Denmark) (Bergmann et al., 2025), and Helsinki (Finland) (Buzorius et al., 1999). Nevertheless, this might not be true for all urban areas and should be carefully assessed in each study. While road traffic, the main source of inner-city exposure differences towards UFP in many urban

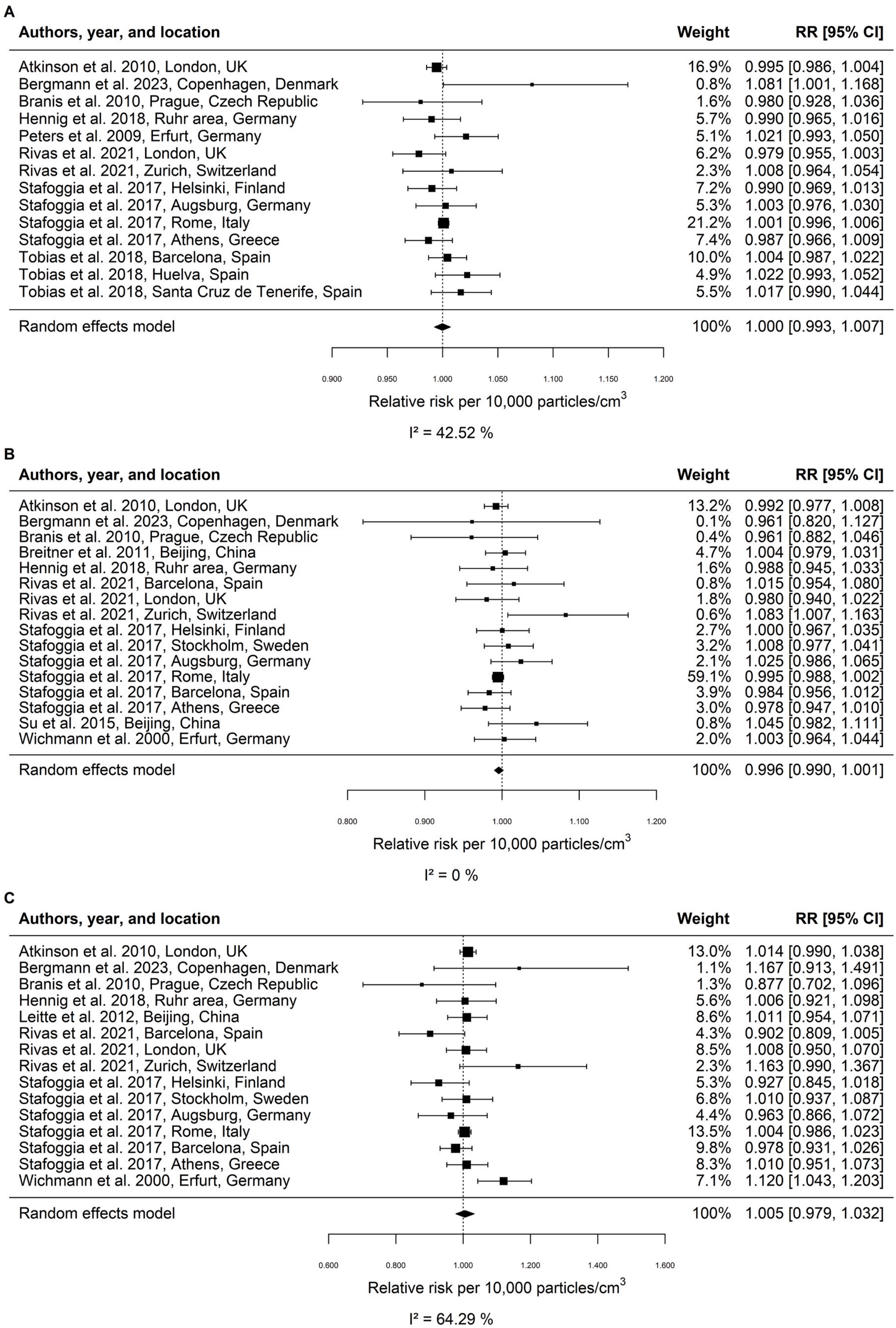


**Fig. 1.** Forest plots of random-effects meta-analyses showing individual study and summary estimate of relative risks and 95 % confidence intervals of (A) natural, (B) cardiovascular, and (C) respiratory mortality associated with each 10,000 pt/cm$^3$ increase in UFP at lag 0.

