



Systematic review and meta-analysis on the health effects of long-term exposure to ultrafine particles

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The evidence on long-term health effects of UFPs has grown, with potential adverse effects on a wide range of outcomes. More research is needed with improved methods for distinguishing the health effects of UFPs from those of co-pollutants. <https://bit.ly/4oCh3aE>

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Abstract

Background Ultrafine particles (≤ 100 nm diameter) may have a higher toxicity than larger particles but are still not regulated nor part of routine air pollution monitoring. So far, health effects of long-term exposure to ambient ultrafine particles are not well understood, owing to a lack of exposure data and epidemiological studies.

Methods We conducted a systematic review and meta-analysis on the health effects of long-term exposure to ultrafine particles, including studies published until December 2024. A meta-analysis was conducted for outcomes with at least four available effect estimates. Confidence in the body of evidence was evaluated using the Office of Health Assessment and Translation method.

Results We identified 85 studies investigating various mortality, morbidity and subclinical outcomes. In meta-analyses of single-pollutant models, we found positive associations with natural mortality (hazard ratio 1.06, 95% CI 1.04–1.08) and C-reactive protein (10.14% increase (95% CI –0.51–21.99%) per 10 000 $\mu\text{g}\cdot\text{m}^{-3}$ increase in long-term exposure to ultrafine particles, with low and inadequate levels of evidence, respectively. The remaining studies revealed overall limited evidence for adverse effects on a wide range of outcomes. Less than half of the studies adjusted for co-pollutants.

Conclusion The evidence base on long-term health effects of ultrafine particles has increased substantially in the past decade, while the overall evidence for independent effects of long-term ultrafine particle exposure remains inadequate to low. More studies are needed to draw firm conclusions about the independent adverse effects of long-term ultrafine particles on various health end-points, with a special focus on the influence of co-pollutant adjustment.

Introduction

Air pollution is the leading risk factor contributing to the global burden of disease and the second largest risk factor for mortality worldwide, with the majority of its impact attributed to ambient fine particulate matter (*i.e.* particulate matter with an aerodynamic diameter of up to 2.5 μm ($\text{PM}_{2.5}$)) [1, 2]. Exposure to $\text{PM}_{2.5}$ is associated with a wide range of negative health impacts, including respiratory, cardiometabolic and cognitive health, as well as early childhood development [2]. However, few studies have assessed the health effects of ultrafine particles (UFPs), the smallest fraction of PM with aerodynamic diameters of up to 100 nm. In urban environments, UFPs primarily originate from combustion processes related to road traffic [3]. Owing to their low mass, UFPs contribute minimally to particle mass concentration, which is used in routine measurements of larger particles like $\text{PM}_{2.5}$. Instead, they are most commonly quantified in



terms of particle number concentration (PNC), which serves as a good proxy for UFPs because they make up >80% of the total PNC [4]. Increasing evidence suggests that UFPs are potentially more toxic than larger particles and may have independent adverse health effects [5]. Their large mass-specific surface area and high surface reactivity enable them to adsorb large amounts of toxic metals and organic compounds, while UFPs are particularly prone to deposit deep inside the lungs or translocate to other organs [6].

In contrast to studies on long-term exposure to $PM_{2.5}$, there is a scarcity of studies addressing long-term exposure to UFPs, mostly due to challenges in exposure assessment. Reliance on measurements at central sites to represent broad population exposure, a central feature in many early epidemiological studies of long-term exposure to $PM_{2.5}$ and other pollutants, is likely to cause errors in exposure estimates of UFPs or other pollutants that vary highly in space and time. The application of more modern methods of fine-scale exposure assessment of PM using modelling techniques has been hampered by the high spatial and temporal variability of UFP concentrations and the lack of dense monitoring networks for UFPs.

A comprehensive Health Effects Institute (HEI) review from 2013 identified no studies on health effects related to long-term exposure to UFP [7]. The HEI review was followed up by a systematic review by OHLWEIN *et al.* [8] that identified 10 epidemiological studies on long-term exposure to UFP, published up to 2017. A more recent review by VALLABANI *et al.* [9] on the toxicity and health effects of UFP included 14 additional studies, published up to 2022, on long-term exposure to UFPs and a variety of health outcomes. However, this review was restricted to studies on source-specific UFPs related to different transport modes. A HEI systematic review in 2022 identified 10 long-term studies but focused solely on traffic-related air pollution using strict exposure criteria [10].

In recent years, the development of new measurement and modelling techniques has led to an increase in the number of epidemiological studies examining the health effects of long-term exposure to UFPs. Therefore, the aim of this study was to systematically review and evaluate the epidemiological literature. We included studies on long-term exposure to UFPs and health, encompassing mortality, morbidity and subclinical outcomes. We conducted meta-analyses for outcomes with a sufficient number of studies.

Methods

This study is part of an extensive systematic review on the long-term and short-term health effects of UFPs and particulate matter $<1 \mu m$ (PM_1). In this manuscript, we focus on the long-term effects of UFPs, while short-term effects will be presented in separate manuscripts owing to the large volume of short-term papers. We conducted our systematic review in line with a PROSPERO protocol (CRD42022348060) [11]. The original protocol was amended to extend the search period until the end of 2024.

PECOS question and UFP definition

We based our search on the following PECOS (Population, Exposure, Comparator, Outcome and Study) [12] question: “In the general population or in population subgroups, including preclinical or diseased participants (P), what is the increase in risk of health effects (O) per unit increase (C) of long-term exposure to UFPs (E), observed in epidemiological studies (S)?”

We employed a broad definition of UFPs, encompassing particles with diameters $<100 \text{ nm}$ as well as total PNC and accumulation mode particles (quasi-UFP), which may be larger than 100 nm , but considerably smaller than 1000 nm [13]. We documented the exact size range and other features of the exposure assessment to allow further examination into the exact definition of UFP exposure.

Search strategy

We systematically searched PubMed and LUDOK (the Swiss literature database on air pollution and health) [14] for epidemiological studies investigating the health effects of long-term exposure to UFPs for the period 1 January 2011 to 31 December 2024. We chose not to seek articles published prior to 2011 because two prior reviews [7, 8] had not yielded any studies on long-term exposure to UFPs and health before 2011. The search consisted of three different concepts, operationalised 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. The final number of hits was obtained by combining these three concepts (see table S1 for search strategy and number of hits).

Further, we conducted hand searches of reference lists of reviews and conference proceedings (*i.e.* the International Society for Environmental Epidemiology conferences 2020–2023) that were not identified in the initial search. We also checked reference lists of included studies and reviews, as well as benchmark articles known in the field, and included any additional relevant articles (see supplementary material for

further details). Results were reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [15] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [16] guidelines for systematic review reports.

Study eligibility criteria

Studies were eligible for inclusion in the extensive review if they met the following criteria: 1) original epidemiological study adopting a cohort, cross-sectional, case-control, case-cohort, time series, panel, or controlled exposure and intervention designs; 2) reported on the general population or on subpopulations, including preclinical or diseased participants, of all ages, with no geographical restrictions; 3) assessed short-term (*i.e.* one day to several days, assessed in separate manuscripts) or long-term (*i.e.* a duration of months to years, similar to other reviews [16, 17]) exposure to one of the following surrogates of UFP measures: total PNC or size-fractionated PNC for particles <100 nm, nucleation-mode particles and Aitken-mode particles, or containing at least one quasi-UFP effect measure (PNC <3000 nm, particulate matter <0.25 µm (PM_{0.25}), particulate matter <0.1 µm (PM_{0.1}), lung deposited surface-area concentration, PM₁ mass concentration or accumulation mode particles); 4) defined health outcomes such as morbidity or mortality of International Classification of Diseases (ICD)-coded diseases or subclinical conditions; 5) quantifiable measures of association between exposure-outcome pair (odds ratio (OR), risk ratio, relative risk, hazard ratio (HR), β-estimate or % change); and 6) written in English or German. Morbidity outcomes were defined as clinical outcomes having an ICD code, including both prevalent and incident conditions; subclinical outcomes were outcomes that did not include an ICD code but are clinically relevant and useful for disease diagnosis or development, such as blood pressure and hypertension, C-reactive protein, lung function, cognitive function or birth weight.

The exclusion criteria eliminated studies reporting on 1) exposure to industrially engineered nanoparticles, exclusively indoor or occupational settings or restricted to diesel particles, black carbon (BC) or elemental carbon (EC) only; 2) distance to major roadways or traffic density as a substitute for exposure measurements; 3) health outcomes of unclear clinical health relevance (*i.e.* epigenetics, metabolomics, methylation); 4) non-human (*in vivo*, *in vitro*), animal or toxicological studies; 5) studies without individual level or aggregated time series data (*i.e.* fully ecological outcome, exposure and covariate data); and 6) methodological papers.

The inclusion and exclusion criteria related to each PECOS domain are presented in table S2. For the analysis presented in this review, we further excluded studies on short-term exposure and on PM₁. However, because they were part of the more extensive review, they are included in the total number of hits presented in the Results section.

Screening and data extraction

We imported all identified articles into EndNote 20 (Philadelphia, PA, USA), removed duplicates, and screened titles and abstracts. The initial screening was conducted by PH-T, HJ and MB, partly in duplicate. That is, each screener simultaneously checked 10% of the articles screened by their counterpart. Full-texts and supplements were retrieved for those articles included after title and abstract screening. Full-text screening was done for further review of the articles according to our inclusion and exclusion criteria. Three authors (PH-T, HJ and RK) independently extracted study details into a standardised Microsoft Access questionnaire, which included details on study design, population, exposure and outcome assessment and effect estimates (see supplementary material for further details).

Risk of bias assessment

All identified articles were evaluated using risk of bias (RoB) criteria from the Quality Assessment Tool for Observational Studies by the National Institutes of Health [18], adapted as in the review by OHLWEIN *et al.* [8]. This critical appraisal tool evaluates the RoB in the domains of selection bias, information bias, measurement bias and confounding by assessing the selection of the participants, the validity of the exposure models, the outcome measurements and the statistical analyses. Four authors (PH-T, HJ, RK and MB) conducted the RoB assessment in duplicate. Inconsistencies between two reviewers' assessments were resolved by another author (BH). The RoB questions, as well as criteria for their evaluation, are presented in the supplementary material.

Data synthesis and analysis

As a first step, we summarised the findings for each health outcome qualitatively, including both single-pollutant and multi-pollutant estimates. Next, a meta-analysis was conducted if at least four effect estimates were available for an outcome. We note that any number of required studies for meta-analysis is arbitrary. For the meta-analyses, we selected effect estimates from single-pollutant, fully adjusted models.

Different surrogates of UFPs measured as PNC were not converted to make them more comparable and hence used interchangeably. $PM_{0.1}$ or other mass surrogates were not combined with PNC-based measures in meta-analyses. We converted relative risk or HR estimates to β -estimates associated with a one-unit increase (one particle (pt) \cdot cm⁻³) in exposure (see supplementary material for formula). Next, we conducted a random-effects meta-analysis for each exposure–outcome pair using the restricted maximum likelihood method because of expected differences in populations. Results are presented as relative risk, HR or % change (depending on the outcome) and corresponding 95% confidence intervals (CIs) associated with a 10 000 pt \cdot cm⁻³ increase in UFPs. Summary and individual study estimates are presented in forest plots. Statistical heterogeneity was assessed by I^2 statistics. For interpretation of the I^2 statistics, we classified values <50% as indicating low heterogeneity, 50–75% as moderate heterogeneity and >75% as high heterogeneity.

If applicable, we assessed heterogeneity between studies in terms of the included particle fractions. Robustness of the results was tested by excluding estimates from studies with a high RoB in at least one domain and those estimates that contributed most of the weight in a meta-analysis.

Publication bias was assessed by means of funnel plots and Egger's regression tests [19]. However, it should be noted that the Egger's test does not perform well if the number of studies is small (*i.e.* <10) [20]. Hence, we exercised caution when interpreting analyses of publication bias.

Statistical analyses were done in R (version 4.3.3; www.r-project.org) using the *metafor* package [21] for meta-analysis.

Assessment of the confidence in the body of evidence

Owing to the heterogeneity of assessed outcomes, we only rated the confidence in the body of evidence for outcomes that entered the meta-analysis. We applied the Office of Health Assessment and Translation (OHAT) method to rate the confidence of the association [22], in a modified version [10]. This method involves categorising studies on a specific health outcome based on key study design features. Each group of studies then receives an initial confidence rating based on these features, where we considered cohort studies as “moderate” and cross-sectional studies as “low” confidence. This rating is subsequently adjusted: downgraded for factors that reduce confidence (*i.e.* RoB, unexplained inconsistency, imprecision and publication bias) and upgraded for factors that enhance confidence (*i.e.* monotonic exposure–response, consideration of residual confounding and consistency across populations). In the RoB assessment, we adopted a conservative approach by downgrading groups of studies only when there was a substantial risk of bias present in the majority of included studies and/or in those studies that contributed the greatest weight to the meta-analysis. Additionally, we conducted sensitivity analyses by excluding effect estimates derived from studies with overall high RoB. Accordingly, we rated the overall level of confidence for each outcome as “high”, “moderate”, “low” or “very low”. Finally, we translated these confidence ratings into a level of evidence for health effects, determining whether there is a likely association or not. Three descriptors, “high”, “moderate” and “low”, are directly linked to the confidence rating, determining whether there is a health effect. In case of a very low confidence rating or no evidence found, the conclusion was classified as “inadequate evidence”. Two authors (MB and BH) conducted the assessment in duplicate.

Results

Descriptive statistics

The search between 1 January 2011 and 31 December 2024 yielded 5259 articles from PubMed, LUDOK and hand searches combined, with 4935 unique entries. After title and abstract screening, 47 articles were further assessed for eligibility. Finally, 85 articles on long-term exposure to UFPs were included after full-text review (figure 1).

Table 1 presents summary statistics of the 85 included studies, while individual study information is presented in table 2. Most studies were conducted in North America (47.1%) and Western Europe (47.1%) and followed cohort (67.1%) or cross-sectional (24.7%) designs. Among the cohort studies, 42.1% used administrative data, including studies from Canada, Denmark, the Netherlands, USA, China and Italy. The studies investigated morbidity (37.6%), subclinical (37.6%), pregnancy-related (11.8%) and mortality (8.2%) outcomes across various organ systems and disease groups, including cardiovascular, metabolic, respiratory, inflammation, neurological, psychiatric, cancer and pregnancy-related conditions. Among these, cardiovascular (22.4%), respiratory (17.6%) and neurological (17.6%) outcomes were most common.

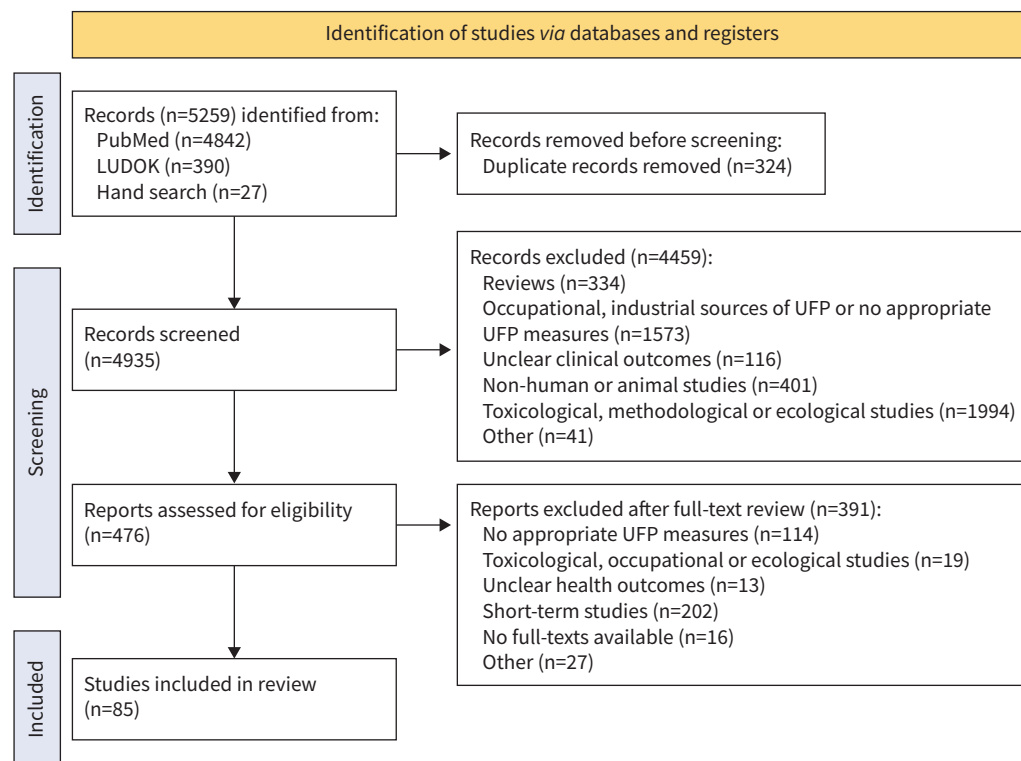


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart of systematic search covering the period 1 January 2011 to 31 December 2024. UFP: ultrafine particles.

To assess UFP exposure, most studies applied modelling techniques such as land-use regression (LUR) (43.5%) or chemical transport models (CTM) (23.5%), with a few studies relying on central site monitoring (8.2%). The spatial resolution of the exposure models varied between 100 m×100 m and 4 km×4 km. Most studies used UFPs as their exposure (85.9%), while 14.1% assessed quasi-UFPs, of which most were accumulation mode particles. More than two thirds of the studies (72.9%) examined UFPs with lower particle cut-offs ranging between 2.5 and 16 nm. Others examined accumulation mode particles without specifying the minimum particle size (10.6%), while 16.5% did not provide any information on the lower particle cut-off. The majority quantified UFPs using PNC (94.1%), and 5.9% assessed particle mass concentrations.

Almost half of the studies adjusted their main UFP results for PM_{2.5} in two-pollutant or multi-pollutant models (45.9%). Moreover, 43.5% adjusted for NO₂, 23.5% for noise and 14.1% for EC or BC. Other studies adjusted for various other exposures in two-pollutant or multi-pollutant models, including sulfur dioxide, ozone, coarse particles, PM₁₀ or green space (table 2).

RoB and study quality

In the RoB assessment, eight of 85 studies received a moderate or high RoB rating owing to participants recruited from several populations or time periods (table S3). 17 studies received a moderate RoB rating for not stating inclusion and exclusion criteria. Loss to follow-up, leading to potential survivor bias, was rated as moderate or high RoB in 28 cohort studies. 18 studies received a moderate or high rating of RoB due to applying exposure models with large spatial resolution, which might not be valid for their population. 33 studies, including cross-sectional and cohort studies, assessed exposure only once during the study period and received a moderate or high RoB rating owing to potential changes in exposure distribution over time. 42 studies received a moderate RoB rating for not blinding exposure assessors. Lastly, confounder assessment was rated as at a moderate RoB in 68 studies, which was mostly related to missing adjustment for either lifestyle factors or co-pollutants (*i.e.* NO₂).

Approximately half of the studies, mostly cohort studies, included populations that were not completely representative of the general population.