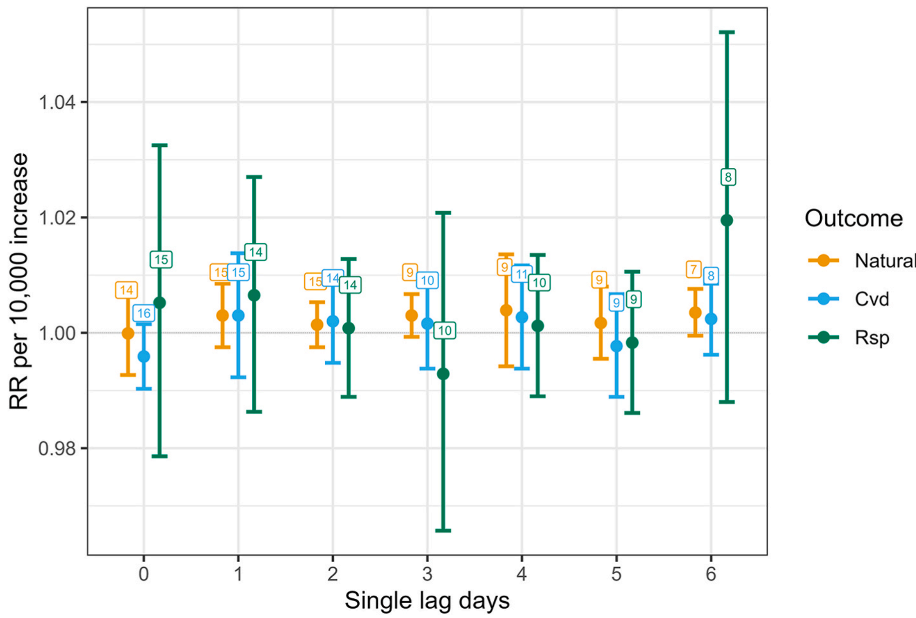


**Fig. 2.** Summary estimates of relative risks and 95 % confidence intervals from random-effects meta-analyses for natural, cardiovascular, and respiratory mortality associated with a 10,000 pt/cm$^3$ increase in UFP on the same day as the outcome (lag 0) and lagged up to six days (lag 6). The boxes indicate the number of estimates included in the meta-analysis. Abbreviations: Cvd, cardiovascular; RR, relative risk; Rsp, respiratory.

areas, usually follows clear diurnal patterns, other sources such as residential wood-burning, airports, or construction sites may play important roles in some areas and cannot necessarily be captured by single monitoring stations. As a promising opportunity for improving exposure accuracy, some recently developed spatio-temporal exposure models, such as chemical transport models using historical weather data (Yu and Luo, 2009; Hu et al., 2015; Nonnemacher et al., 2014), land-use regression models incorporating daily fixed-site or mobile measurements, (Kerckhoffs et al., 2021; Lloyd et al., 2023), hybrid models (Lloyd et al., 2021; Khan et al., 2019), or satellite-based predictions provide daily UFP concentrations at a fine spatial resolution across urban areas or entire countries. Paired with available information on study participants' residential address and its history (or mobility), these models can be applied in studies on the health effects of short-term exposure to UFP using, for example, case-crossover designs. Models providing data at a fine temporal resolution, such as hourly means, could be applied to capture local peak exposures, if the exact time of the health outcome is known, such as previously done for outcomes like myocardial infarction (Chen et al., 2020). A possible reason for the underutilisation of modelled exposure data in studies on short-term health effects of UFP may be that these studies typically rely on aggregated data of daily health event counts, whereas applying spatio-temporal models would require individual addresses of participants. Moreover, time-activity patterns are known to influence personal exposure, and most people spend 80 %–90 % of their time indoors (Schweizer et al., 2007). Lack of consideration of infiltration rates and time-activity adds to exposure measurement error, which is often assumed to bias the estimated ambient air pollution and health estimates toward the null, possibly explaining why studies have failed to show consistent short-term associations with mortality (Richmond-Bryant and Long, 2020; Goldman et al., 2011; Zeger et al., 2000). Future studies could incorporate models that combine spatio-temporal UFP concentrations with microscale personal exposures to model time-activity-adjusted exposure, such as done in some studies on long-term UFP exposure (Corlin et al., 2018; Lane et al., 2016; Li et al., 2017).