TABLE 1 Summary statistics of the included studies on long-term exposure to UFPs and health outcomes

Study characteristics	Finding
Location	
North America	40 (47.1)
Northeast Asia	3 (3.5)
Western Europe	40 (47.1)
Western Pacific	2 (2.4)
Study design	
Cohort	57 (67.1)
Case-control	5 (5.9)
Case-cohort	1 (1.2)
Cross-sectional	21 (24.7)
Other [#]	1 (1.2)
Exposure technique	
Model-based	76 (89.4)
Measurement-based	9 (10.6)
Exposure assessment model	
LUR model	37 (43.5)
CTM	20 (23.5)
Hybrid	11 (12.9)
Interpolation/Kriging	5 (5.9)
Dispersion model	3 (3.5)
Central site monitoring	7 (8.2)
Mobile monitoring	2 (2.4)
Exposure metric[¶]	
UFP	73 (85.9)
Quasi-UFP	12 (14.1)
Co-pollutant adjustment[†]	
PM _{2.5}	39 (45.9)
NO ₂	37 (43.5)
BC/EC	12 (14.1)
Noise	20 (23.5)
Outcome type	
Mortality	7 (8.2)
Morbidity	32 (37.6)
Subclinical	32 (37.6)
Pregnancy-related	10 (11.8)
Multiple types	4 (4.7)
Organ system[†]	
Cardiovascular	19 (22.4)
Metabolic	13 (15.3)
Respiratory	15 (17.6)
Inflammation	10 (11.8)
Neurological	15 (17.6)
Pregnancy	9 (10.6)
Cancer	10 (11.8)
Psychiatric	5 (5.9)
Other [§]	3 (3.5)
Total studies	85 (100)

Data are presented as n (%). PM_{2.5}: particulate matter <2.5 µm; BC: black carbon; CTM: chemical transport model; EC: elemental carbon; LUR: land-use regression; NO₂: nitrogen dioxide; PNC: particle number concentration; UFP: ultrafine particle. [#]: difference-in-difference study design using time series data in Qi *et al.* 2024 [23]; [¶]: UFP refers to particles <100 nm, while quasi-UFP also include larger particles (e.g. PNC <3000 nm, PM_{0.25}, PM_{0.1}, lung deposited surface-area concentration or accumulation mode particles); [†]: some studies appear in more than one category; [§]: others included self-perceived health status [24], genes related to cell signalling and immune response [25] and cardiometabolic phenotypes [26].

Health effects associated with long-term exposure to UFPs

Mortality

Out of the eight studies examining mortality, most focused on natural or all-cause (n=5), cardiovascular (n=4) or respiratory (n=4) mortality (table 3). We observed mostly positive, significant associations across

TABLE 2 Characteristics of the 85 included studies

Study	Location	Study name and design	Population	Sample size (n)	Exposure assessment/ spatial resolution	Exposure time window	Particle size range/type (nm)	Co-pollutant adjustment	Outcome(s)
AGUILERA 2016 [27]	Switzerland	SALPALDIA cohort, cross-sectional	General population	1503	Spatial LUR/ address-specific	TWA between two follow-up assessments 2001–2011	10–300	PM _{2.5} PM ₁₀	Atherosclerosis (subclinical); CIMT
ASSIBEY-MENSAH 2019 [28]	New York, USA	Cohort (administrative)	Pregnant women	16 637	Spatiotemporal LUR of wintertime UFPs/ address-specific	Monthly means during pregnancy 2008–2013	10–100	–	Hypertensive disorders of pregnancy
BAI 2018 [29]	Toronto, Canada	ONPHEC (administrative)	General population	1 056 012 (diabetes) 893 499 (hypertension)	Spatial LUR/ address-specific	3-year moving averages 1996–2012	10, >1000	NO ₂ PM _{2.5} Traffic noise	Incidence of diabetes and hypertension
BAI 2019 [30]	Toronto, Canada	ONPHEC (administrative)	General population	1 135 817	Spatial LUR/ address-specific	3-year moving averages 1996–2012	10, >1000	Traffic noise	Incidence of MI and congestive heart failure
BLANCO 2024 [31]	Seattle, USA	Adult Changes in Thought (ACT) cohort	General population	4283	Spatial LUR derived from mobile monitoring/ address-specific	10-year moving TWA 1994–2020	10–420	PM _{2.5} NO ₂ BC	Dementia incidence
BOOKSTEIN 2024 [32]	California, USA	MEC	General population	71 387	Dispersion model of airport-related UFPs/1×1 km	Monthly TWA 1993–2013	<100	–	Lung cancer incidence
BOUMA 2023 [33]	The Netherlands (national)	Dutch National Cohort (administrative)	General population	1 080 000	LUR model-Kriging/ address-specific	Annual mean at baseline 2013	10, >1000	NO ₂ PM _{2.5} PM ₁₀ EC	Natural and cause-specific mortality (CVD, lung cancer and respiratory)
BOUMA 2023 [34]	The Netherlands (national)	PIAMA cohort	Children	2295	LUR model-Kriging/ address-specific	Annual mean at birth and at each examination	10, >1000	–	Allergic sensitisation
CARTER 2023 [35]	California, USA	Cohort (administrative)	Mother–child pairs	318 078	CTM of airport-related UFPs/4×4 km	Pregnancy mean 2000–2016	<100	Other UFP sources Noise	Autism spectrum disorder incidence in children
CLIFFORD 2018 [36]	Brisbane, Australia	Cross-sectional	School children	1197	Spatiotemporal LUR/ address-specific	Annual means 2010–2012	>6	NO ₂ PM _{2.5}	Prevalence of asthma, respiratory disease, hs-CRP

Continued

TABLE 2 Continued									
Study	Location	Study name and design	Population	Sample size (n)	Exposure assessment/ spatial resolution	Exposure time window	Particle size range/type (nm)	Co-pollutant adjustment	Outcome(s)
CORLIN 2018 [37]	Boston, USA	CAFEH study, cross-sectional	General population +specific population: Puerto Rican, 45–75 years old, English or Spanish	409	Hybrid: spatiotemporal LUR+microscale personal exposure/ address-specific +personal exposure	Annual mean at each study visit 2004–2015	TAA-UFP 4–3000	–	Prevalence of blood pressure, pulse pressure
CORLIN 2018 [38]	Boston, USA	Boston Puerto Rican Health study, cross-sectional	General population +specific population: Puerto Rican, 45–75 years old, English or Spanish	791	Hybrid: spatiotemporal LUR+microscale personal exposure/ address-specific +personal exposure	Annual mean at each study visit 2004–2015	TAA-UFP 4–3000	–	Prevalence of blood pressure, pulse pressure, hs-CRP
DA SILVA FLECK 2023 [39]	Montreal, Canada	Cohort (administrative)	Children	352 966	Spatiotemporal LUR/100×100 m	Annual mean at birth; childhood TWA 2000–2015	<100	PM _{2.5} NO ₂	Asthma incidence
DE BONT 2019 [40]	Barcelona, Spain	BREATHE, cross-sectional	School children	2660	Measurement +central monitoring/ school-specific	Annual mean 2012–2013	10–700	–	Obesity
DOWNWARD 2018 [41]	The Netherlands	EPIC-NL study (Prospect and Morgen cohorts)	General population	33 831	Spatial LUR/ address-specific	Annual mean at baseline 1993–1997	10, >1000, 10–300	PM _{2.5} PM coarse PM ₁₀ PM _{2.5} abs NO _x NO ₂	Incidence of total and specific CVD (coronary heart disease, cerebrovascular events, MI, heart failure)
ENDES 2017 [42]	Switzerland	SAPALDIA cohort, cross-sectional	General population	6088	Spatiotemporal LUR/ address-specific	Annual mean 2010	16–300	–	Arterial stiffness
FANG 2022 [43]	Beijing, China	Cohort (administrative)	Pregnant women	24 001	Measurement/ central monitoring	Pregnancy mean 2014–2017	Nucleation, Aitken and accumulation Mode	NO ₂ SO ₂ CO Ozone	Preterm birth
FORNS 2017 [44]	Barcelona, Spain	BREATHE cohort	Children	1439	Measurement/ central monitoring	Two 1-week measurements 2012/2013	10–700	NO ₂ Noise	Cognitive function

Continued

TABLE 2 Continued

Study	Location	Study name and design	Population	Sample size (n)	Exposure assessment/ spatial resolution	Exposure time window	Particle size range/type (nm)	Co-pollutant adjustment	Outcome(s)
GAN 2023 [45]	USA	Uniform Data Set cohort	General population	5646	Spatial LUR/ address-specific	Annual means 2016–2017	>5	–	Cognitive function
GLAUBITZ 2022 [46]	Ruhr area, Germany	1000BRAINS cohort	General population	574	CTM/ 1×1 km	3-year mean at baseline 2001–2003	Accumulation mode	Traffic noise	Functional connectivity in the brain
GOIN 2021 [47]	Oakland, USA	Cohort (administrative)	Pregnant women	1095	Measurement/ mobile monitoring	Pregnancy mean 2014–2016	>2.5	–	Pre-eclampsia
GOLDBERG 2017 [48]	Montreal, Canada	Case–control	Breast cancer patients	1278	Spatial LUR/ address-specific	Annual mean at recruitment 2008–2011	10, >1000	–	Breast cancer incidence
GOOBIE 2024 [49]	USA (nationwide)	Simmons registry and Pulmonary Fibrosis Foundation Patient Registry cohort	fiLD patients	3335	Spatial LUR/ census-block resolution	Annual mean at most recent address 2000–2021	PNC (different size ranges)	PM _{2.5} NO ₂	Natural mortality or lung transplantation, baseline lung function
GOODRICH 2024 [50]	California, USA	CHARGE, case–control study	Children (2–5 years old)	1413	CTM/4×4 km or 24×24 km	Pre-pregnancy, trimester-specific and first 2 years of life means 2000–2016	<100	PM _{0.1–2.5} PM _{2.5–10} NO ₂ Ozone	Cognitive and adaptive outcomes (Vineland Adaptive Behavior Scales and Mullen Scales of Early Learning)
GOODRICH 2024 [51]	California, USA	CHARGE, case–control study	Children (2–5 years old)	1144	CTM/4×4 km or 24×24 km	Pre-pregnancy, trimester-specific and first 2 years of life means 2000–2016	<100	PM _{0.1–2.5} PM _{2.5–10} NO ₂ Ozone	Autism spectrum disorder incidence
HENNIG 2020 [52]	Ruhr area, Germany	Heinz-Nixdorf-Recall cohort	General population	3480	CTM/1×1 km	3/4-year means at baseline and follow-up 2000–2003 and 2006–2008	Accumulation mode	Traffic noise	Atherosclerosis
HERDER 2020 [53]	Augsburg area, Germany	KORA cohort	General population	424	Spatial LUR/ address-specific	Annual mean at baseline 2006–2008	>7 10–420	–	DSPN prevalence and incidence
HERDER 2023 [54]	Augsburg area, Germany	KORA cohort	General population	423	Spatial LUR/ address-specific	Annual mean at baseline 2006–2008	>7 10–420	NDVI Traffic noise Temperature	DSPN incidence
JERRETT 2023 [55]	Southern California, USA	Kaiser Permanente Southern California cohort	COVID-19 hospitalised patients	21 415	CTM/1×1 km	Annual mean 2016	Mass of particles ≤100	–	COVID-19 mortality

Continued

TABLE 2 Continued									
Study	Location	Study name and design	Population	Sample size (n)	Exposure assessment/ spatial resolution	Exposure time window	Particle size range/type (nm)	Co-pollutant adjustment	Outcome(s)
JONES 2024 [56]	Southern California, USA	Los Angeles Ultrafines Study cohort	General population	45 012	Spatiotemporal LUR/ address-specific	10-year moving TWA 1995–2017	10–700	–	Lung cancer incidence
LANE 2015 [57]	Sommerville/ Boston, USA	CAFEH, cross-sectional	General population	204	Hybrid: measurements (mobile+personal exposure)/ address-specific +personal exposure	Annual mean at recruitment 2009–2010	TAA-PNC 4–3000	–	hs-CRP, IL-6
LANE 2016 [58]	Boston, USA	CAFEH, cross-sectional	General population	408	Hybrid: measurements (mobile and personal exposure)/ address-specific +personal exposure	Annual mean at recruitment 2009–2012	TAA-PNC 4–3000	–	hs-CRP, IL-6, TNFR11
LAURENT 2014 [59]	California, USA	Cross-sectional (administrative)	Mother–child pairs	960	CTM/1×1 km	Trimester means 2001–2008	Source-specific PM _{0.1}	–	Birth weight
LAURENT 2016 [60]	California, USA	Case–cohort	Mother–child pairs	–	Hybrid: CTM and dispersion	Trimester means 2001–2008	Source-specific PM _{0.1} and PNC	–	Birth weight
LAURENT 2016 [61]	California, USA	Case–control	Mother–child pairs	–	Hybrid: CTM and dispersion	Trimester means 2001–2008	Source-specific PM _{0.1}	–	Preterm birth
LAVIGNE 2019 [62]	Toronto, Canada	MOMBABY and BORN cohort (administrative)	Mother–child pairs	160 641	Spatial LUR/ postal code	Pregnancy mean 012–2015	10, >1000	NO ₂ PM _{2.5}	Asthma incidence
LAVIGNE 2019 [63]	Toronto, Canada	BORN Ontario cohort (administrative)	Mother–child pairs	158 743	Spatial LUR/ postal code	Pregnancy mean 2006–2012	10, >1000	NO ₂ PM _{2.5}	Congenital heart defect
LAVIGNE 2020 [64]	Toronto, Canada	BORN Ontario cohort (administrative)	Mother–child pairs	653 702	Spatial LUR/ postal code	Pregnancy mean 1998–2017	10, >1000	NO ₂ PM _{2.5}	Incidence of total and specific cancers (lymphoid leukaemia, astrocytoma, neuroblastoma)
LI 2017 [65]	Boston, USA	CAFEH, cross-sectional	General population	704	Hybrid: spatiotemporal LUR+microscale personal exposure/ address-specific +personal exposure	Annual mean at recruitment 2009–2012	TAA-PNC 4–3000	–	Prevalence of stroke, hypertension, diabetes

Continued

TABLE 2 Continued

Study	Location	Study name and design	Population	Sample size (n)	Exposure assessment/ spatial resolution	Exposure time window	Particle size range/type (nm)	Co-pollutant adjustment	Outcome(s)
LI 2019 [66]	New York, USA	FLRPDS cohort (administrative)	Mother–child pairs	76 500	Measurement/ central monitoring	Pregnancy mean 2005–2016	≤100	Ozone	Birthweight
LIAO 2024 [24]	Augsburg area, Germany	KORA, cross-sectional	General population	2610	Spatial LUR/ address-specific	Annual mean 2014–2015	>7, 10–420	Ozone	Self-perceived health status
LLOYD 2024 [67]	Montreal and Toronto, Canada	CanCHEC cohort (administrative)	General population	1 544 000	Spatiotemporal LUR/ deep-learning models based on mobile monitoring/ 6-digit residential postal codes (100–200 m length)	3-year moving TWA 2001–2015	PNC; different instruments and size ranges	BC PM _{2.5} Oxidant gases	Malignant brain tumour incidence
LLOYD 2024 [68]	Montreal and Toronto, Canada	CanCHEC cohort (administrative)	General population	1 544 000	Spatiotemporal LUR/ deep-learning models based on mobile monitoring/ 6-digit residential postal codes (100–200 m length)	3-year moving TWA 2001–2015	PNC; different instruments and size ranges	BC PM _{2.5} Oxidant gases	Natural mortality and cause-specific (CVD, cardiometabolic, IHD, cerebrovascular, respiratory, lung cancer)
LOMME 2023 [69]	The Netherlands	EPIC-NL and AMIGO cohorts	General population	50 087	Spatial LUR/ address-specific	Annual mean at baseline 1993–1997/ 2011–2012	PNC >10	–	Parkinson's disease prevalence
LUBCZYSKA 2021 [70]	Rotterdam, Netherlands	Generation R Study cohort	Pre-adolescent	3133	Spatiotemporal LUR/ address-specific	Pregnancy and childhood annual mean 2000–2006	10, >1000	NO ₂ NO _x PM _{2.5} PM ₁₀ Ozone BC	Brain volume
LUCHT 2019 [71]	Ruhr area, Germany	Heinz-Nixdorf-Recall cohort	Non-diabetic participants	4417	CTM/1×1 km	Annual mean at baseline 2001–2003	Accumulation mode	PM _{2.5} PM ₁₀ NO ₂ Traffic noise	Diabetes biomarkers, liver function

Continued

TABLE 2 Continued

Study	Location	Study name and design	Population	Sample size (n)	Exposure assessment/ spatial resolution	Exposure time window	Particle size range/type (nm)	Co-pollutant adjustment	Outcome(s)
LUCHT 2020 [72]	Ruhr area, Germany	Heinz-Nixdorf-Recall cohort	General population	4814	CTM/1×1 km	Annual mean at baseline 2001–2003	Accumulation mode	Traffic noise	Diabetes incidence, hs-CRP
LUCHT 2022 [73]	Ruhr area, Germany	1000BRAINS cohort	General population	688	CTM/1×1 km	Annual mean at baseline 2001–2003	Accumulation mode	PM _{2.5} PM ₁₀ NO ₂ Traffic noise	Default mode network
MATTHIESSEN 2023 [74]	Ruhr area, Germany	Heinz-Nixdorf-Recall cohort, cross-sectional	General population	4814	CTM/1×1 km	3-year mean at baseline 2000–2003	PNC	–	Non-alcoholic fatty liver disease prevalence
NIEDERMAYER 2024 [75]	Augsburg area, Germany	KORA, cross-sectional	General population	3034	Spatial LUR/ address-specific	Annual mean 2018	>7, 10–420	–	Diabetes and obesity prevalence
NOBILE 2023 [76]	Rome, Italy	Cohort (administrative)	General population	1 733 331	Spatial LUR/ address-specific	Annual mean at baseline 2011	10–3000	PM _{2.5} BC Noise	Incidence of psychiatric disorders
NÜBBAUM 2020 [77]	Ruhr area, Germany	1000BRAINS cohort	General population	615	CTM/1×1 km	Mean of 2006–2008	Accumulation mode	– Traffic noise	Cognitive function, brain structure
OGURTSOVA 2023 [78]	Ruhr area, Germany	Heinz-Nixdorf-Recall cohort	General population	2554	CTM/1×1 km	3-year mean at baseline 2006–2008	Accumulation mode	–	Cognitive decline
OHLWEIN 2021 [79]	Ruhr area, Germany	Heinz-Nixdorf-Recall cohort	General population	4814	CTM/1×1 km	Annual mean of year before baseline and each follow-up examination 2000–2015	Accumulation mode	NO ₂ PM _{2.5} PM ₁₀	Serum free light chains
OSTRO 2015 [80]	California, USA	California Teacher Study cohort	Female teachers and administrators	–	CTM/4×4 km	Mean of 2001–2007	Mass of particles ≤100	PM _{0.1} constituents	Natural and cause-specific mortality (cardiovascular, IHD, pulmonary) Atherosclerosis
PERALTA 2022 [81]	The Netherlands	PIAMA, cross-sectional	Adolescents	398	LUR-Kriging/ address-specific	Annual mean 1996	10, >1000	–	
PETERS 2024 [82]	The Netherlands (nationwide)	Dutch National Cohort (administrative)	General population	10 735 734	LUR model-Kriging/ address-specific	Annual mean at baseline 2013	10, >1000	NO ₂ PM _{2.5} PM ₁₀ EC	Mortality (ALS, Parkinson's disease, non-vascular dementia, Alzheimer's disease, multiple sclerosis)