Next, we observed substantial variation in UFP monitoring, including the captured particle size fractions, station location and height, and instrumentation because standard methods to characterize UFP have not been established. This raises the question of how to capture UFP exposure best for use in health effect studies and whether we are currently measuring the most relevant UFP metric. Regarding size fractions, when comparing all studies with the studies applying an upper size limit of 100 nm, no qualitative differences were found. Capturing PNC without an upper size limit might therefore suffice for representing UFP (Hofman et al., 2016). In contrast, the lower size limit is usually critical because most UFP are less than 20 nm, and even small differences in the low cut-off point in the range below 20 nm can lead to substantial differences in PNC. Hence, there is more uncertainty in measuring the smallest particle fraction, and the lower particle cut-offs of different instruments vary considerably, typically ranging from 2 nm to 20 nm. The WHO recommends a lower cut-off of 10 nm, which was used in some, but not all the studies identified in this review. However, restricting studies to those with a lower cut-off below 15 nm (as there were not enough studies using 10 nm), did not yield different results in our meta-analysis. Notably, a variety of different instruments was used for UFP monitoring, each with distinct functioning and varying levels of uncertainty, especially in their ability to measure the smallest particle size fractions. The standardization of instruments for UFP monitoring would improve the comparability of different studies. The revised European Union Ambient Air Quality Directive, which was approved in the fall of 2024, will improve the harmonization and availability of measurements by including mandatory UFP monitoring in the EU and is a great step forward. Related to this, a recent report of the "Research Infrastructures Services Reinforcing Air Quality Monitoring Capacities in European Urban&Industrial AreaS" (RI-URBANS) EU-project provided valuable guidance for studies of the short-term health effects of UFP, including detailed descriptions of the required data and analytical considerations (Nogueira dos Santos et al., 2024). Preliminary results of this project indicate a significant positive association of UFP with natural mortality, robust to co-pollutant adjustment (Nogueira dos Santos et al., 2024). Notably, our meta-analysis included earlier studies from four of the seven European cities that were part of RI-URBANS.

Different size fractions of UFP reflect different sources, such as nucleation from precursor substances (Brines et al., 2015), aviation (Shirmohammadi et al., 2017), traffic (Moreno-Ríos et al., 2021), or wood-burning, and some of them may be of greater public health concern than others. Of the three studies that have used source apportionment methods to distinguish between different sources of UFP, one

**Table 3**
Risk of bias assessment. Green circles, yellow triangles, and red diamonds indicate responses of either 'yes', 'somewhat'/'not specified'/'partly', or 'no', respectively. In the 'Overall' column, green, yellow, and red circles indicate either 'low', 'medium', or 'high' risk of bias, respectively. The reasons for rating medium/high risk of bias are described in Section 3.2.

| Reference | Quality | | | | | Exposure | | Outcome | Confounding | Overall |
|---|---|---|---|---|---|---|---|---|---|---|
| | Was the research question or objective in this paper clearly stated? | Was the study population clearly specified and defined? | Is the analysed sample representative for the general population? | Were all the subjects selected or recruited from the same or similar populations? | Were all the subjects selected or recruited from the same time-period? | Were the exposure measures valid for the population? | Was the exposure assessment (independent variable) implemented consistently across all study participants? | Were the outcome measures (dependent variables) clearly defined and implemented consistently across all study participants? | Was the confounder adjustment adequate? | Did the study have an overall low risk of bias? |
| Atkinson et al., 2010 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Bergmann et al., 2023 | ● | ● | ▲ | ● | ● | ● | ● | ● | ● | ▲ |
| Braniš et al., 2010 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Breitner et al., 2009 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Breitner et al., 2011 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Halonen et al., 2009 | ● | ● | ▲ | ● | ● | ▲ | ● | ● | ● | ▲ |
| Hennig et al., 2018 | ● | ● | ▲ | ● | ● | ▲ | ● | ● | ● | ▲ |
| Lanzinger et al., 2016 | ● | ● | ● | ▲ | ▲ | ▲ | ● | ● | ● | ▲ |
| Leitte et al., 2012 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Meng et al., 2013 | ● | ● | ● | ● | ● | ● | ● | ● | ▲ | ▲ |
| Olstrup et al., 2019 | ● | ▲ | ▲ | ● | ● | ● | ● | ● | ▲ | ▲ |
| Park et al., 2022 | ● | ● | ▲ | ● | ● | ● | ● | ● | ● | ▲ |
| Peters et al., 2009 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Rivas et al., 2021 | ● | ● | ▲ | ▲ | ▲ | ● | ▲ | ● | ● | ▲ |
| Samoli et al., 2016 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Schwarz et al., 2023 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Stafoggia et al., 2017 | ● | ● | ▲ | ▲ | ▲ | ▲ | ● | ● | ● | ▲ |