Continued

TABLE 2 Continued									
Study	Location	Study name and design	Population	Sample size (n)	Exposure assessment/ spatial resolution	Exposure time window	Particle size range/type (nm)	Co-pollutant adjustment	Outcome(s)
PILZ 2018 [83]	Augsburg area, Germany	KORA, cross-sectional	General population	2279	Spatial LUR/ address-specific	Annual mean 2013/2014	>7, 10–420	PM _{2.5} Traffic noise	hs-CRP
POND 2022 [84]	USA (nationwide)	NHIS cohorts	General population	617 966+396 470	Spatial LUR/ census-block level	Annual mean at census time 1986–2014	–	PM _{2.5} PM coarse SO ₂	Mortality (natural, cardiopulmonary, cancer)
POULSEN 2023 [85]	Denmark	Cohort (administrative)	General population	1964	Hybrid: DEHM/ UBM/AirGIS/ address-specific	5-year moving TWA 1995–2017	10–1000	EC NO ₂	Stroke incidence
POULSEN 2023 [86]	Denmark	Cohort (administrative)	General population	1 964 702	Hybrid: DEHM/ UBM/AirGIS/ address-specific	5-year moving TWA 1995–2017	10–1000	–	MI incidence
Qi 2024 [23]	New York State, USA	NYS Vital Records (administrative), difference-in-difference design	General population	883 725 cases	CTM/county subdivision level	Annual mean in year of death 2013–2020	–	Ozone SO ₂ Ammonia	Natural and cause-specific mortality (cardiovascular, respiratory, mental disorders, diseases of the nervous system)
RIDDELL 2022 [87]	San Jose and Oakland, USA	Cross-sectional (administrative)	Mother–child pairs	8823	Measurement/ mobile/ street-level (30 m segments)	Median annual average daytime 2015–2017	>2.5	NO ₂ BC	Preterm birth
ROBINSON 2022 [88]	Brisbane, Australia	UPTECH, cross-sectional	School children	655	Spatiotemporal LUR/ address-specific	Annual mean 2010–2012	>6	NO ₂ PM _{2.5}	Functional residual capacity, lung biomarkers, respiratory disease
RODINS 2020 [89]	Ruhr area, Germany	Heinz-Nixdorf-Recall cohort	General population	4814	CTM/1×1 km	Annual average of baseline 2000–2015	Accumulation mode	Traffic noise	Incidence of total CVD and stroke
SØRENSEN 2022 [90]	Denmark	Cohort (administrative)	General population	1 922 545	Hybrid: DEHM/ UBM/AirGIS/ address-specific	5-year moving TWA 1995–2017	10–1000	NO ₂ PM _{2.5} EC Traffic noise	Diabetes incidence
SUNYER 2015 [91]	Barcelona, Spain	BREATHE cohort	Children	2897	Measurement/ central monitoring	Annual average 2012–2013	10–700	–	Cognitive function
VIEHMANN 2015 [92]	Ruhr area, Germany	Heinz-Nixdorf-Recall cohort	General population	3275	CTM/1×1 km	Annual mean at baseline and follow-up 2000–2003, 2006–2008	2–2200	PM _{2.5} PM ₁₀	hs-CRP, fibrinogen, white cell count, platelets

Continued

TABLE 2 Continued

Study	Location	Study name and design	Population	Sample size (n)	Exposure assessment/ spatial resolution	Exposure time window	Particle size range/type (nm)	Co-pollutant adjustment	Outcome(s)
VLAANDEREN 2022 [25]	The Netherlands	NTR and NESDA cohorts, cross-sectional	General population	2438+1567	Spatial LUR/ address-specific	Annual mean at examination 2004–2008	10–1000	PM _{2.5} PM ₁₀ PM _{2.5-10} PM abs NO ₂ NO _x	Genes related to cell signalling and immune response
VogLI 2024 [93]	Augsburg area, Germany	KORA, cross-sectional	General population	3969	Spatial LUR/ address-specific	Annual mean at examination 1999–2001	>7, 10–420	PM _{2.5} Ozone	hs-CRP, fibrinogen, SAA, IL-6, adiponectin
Voss 2021 [94]	Augsburg area, Germany	KORA cohort	General population	4261	Spatial LUR/ address-specific	Annual mean at baseline 2006–2008	>7, 10–420	PM _{2.5} Ozone Traffic noise	Metabolic syndrome prevalence and incidence
WEICHENTHAL 2017 [95]	Toronto, Canada	ONPHEC cohort (administrative)	General population	1 100 000	Spatial LUR/ address-specific	3-year moving averages 1996–2012	10, >1000	NO ₂ PM _{2.5}	Incidence of lung cancer, asthma and COPD
WEICHENTHAL 2017 [96]	Montreal, Canada	PROtEuS, case–control	General population	3927	Spatial LUR/ address-specific	Annual mean at baseline 2005–2009, 1996	10, >1000	NO ₂	Prostate cancer incidence
WEICHENTHAL 2020 [97]	Montreal, Toronto, Canada	CanCHEC cohort (administrative)	General population	1 938 100	Spatial LUR/ address-specific	3-year moving TWA 2001–2016	10, >1000	NO ₂ PM _{2.5}	Brain tumour/meningioma incidence
WING 2020 [98]	Los Angeles, USA	Cross-sectional (administrative)	Mother–child pairs	174 186	Dispersion model of airport UFPs/ address-specific	Trimester- and pregnancy mean 2008–2016	–, –	NO ₂ Airport noise	Preterm birth
WOECKEL 2024 [26]	Augsburg area, Germany	KORA, cross-sectional	General population	400	Spatial LUR/ address-specific	Annual mean at examination 2014/2015	>7, 10–420	PM _{2.5} PM ₁₀ PM _{2.5-10} PM abs NO ₂ NO _x	MRI phenotypes
WRIGHT 2021 [99]	Boston, USA	ACCESS and PRISM cohort	Mother–child pairs	376	Hybrid: spatial LUR +reference-site model/ address-specific	Pregnancy mean 2002–2009	7–3000, >4	NO ₂	Asthma incidence
Wu 2021 [100]	Los Angeles, USA	MEC	General population	75 936	Dispersion model of airport UFPs/ 1×1 km	TWA 1993–2013	10, >1000	NO _x NO ₂ CO Ozone PM _{2.5} PM ₁₀	Brain tumour/meningioma incidence

Continued

TABLE 2 Continued

Study	Location	Study name and design	Population	Sample size (n)	Exposure assessment/ spatial resolution	Exposure time window	Particle size range/type (nm)	Co-pollutant adjustment	Outcome(s)
Wu 2022 [101]	Liaoning Province, China	SNEC, cross-sectional	Children	47 990	Neural network simulated WRF-Chem model/ address-level	4-year mean 2009–2012	PNC	PM _{2.5} PM ₁₀ PM ₁	Childhood obesity
Yao 2022 [102]	Augsburg area, Germany	KORA cohort	General population	2583	Spatial LUR/ address-specific	Annual mean at baseline and follow-up 1999–2014	>7, 10–420	PM _{2.5} Ozone	Metabolites
Yu 2021 [103]	The Netherlands	PIAMA cohort	Adolescents	3687	LUR-Kriging/ address-specific	Annual means at baseline and follow-up 1996–2013	10, >1000	NO ₂ PM _{2.5} PM ₁₀ PM coarse BC	Lung function
Yu 2022 [104]	The Netherlands	PIAMA cohort	Adolescents	706	LUR-Kriging/ address-specific	Annual means at baseline and follow-up 1996–2017	10, >1000	NO ₂ PM _{2.5} PM ₁₀ PM coarse BC	Asthma incidence
Yu 2024 [105]	California, USA	Cohort (administrative)	Mother–child pairs	318 371	CTM/4×4 km	Pregnancy TWA 2001–2014	<100	1-year postnatal PM _{0.1}	Autism spectrum disorder
ZHANG 2021 [106]	Augsburg area, Germany	KORA cohort	General population	4261	Spatial LUR/ address-specific	Annual means at baseline and follow-up 1999–2014	>7, 10–420	PM _{2.5} Ozone Traffic noise	Insulin sensitivity (HOMA-B, HOMA-IR)
Zou 2022 [107]	Beijing, China	Cohort (administrative)	Pregnant women	24 001	Measurement/ central monitoring	Trimester means 2014–2017	Nucleation mode	NO ₂ Ozone CO SO ₂	Hypertension, diabetes, glucose levels

abs: absorbance; ALS: amyotrophic lateral sclerosis; BC: black carbon; CIMT: carotid intima-media thickness; CO: carbon monoxide; COPD: chronic obstructive pulmonary disease; CTM: chemical transport model; CVD: cardiovascular disease; DEHM/UBM/AirGIS: Danish Eulerian Hemispheric Model/Urban Background Model/Air geographic information system; DSPN: distal sensorimotor polyneuropathy; EC: elemental carbon; fILD: fibrotic interstitial lung disease; HOMA-B: homoeostasis model assessment of β -cell function; HOMA-IR: homoeostasis model assessment of insulin resistance; hs-CRP: high-sensitivity C-reactive protein; IHD: ischaemic heart disease; IL-6: interleukin-6; LUR: land-use regression; MI: myocardial infarction; MRI: magnetic resonance imaging; NDVI: normalised difference vegetation index; NO₂: nitrogen dioxide; NOx: nitrogen oxides; ONPHEC: Ontario Population Health and Environment Cohort; PM_{0.1}: particulate matter <0.1 μ m; PM_{2.5}: particulate matter <2.5 μ m; PM₁₀: particulate matter <10 μ m; PM coarse: particulate matter between 2.5 μ m and 10 μ m; PNC: particle number concentration; SAA: serum amyloid A; SO₂: sulfur dioxide; TAA: time-activity-adjusted; TNFRII: tumour-necrosis factor α receptor II; TWA: time-weighted average; UFP: ultrafine particle.

TABLE 3 Summary of findings in the studies on mortality outcomes

Outcome group	Study	Study outcome	Single-pollutant association (estimate and 95% CI)	Multi-pollutant association	
Natural	BOUMA 2023 [33]	Natural (all-cause) Natural mortality or lung transplantation in patients with fILD	HR 1.01 (1.01–1.02) per 2723 pt·cm ⁻³	+++	
	OSTRO 2015 [80]		HR 1.01 (0.98–1.05) per 969 ng·m ⁻³		
	LLOYD 2024 [68]		HR 1.07 (1.06–1.09) per 10 000 pt·cm ^{-3#}		+
	POND 2022 [84]		HR 1.03 (1.02–1.04) per 5007 pt·cm ⁻³		+(+)
	Qi 2024 [23]		RR 1.10 (1.05–1.17) per 834 pt·cm ^{-3¶}		
GOOBIE 2024 [49]		HR 1.01 (0.98–1.03) per 1000 pt·cm ⁻³	+		
Cardiovascular	BOUMA 2023 [33]	All CVD	HR 1.01 (1.00–1.01) per 2723 pt·cm ⁻³	(+) 0	
	OSTRO 2015 [80]		HR 1.01 (0.98–1.05) per 969 ng·m ⁻³		
	LLOYD 2024 [68]	Cardiopulmonary	HR 1.07 (1.05–1.10) per 10 000 pt·cm ^{-3#}	+	
	Qi 2024 [23]		RR 1.11 (1.05–1.18) per 834 pt·cm ^{-3¶}		
	POND 2022 [84]	IHD	HR 1.04 (1.02–1.06) per 5007 pt·cm ⁻³	(+) (+)	
	OSTRO 2015 [80]		HR 1.10 (1.02–1.18) per 969 ng·m ⁻³		
	LLOYD 2024 [68]	Cardiometabolic	HR 1.09 (1.06–1.13) per 10 000 pt·cm ^{-3#}	+	
	Qi 2024 [23]		RR 1.05 (0.98–1.13) per 834 pt·cm ^{-3¶}		
	LLOYD 2024 [68]	Cerebrovascular	HR 1.08 (1.05–1.00) per 10 000 pt·cm ^{-3#}	+	
	LLOYD 2024 [68]		HR 1.06 (1.01–1.12) per 10 000 pt·cm ^{-3#}		
Qi 2024 [23]	Hypertension	RR 1.21 (1.10–1.35) per 834 pt·cm ^{-3¶}			
Qi 2024 [23]		RR 1.03 (0.92–1.15) per 834 pt·cm ^{-3¶}			
Respiratory	BOUMA 2023 [33]	All respiratory	HR 1.02 (1.01–1.03) per 2723 pt·cm ⁻³	0 0	
	OSTRO 2015 [80]		HR 1.01 (0.93–1.10) per 969 ng·m ⁻³		
	LLOYD 2024 [68]		HR 1.17 (1.13–1.22) per 10 000 pt·cm ^{-3#}		
Respiratory	Qi 2024 [23]	Cardiopulmonary	RR 1.09 (1.00–1.18) per 834 pt·cm ^{-3¶}	+	
	POND 2022 [84]		HR 1.04 (1.02–1.06) per 5007 pt·cm ⁻³		
	JERRETT 2023 [55]		HR 1.06 (1.02–1.10) per 0.35 µg·m ⁻³		
Cancer	BOUMA 2023 [33]	Lung cancer	HR 1.04 (1.03–1.05) per 2723 pt·cm ⁻³	++	
	LLOYD 2024 [68]		HR 1.06 (1.02–1.10) per 10 000 pt·cm ^{-3#}		
	POND 2022 [84]		HR 1.05 (1.02–1.08) per 5007 pt·cm ⁻³		
Psychiatric	Qi 2024 [23]	Psychiatric diseases	RR 1.06 (0.98–1.14) per 834 pt·cm ^{-3¶}	(+) [‡]	
Neurological	PETERS 2024 [82]	ALS	HR 1.01 (0.96–1.06) per 2723 pt·cm ⁻³	0 0	
		Parkinson's disease	HR 0.99 (0.97–1.02) per 2723 pt·cm ⁻³		
		Non-vascular dementia	HR 0.99 (0.98–1.00) per 2723 pt·cm ⁻³	--	
		Alzheimer's disease	HR 1.00 (0.98–1.01) per 2723 pt·cm ⁻³	++	
		Multiple sclerosis	HR 1.00 (0.94–1.06) per 2723 pt·cm ⁻³		
	Qi 2024 [23]	Nervous system diseases	RR 0.94 (0.78–1.13) per 834 pt·cm ^{-3¶}		

Colours indicate adjustment for +NO₂, +PM_{2.5} and +PM_{2.5} and NO₂. +: positive estimate with p<0.05; (+): positive estimate with p>0.05; 0: estimate is close to the null and p>0.05; (-): negative estimate with p>0.05; -: negative estimate with p<0.05; ALS: amyotrophic lateral sclerosis; CVD: cardiovascular disease; fILD: fibrotic interstitial lung disease; HR: hazard ratio; IHD: ischaemic heart disease; NO₂: nitrogen dioxide; PM_{2.5}: particulate matter <2.5 µm; pt: particles; RR: relative risk. #: adjusted for black carbon and oxidant gases; ¶: adjusted for ammonia, ozone and sulfur dioxide (no single-pollutant models).

natural, cardiovascular, respiratory, cancer and psychiatric mortality outcomes. No associations were found in a study examining five neurological mortality outcomes.

Approximately half of the estimates (58.3%) were adjusted for co-pollutants in two-pollutant or multi-pollutant models. Only a few of the estimates, particularly those for natural and lung cancer mortality, as well as some cardiovascular outcomes (including all cardiovascular diseases, cerebrovascular disease, ischaemic heart disease and cardiometabolic mortality), remained positive after adjustment for NO₂ or PM_{2.5} (table S4).

We conducted a meta-analysis on natural mortality, which initially had five available estimates. We subsequently excluded two studies from the analysis: one that used mass concentration as the increment unit [80] and another that applied a difference-in-difference design using time series data [23], which we considered too different from the survival analysis approach used in the other studies. In a study that analysed two cohorts, where one was a subset of the other, we chose the estimate based on the larger

cohort [84]. Meta-analyses were not conducted for cardiovascular or respiratory mortality, each of which had only two estimates after exclusion of non-comparable studies [23, 80]. Based on three estimates, a 10 000 $\text{pt}\cdot\text{cm}^{-3}$ increase in long-term exposure to UFPs was significantly associated with natural mortality (HR 1.06, 95% CI 1.04–1.08) in single-pollutant models (figure 2). Heterogeneity was high at 77.4%. Excluding the estimate from a study that was rated at a high RoB in the questions on exposure assessment [84] did not change the meta-analytic estimate significantly (HR 1.06, 95% CI 1.02–1.09 based on two estimates). Owing to the small number of estimates, we did not conduct further analyses of publication bias, possible causes of heterogeneity or two-pollutant models.

Morbidity

There were 32 studies on morbidity (table 4), including incidence of stroke (n=3), coronary heart disease (n=3), myocardial infarction (MI) (n=3), childhood asthma (n=3), diabetes (n=3), lung cancer (n=3), brain tumour (n=3), childhood autism (n=3) and prevalence of diabetes (n=3). The most consistent positive associations were observed with MI, diabetes, stroke, brain tumour and childhood autism incidence. Other outcomes such as heart failure, COPD, prostate cancer and schizophrenia spectrum disorder incidence showed associations with UFPs, albeit with only one or two available studies for each outcome.

The available two-exposure and multi-exposure results showed that some estimates, including those for hypertension, diabetes incidence, cancers and partly for MI incidence, were robust to NO_2 and $\text{PM}_{2.5}$ adjustment. However, only 31 of the 51 single-pollutant estimates (60.8%) were adjusted for one or several other co-pollutants.

Subclinical outcomes

Among the 32 studies with overall 67 single-pollutant estimates on subclinical outcomes (table 5), most studies focused on markers of inflammation such as high-sensitivity C-reactive protein (n=8), fibrinogen (n=4) and interleukin-6 (n=3), as well as on cardiovascular pathologies such as atherosclerosis (n=3). The remaining studies assessed a variety of cardiovascular, respiratory, inflammatory and neurological outcomes. Overall, there were less consistent associations than with mortality and morbidity. Positive associations were observed with atherosclerosis, childhood obesity (body mass index), interleukin-1 receptor antagonists, C-reactive protein, fibrinogen, free light chains (IgG), distal sensorimotor polyneuropathy, cognitive development in children and cognitive function in adults. However, the majority of studies found nonsignificant or null associations.

Only 17 of the 67 single-pollutant analyses (25.4%) were adjusted for one or several other co-pollutants in additional analyses. Most of the adjusted estimates were attenuated, except for interleukin-1 receptor antagonist, free light chains, C-reactive protein, childhood obesity and cognitive function in children. However, there was only one adjusted estimate per outcome.

In a meta-analysis of five estimates on the association between long-term exposure to UFPs and C-reactive protein, excluding a study focusing on children [36], a study whose population was a subset of another included study [57] and a study on accumulation mode particles [72], we found a 10.14% (95% CI –0.56–21.99%) increase in C-reactive protein per 10 000 $\text{pt}\cdot\text{cm}^{-3}$ increase in exposure (figure 3). Heterogeneity was moderate ($I^2=67.5\%$) and there was an indication of publication bias in Egger's test ($p=0.005$) and funnel plot (figure S1). Excluding the study [92] that contributed most of the weight (33%)

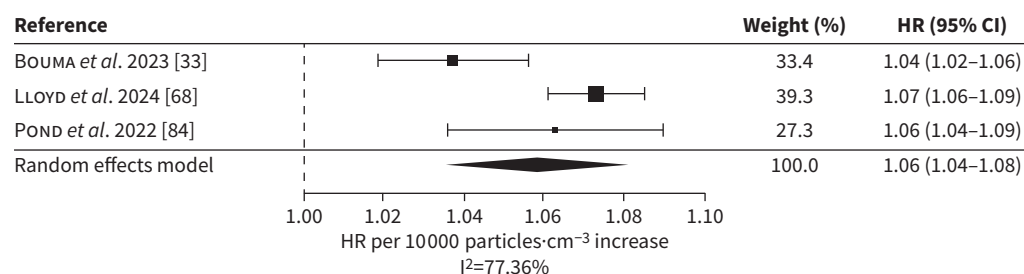


FIGURE 2 Forest plot of random-effects meta-analysis showing individual study and summary estimate of hazard ratios (HRs) and 95% confidence intervals (CIs) of natural mortality associated with each 10 000 particles·cm⁻³ increase in long-term exposure to ultrafine particles.