(*continued on next page*)

**Table 3** (*continued*)

| Reference | Quality | | | | | Exposure | | Outcome | Confounding | Overall |
|---|---|---|---|---|---|---|---|---|---|---|
| | Was the research question or objective in this paper clearly stated? | Was the study population clearly specified and defined? | Is the analysed sample representative for the general population? | Were all the subjects selected or recruited from the same or similar populations? | Were all the subjects selected or recruited from the same time-period? | Were the exposure measures valid for the population? | Was the exposure assessment (independent variable) implemented consistently across all study participants? | Were the outcome measures (dependent variables) clearly defined and implemented consistently across all study participants? | Was the confounder adjustment adequate? | Did the study have an overall low risk of bias? |
| Stölzel et al., 2007 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Su et al., 2015 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Tobías et al., 2018 | ● | ● | ● | ▲ | ▲ | ● | ● | ● | ● | ▲ |
| Wichmann et al., 2000 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |

**Table 4**

Rating of the confidence in the body of evidence using the Office of Health Assessment and Translation (OHAT) method (Office of Health Assessment and Translation, 2019) adapted according to HEI review (Health Effects Institute, 2022).

| High ++++<br>Moderate +++<br>Low ++<br>Very low + | Factors decreasing confidence "0" if no concern; "-" if serious concern to downgrade confidence | | | | Factors increasing confidence "0" if not present; "+" if sufficient to upgrade confidence | | | |
|---|---|---|---|---|---|---|---|---|
| Initial confidence rating | Risk of Bias | Unexplained inconsistency | Imprecision | Publication bias | Monotonic exposure-response | Consideration of residual confounding | Consistency across populations | Final confidence rating |
| ++<br>Time series design rated as low confidence. | 0<br>No studies at high risk of bias. | 0<br>Low to moderate heterogeneity. | −1<br>Wide confidence intervals overlapping unity. | 0<br>No indication in funnel plots and Egger's tests. | 0<br>Four studies (Schwarz et al., 2023; Bergmann et al., 2023; Peters et al., 2009; Wichmann et al., 2000) assessed exposure-response curves, with inconclusive findings. | 0<br>Confounding in both directions possible. | +1<br>Associations were consistent across several outcomes and exposure periods. | ++ |

Definitions according to OHAT (Office of Health Assessment and Translation, 2019).

- Confidence ratings
  - High confidence (++++): High confidence in the association between exposure to the substance and the outcome. The true effect is highly likely to be reflected in the apparent relationship.
  - Moderate confidence (+++): Moderate confidence in the association between exposure to the substance and the outcome. The true effect may be reflected in the apparent relationship.
  - Low confidence (++): Low confidence in the association between exposure to the substance and the outcome. The true effect may be different from the apparent relationship.
  - Very low confidence (+): Very low confidence in the association between exposure to the substance and the outcome. The true effect is highly likely to be different from the apparent relationship.
- Evidence ratings
  - High level of evidence: There is high confidence in the body of evidence for an association between exposure to the substance and the health outcome(s).
  - Moderate level of evidence: There is moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome(s).
  - Low level of evidence: There is low confidence in the body of evidence for an association between exposure to the substance and the health outcome(s), or no data are available.
  - Evidence of no health effect: There is high confidence in the body of evidence that exposure to the substance is not associated with the health outcome(s).
  - Inadequate evidence: There is insufficient evidence available to assess if the exposure to the substance is associated with the health outcome(s).

study suggests possibly stronger health effects associated with primary particles (mainly from traffic) than with secondary particles (Tobías et al., 2018), while the other studies found no or inconsistent differences (Samoli et al., 2016; Rivas et al., 2021) in the associations of total or source-related particles and mortality. In addition, several studies have analysed smaller particle fractions such as the nucleation mode (<30 nm) or Aitken mode (30–100 nm), which may have distinct toxicological properties, with substantial variation in the assessed size fractions and lags. Results of those studies are inconclusive, with some finding stronger associations for larger particles (Park et al., 2022; Halonen et al., 2009; Hennig et al., 2018; Leitte et al., 2012), some finding stronger associations with smaller particles (Schwarz et al., 2023; Breitner et al., 2011), and some finding no differences (Breitner et al., 2009; Braniš et al., 2010), leaving a research gap on the effects of different particle sizes and sources.