TABLE 4 Summary of findings in the studies on prevalence and incidence of morbidity outcomes

Outcome group	Study	Study outcome	Single-pollutant association (estimate and 95% CI)	Multi-pollutant association
Cardiovascular	DOWNWARD 2018 [41]	All CVD incidence	HR 1.18 (1.03–1.34) per 10 000 pt·cm ⁻³	++
	RODINS 2020 [89]		HR 1.07 (0.93–1.23) per 100 pt·cm ⁻³	
	DOWNWARD 2018 [41] [#]	Stroke incidence	HR 1.11 (0.88–1.41) per 10 000 pt·cm ⁻³	(+) (+)
	POULSEN 2023 [85]		HR 1.04 (1.03–1.05) per 4248 pt·cm ⁻³	+
	RODINS 2020 [89]		HR 1.06 (1.01–1.10) per 100 pt·cm ⁻³	
	LI 2017 [65]	Stroke prevalence	OR 1.61 (0.88–2.92)	
	BAI 2018 [29]	Hypertension incidence	HR 1.03 (1.02–1.04) per 9694 pt·cm ⁻³	++
	LI 2017 [65]	Hypertension prevalence	OR 1.28 (0.81–2.02)	
	BAI 2019 [30]	CHD incidence	HR 1.03 (1.02–1.05) per 10 005 pt·cm ⁻³	(+) +
	DOWNWARD 2018 [41]		HR 1.12 (0.94–1.33) per 10 000 pt·cm ⁻³	(+) +
	RODINS 2020 [89]		HR 0.98 (0.83–1.15) per 623 pt·cm ⁻³	
	BAI 2019 [30]	MI incidence	HR 1.05 (1.02–1.07) per 10 029 pt·cm ⁻³	++
	DOWNWARD 2018 [41]		HR 1.34 (1.00–1.79) per 10 000 pt·cm ⁻³	(+) +
	POULSEN 2023 [86]		HR 1.04 (1.03–1.06) per 4248 pt·cm ⁻³	
DOWNWARD 2018 [41]	Heart failure incidence	HR 1.76 (1.17–2.66) per 10 000 pt·cm ⁻³	(+) +	
Respiratory	WEICHTHAL 2017 [95]	Asthma incidence	HR 1.00 (1.00–1.01) per 10 097 pt·cm ⁻³	0 0 0
	CLIFFORD 2018 [36]	Childhood asthma prevalence	OR 0.96 (0.84–1.11) per 1000 pt·cm ⁻³	0
	LAVIGNE 2019 [62]		HR 1.09 (1.06–1.12) per 10 770 pt·cm ⁻³	(+) (+) +
	DA SILVA FLECK 2023 [39]	Childhood asthma incidence	HR 0.99 (0.98–1.00) per 3427 pt·cm ⁻³	0
	WRIGHT 2021 [99]		OR 4.28 (1.41–15.7) per 10 000 pt·cm ⁻³	+
	YU 2022 [104]		OR 1.08 (1.02–1.14) per 2342 pt·cm ⁻³	0 (+)
	WEICHTHAL 2017 [95]	COPD incidence	HR 1.06 (1.04–1.08) per 10 097 pt·cm ⁻³	0 + 0
Metabolic	BAI 2018 [29]	Diabetes incidence	HR 1.06 (1.05–1.08) per 9948 pt·cm ⁻³	+++
	LUCHT 2020 [72]		RR 1.29 (1.10–1.52) per 494 pt·mL ⁻¹	
	SØRENSEN 2022 [90]		HR 1.06 (1.05–1.07) per 4248 pt·cm ⁻³	++
	LI 2017 [65]	Diabetes prevalence	OR 1.09 (0.61–1.96) per IQR	
NIEDERMAYER 2024 [75]		OR 0.99 (0.74–1.25) in women, 1.30 (1.06–1.61) in men, per 1924 pt·cm ⁻³		
Cancer	WEICHTHAL 2017 [95]	Lung cancer incidence	HR 1.00 (0.97–1.04) per 10 097 pt·cm ⁻³	0 0 0
	BOOKSTEIN 2024 [32]		HR 1.01 (0.97–1.05) per IQR	
	JONES 2024 [56]		HR 1.03 (0.99–1.08) per 10 000 pt·cm ⁻³	
	GOLDBERG 2017 [48]	Breast cancer incidence	OR 1.00 (0.93–1.09) per 3845 pt·cm ⁻³	
	LAVIGNE 2020 [64] [¶]	Childhood cancers incidence	HR 1.07 (1.00–1.15) per 10 000 pt·cm ⁻³	++
	WEICHTHAL 2017 [96]	Prostate cancer incidence	OR 1.10 (1.01–1.19) per 4051 pt·cm ⁻³	+
	WEICHTHAL 2020 [97]	Brain tumour incidence	HR 1.10 (1.03–1.17) per 10 000 pt·cm ⁻³	+++
	WU 2021 [100]		HR 1.12 (0.98–1.27) per IQR	(+) +
	LLOYD 2024 [67]		HR 1.03 (0.95–1.12) per 10 000 pt·cm ⁻³	(+)
	WU 2021 [100]	Meningioma incidence	HR 0.98 (0.90–1.08) per IQR	
Psychiatric	NOBILE 2024 [76] (incidence)	Schizophrenia spectrum disorder	HR 1.11 (1.05–1.17) per 2673 pt·cm ⁻³	+
		Bipolar disorder	HR 0.98 (0.93–1.04) per 2673 pt·cm ⁻³	
		Depression	HR 1.06 (1.02–1.11) per 2673 pt·cm ⁻³	+
		Anxiety, stress-related and somatoform disorders	HR 1.04 (0.98–1.12) per 2673 pt·cm ⁻³	0
		Personality and behaviour disorders	HR 0.92 (0.84–1.00) per 2673 pt·cm ⁻³	
		Substance use disorders	HR 1.00 (0.93–1.09) per 2673 pt·cm ⁻³	
		Antipsychotic drugs	HR 0.99 (0.98–1.00) per 2673 pt·cm ⁻³	(-)
		Antidepressant drugs	HR 1.01 (1.00–1.02) per 2673 pt·cm ⁻³	+
		Mood stabiliser drugs	HR 1.01 (1.00–1.01) per 2673 pt·cm ⁻³	0
	CARTER 2023 [35]	Childhood autism incidence	HR 1.02 (1.01–1.03) per IQR	+
GOODRICH 2024 [51] [†]		cPIP 0.76		
Neurological	BLANCO 2024 [31]	Dementia incidence	HR 1.00 (0.93–1.06) per 2000 pt·cm ⁻³	0 (+) [§]
	LOMME 2023 [69]	Parkinson's disease prevalence	OR 1.29 (0.87–1.93) per Q4 versus Q1	

Continued

TABLE 4 Continued

Outcome group	Study	Study outcome	Single-pollutant association (estimate and 95% CI)	Multi-pollutant association
Digestive system	MATTHIESSEN 2023 [74]	Non-alcoholic fatty liver disease	OR 1.10 (1.00, 1.22) per 26 558 pt·mL ⁻¹	

Colours indicate adjustment for +NO₂, +PM_{2.5} and +PM_{2.5} and NO₂. +: positive estimate with p<0.05; (+): positive estimate with p>0.05; 0: estimate is close to the null and p>0.05; (-): negative estimate with p>0.05; -: negative estimate with p<0.05; CHD: coronary heart disease; cPIP: conditional posterior inclusion probability; CVD: cardiovascular disease; HR: hazard ratio; IQR: interquartile range; MI: myocardial infarction; NO₂: nitrogen dioxide; OR: odds ratio; PM_{2.5}: particulate matter <2.5 µm; pt: particles; Q1: first quartile; Q4: fourth quartile; RR: relative risk; UFP: ultrafine particle. #: cerebrovascular events; †: this study also examined astrocytoma (-) (-) (-), acute lymphoid leukaemia 0 (+) (+) and neuroblastoma 0 0 0; ‡: positive associations only with UFPs during the second year of life, but not with pre-pregnancy, pregnancy-, trimester- or year-1-exposures (mixture analysis of particulate matter, NO₂ and ozone exposure); §: adjusted for PM_{2.5}, NO₂ and black carbon.

increased the estimate to 14.56% (95% CI 5.13–24.38%) per 10 000 pt·cm⁻³ increase in UFPs. A meta-analysis was not conducted for fibrinogen, because one of the four available studies focused on accumulation mode particles [71].

Pregnancy and birth outcomes

Pregnancy-related or birth-related outcomes were examined in 11 studies, including preterm birth (n=4) and low birth weight (n=3) (table 6). Positive associations were observed for preterm birth, low birth weight, blood glucose levels and gestational diabetes, while the associations for other outcomes were less consistent. Only five out of 12 estimates (41.7%) were adjusted for co-pollutants, for which associations with blood glucose levels, gestational diabetes and preterm birth were robust to NO₂ adjustment. None was adjusted for PM_{2.5}.

We did not conduct a meta-analysis on the four studies on preterm birth, because one of them focused on PM_{0.1} [61].

Assessment of the confidence in the body of evidence

We rated the initial confidence in the body of evidence as moderate for the four cohort studies and one time series study on natural mortality and low for the eight cross-sectional studies on C-reactive protein (table 7). Despite one study with high RoB in exposure assessment, results for natural mortality did not change after exclusion of this study and therefore no downgrade was applied. For C-reactive protein, a downgrade was applied owing to six studies having a high RoB across different domains. Heterogeneity in meta-analyses was high for mortality, so a downgrade was applied for inconsistency, and moderate for C-reactive protein, where no downgrade was applied. For imprecision, we applied a downgrade for the studies on C-reactive protein, for which the meta-analytic confidence interval was wide and overlapped unity. Publication bias was detected in the studies on C-reactive protein, which is why a downgrade was applied. Among the upgrading factors, two influential studies [57, 58] presented monotonic exposure–response functions for C-reactive protein, so an 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 number of studies was too low to apply an upgrade for consistency across populations. The final confidence assessment yielded a rating of low confidence in the body of evidence for natural mortality and very low confidence for C-reactive protein. Accordingly, we rated the evidence level as low for natural mortality and inadequate for C-reactive protein.

Discussion

General results

We identified 85 studies on the association between long-term exposure to UFPs and health outcomes published between 2011 and 2024, showing a substantial increase with 75 new studies since the OHLWEIN *et al.* review [8].

The identified studies evaluated a large variety of mortality, morbidity and subclinical outcomes. In two meta-analyses of single-pollutant models, long-term exposure to UFPs was significantly associated with natural mortality and increases in C-reactive protein, with low and inadequate levels of evidence, respectively. Other outcomes were too heterogeneous, with too few studies per specific outcome, to conduct meta-analyses, but revealed overall limited evidence for adverse health effects.