In our meta-analysis, we saw an indication of an association between

UFP and natural and respiratory mortality lagged six days. However, this association was small and primarily driven by estimates from Rome (Italy) for natural mortality, where a traffic station was used for UFP monitoring (Stafoggia et al., 2017). Nonetheless, our analysis of grouped cumulative lag periods indicated a similar trend, with stronger associations for medium (three to four days before outcome) and longer (minimum five days) averaging times. This suggests possible associations between UFP exposure and mortality at medium and longer lags or averaging times and emphasizes the importance of including various exposure periods (e.g., both single lags and cumulative lags of up to one week) in analyses. However, this finding should not be over-interpreted due to large confidence intervals and different cumulative lags grouped together. Moreover, in studies with a large amount of missing data – which most studies did not report – analysis of moving averages might be misleading. In general, a more standardized reporting structure for different lags and cumulative averaging times would enhance the potential for later meta-analyses.

Our analysis grouped by city-specific exposure level suggested higher associations in locations with higher exposure levels (mean UFP $>$10,000 pt/cm$^3$). In contrast, a meta-analysis on short-term exposure to UFP and respiratory morbidity found more consistent associations at lower levels $<$6000 pt/cm$^3$ (Samoli et al., 2020). Notably, the observed differences in city-specific mean UFP could reflect the different study periods (with older studies reporting higher levels), the location of monitoring stations, and the captured particle size fractions. Additionally, most studies included in our review were conducted in Europe, highlighting a lack of data from other parts of the world.

Lastly, the associations of UFP exposure with mortality might be better captured by studies focusing on individual-level long-term exposure. With the increasing availability of fine-scale spatial models of UFP, several studies on long-term health effects of UFP have been published in recent years, which are reviewed in another part of our project.

Strengths of our review include the comprehensive literature search and the meta-analysis with specific attention to study locations, particle size and exposure lags, increasing the comparability of estimates as opposed to approaches used in previous reviews. Moreover, we assessed findings from two-pollutant models, which has not been done previously. Limitations of our review concern our approach of combining two separate reviews instead of conducting one search covering a longer period. However, we aligned our search strategy with the HEI review, removed any duplicates resulting from the intentional overlap in search periods, and harmonized the extracted information of included studies. Another limitation is that we did not consider changes in UFP measurement technology over time, which may have led to variation in the exposure assessment methods. Furthermore, we did not assess differences in the placement of UFP monitors or the size of study areas. Lastly, we were not able to address the bias arising from selective reporting of lag results. As such, different studies reported a wide range of lags, with possibly partial reporting of positive results only.

## 5. Conclusion

The current evidence does not clearly support an association between short-term central-site concentrations of UFP and mortality. Future studies should aim to reduce exposure misclassification of UFP, ensuring that the captured day-to-day variations represent the exposure of the study population. Standard methods to characterize UFP are needed, particularly in relation to particle size fractions, instrumentation, and location and height of monitoring stations. Moreover, more stringent reporting of results is needed to improve the comparability of different studies and enhance their use in future meta-analyses. Specifically, this includes the reporting of standardized lags and averaging times of up to one week and of estimates from both single- and two-pollutant models, adjusting for co-pollutants such as $NO_2$ and $PM_{2.5}$, in order to be able to assess the independence of UFP associations from other pollutants. Finally, we need more studies from more diverse study areas, especially other than Europe, for which we currently have very limited evidence.

## CRediT authorship contribution statement

**Marie L. Bergmann:** Writing – original draft, Visualization, Project administration, Investigation, Formal analysis, Data curation. **Pascale Haddad-Thoelke:** Writing – review & editing, Project administration, Investigation, Formal analysis, Data curation. **Haeran Jeong:** Writing – review & editing, Formal analysis, Data curation. **Ron Kappeler:** Writing – review & editing, Formal analysis, Data curation. **Hicran Altug:** Writing – review & editing. **Hanna Boogaard:** Writing – review & editing. **Meltem Kutlar Joss:** Writing – review & editing, Data curation. **Youn-Hee Lim:** Writing – review & editing. **Steffen Loft:** Writing – review & editing. **Zorana J. Andersen:** Writing – review & editing. **Barbara Hoffmann:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

## 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.

## Acknowledgements

The project was financed by the Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection and supervised by the German Environment Agency (FKZ 3721 61 202 0). The public funding agency was involved in the design of the systematic literature search.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2025.122780.

## Data availability

Data will be made available on request.

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