TABLE 5 Summary of findings in the studies on subclinical outcomes

Outcome group	Study	Study outcome	Single-pollutant association (estimate and 95% CI)	Multi-pollutant association
Cardiovascular	ENDES 2017 [42]	Arterial stiffness	OR 1.14 (0.71–1.81) per IQR	0
	AGUILERA 2016 [27]	Atherosclerosis (CIMT)	% change 2.06 (0.03–4.10) per 12 639 pt·cm ⁻³	
	HENNIG 2020 [52]		OR 1.15 (0.95–1.41) per 528 pt·mL ⁻¹	
	PERALTA 2022 [81]		0 [#]	
	CORLIN 2018 [37]	Blood pressure	SBP % change 5.23 (–0.68–11.14), DBP 0.96 (–2.08–4.00) per ln-unit increase	
	CORLIN 2018 [38]		% change 1.81 (0.94–3.48) per 5000 pt·mL ⁻¹	
	CORLIN 2018 [37]	Pulse pressure	% change 4.27 (–0.79–9.32) per ln-unit increase	
	CORLIN 2018 [38]		% change 0.70 (–0.27–1.67) per 5000 pt·mL ⁻¹	
Cardiovascular	WOECKEL 2024 [26]	Global LV wall thickness	% change –1.03 (–2.53–0.48) per 2242 pt·cm ⁻³	0
		Cardiac adipose tissue	% change 1.64 (–3.40–6.68) per 2242 pt·cm ⁻³	
Respiratory	YU 2021 [103]	Lung function	(–) [#]	(–) (–)
	GOOBIE 2024 [49]	FVC in fILD patients	β –0.21 (–0.64–0.22) per 1000 pt·cm ⁻³	–
	CLIFFORD 2018 [36]	D _{LCO} in fILD patients	β 0.16 (–0.29–0.61) per 1000 pt·cm ⁻³	(–)
	ROBINSON 2022 [88]	Respiratory markers in children	0 ⁺ (–) ⁺	0 (–)
Metabolic	DE BONT 2019 [40]	Childhood obesity	OR 1.11 (0.96–1.29) per 13 010 pt·cm ⁻³	+
	WU 2022 [101]		OR 1.32 (1.03–1.69), Q3 compared to Q1	
	NIEDERMAYER 2024 [75]	Obesity prevalence	OR 0.86 (0.76–0.98) in women, 1.15 (1.00–1.31) in men, per 1924 pt·cm ⁻³	
	LUCHT 2019 [71]	IL-1RA	% change 2.84 (1.55–4.28) per 774 pt·mL ⁻¹	
	LUCHT 2020 [72]		% change 4 (1–6) per 494 pt·mL ⁻¹	
	LUCHT 2019 [71]	Adiponectin	% change –0.49 (–1.70–0.76) per 774 pt·mL ⁻¹	
	LUCHT 2020 [72]		% change –6 (–9– –2) per 494 pt·mL ⁻¹	
	VOGLI 2024 [93]		% change –1.06 (–2.83–0.73) per 1945 pt·cm ⁻³	
	VOGLI 2024 [93]	Serum amyloid A	% change 1.92 (–0.79–4.70) per 1945 pt·cm ⁻³	
	ZHANG 2021 [106]	Insulin sensitivity (HOMA-IR)	% change 0.7 (–1.0–2.4) per 2000 pt·cm ⁻³	
YAO 2022 [102]	Metabolites	0 (not numerically reported)		
VOSS 2021 [94]	Metabolic syndrome prevalence	OR 1.04 (0.95–1.13) per 2000 pt·cm ⁻³		
	Metabolic syndrome incidence	OR 1.01 (0.87–1.17) per 2000 pt·cm ⁻³		
Inflammation-associated biomarkers	BOUMA 2023 [34]	Food allergens	OR 1.05 (0.98–1.12) per 2272 pt·cm ⁻³	0 0
		Inhalant allergens	OR 1.02 (0.95–1.10) per 2272 pt·cm ⁻³	0 0
	CLIFFORD 2018 [36]	CRP	Fold change 1.69 (1.07–1.27) per 1000 pt·cm ⁻³	+
	CORLIN 2018 [38]		% change 6.8 (–0.3–14.0) per 5000 pt·mL ⁻¹	
	LANE 2015 [57]		% change 1.26 (–0.02–2.75) per 10 000 pt·cm ⁻³	
	LANE 2016 [58]		% change 9.8 (–8.3–31.4) per 10 000 pt·cm ⁻³	
	LUCHT 2020 [72]		% change 10 (5–16) per 494 pt·mL ⁻¹	
	PILZ 2018 [83]		% change 3.63 (–0.86–8.33) per 2000 pt·cm ⁻³	
	VIEHMANN 2015 [92]		% change 3.8 (0.6–8.4) per 27 000 pt·mL ⁻¹	0
	VOGLI 2024 [93]		% change 3.16 (–0.52–6.98) per 1945 pt·cm ⁻³	
	LANE 2015 [57]	IL-6	% change 0.65 (–0.26–1.55) per 10 000 pt·cm ⁻³	
	LANE 2016 [58]		% change 5.8 (–5.6–18.5) per 10 000 pt·cm ⁻³	
	VOGLI 2024 [93]		% change 1.40 (–7.53–11.20) per 1825 pt·cm ⁻³	
	LANE 2016 [58]	Fibrinogens	% change –1.9 (–5.5–1.6) per 10 000 pt·cm ⁻³	
	LUCHT 2019 [71]		(+) (not numerically reported)	
	VIEHMANN 2015 [92]		% change 1.0 (0–2.0) per 27 000 pt·mL ⁻¹	
	VOGLI 2024 [93]		% change 0.70 (0.04–1.37) per 1945 pt·cm ⁻³	
OHLWEIN 2021 [79]	Free light chains	% change 0.36 (–0.44–1.16) per 710 pt·mL ⁻¹	+	
VIEHMANN 2015 [92]	WCC/platelets	% change 1.0 (–0.1–2.1) per 27 000 pt·mL ⁻¹	+	
VLAANDEREN 2022 [25]	Cell signalling and immune response genes	0 (no effect estimate)		

Continued

TABLE 5 Continued

Outcome group	Study	Study outcome	Single-pollutant association (estimate and 95% CI)	Multi-pollutant association
Neurological	NUßBAUM 2020 [77]	Cognitive development (working memory)	0 ⁺	
	FORNS 2017 [44]	Cognitive development (working memory) in children	% change -18.2 (-27.5- -8.9) per 12 770 pt·cm ⁻³	
	SUNYER 2015 [91]	Cognitive decline	-4.90 (-10-0.22) per 6110 pt·cm ⁻³	
	GAN 2023 [45]		0 ⁺	
	OGURTSOVA 2023 [78]		0 ⁺	0
	GLAUBITZ 2022 [46]	Functional connectivity	0 ⁺	
	HERDER 2020 [53]	DSPN prevalence	RR 1.10 (1.01-1.20) per 1700 pt·cm ⁻³	
	HERDER 2020 [53]	DSPN incidence	RR 1.11 (0.99-1.24) per 1700 pt·cm ⁻³	
	HERDER 2023 [54]		RR 1.13 (1.00-1.28) per 2000 pt·cm ⁻³	
	LUBCZYSKA 2021 [70]	Brain volume in preadolescents	0 ⁺	0 0
	LUCHT 2022 [73]	Cortical thickness in the DMN	0 ⁺	
	NUßBAUM 2020 [77]	Cognitive domains	(-) ⁺	
	SUNYER 2015 [91]		+ ⁺	
NUßBAUM 2020 [77]	Cognitive function	(-) ⁺		
GOODRICH 2024 [50]	Cognitive function in children [‡]	cPIP 0.73-0.96	+	
NUßBAUM 2020 [77]	Area-specific grey-matter thickness	0 ⁺		
Others	LIAO 2024 [24]	Self-perceived health status	EQ-5D % change -0.33 (-0.97-0.33), EQ-VAS -0.89 (-1.68-0.10), per 1900 pt·cm ⁻³	

Colours indicate adjustment for +NO₂, +PM_{2.5} and +PM_{2.5} and NO₂. +: positive estimate with p<0.05; (+): positive estimate with p≥0.05; 0: estimate is close to the null and p>0.05; (-): negative estimate with p>0.05; -: negative estimate with p<0.05; CIMT: carotid intima-media thickness; cPIP: conditional posterior inclusion probability; CRP: C-reactive protein; DBP: diastolic blood pressure; D_{LCO}: diffusing capacity of the lungs for carbon monoxide; DMN: default mode network; DSPN: distal sensorimotor polyneuropathy; EQ-5D: European Quality of Life 5 Dimensions questionnaire; EQ-VAS: European Quality of Life Visual Analogue Scale; FiLD: fibrotic interstitial lung disease; FVC: forced vital capacity; HOMA-IR: homoeostasis model assessment of insulin resistance; IL-1RA: interleukin-1 receptor antagonist; IL-6: interleukin-6; IQR: interquartile range; LV: left ventricle; OR: odds ratio; pt: particles; Q1: first quartile; Q3: third quartile; RR: relative risk; SBP: systolic blood pressure; WCC: white cell count. [‡]: this study examined associations with deciles of CIMT, all of which were nonsignificant; [¶]: this study included forced expiratory volume in 1 s and FVC (estimates were (-) (-) and - 0 (-), respectively); ^{*}: summary of different indicators.

Only a few previous systematic reviews have assessed the association between long-term exposure to UFPs and health outcomes (table S5). First, the systematic review by OHLWEIN *et al.* [8], published in 2019, identified 10 studies on long-term UFP exposure, all of which were included in our current review. This review concluded that the available evidence was not sufficient to make conclusions on independent health effects of UFPs. Second, the systematic review by VALLABANI *et al.* [9] was conducted on source-specific UFPs and was restricted to clinical outcomes. They identified 14 studies on long-term exposure to source-specific UFPs, which were also included in our review. Similarly, they concluded that the evidence was too inconsistent, mostly due to missing co-pollutant adjustment, to document independent effects of UFPs. Third, a recent meta-analysis found a significant positive association between long-term exposure to UFPs and C-reactive protein [108]. However, the five studies included in that analysis were not identical to ours owing to a different definition of UFPs (strictly <100 nm) and long-term exposure (more than 7 days) applied in that review, as well as inclusion of a study that used distance to traffic as its exposure. Lastly, the same authors found a positive association between long-term exposure to UFPs and blood pressure in a meta-analysis of three studies [109].

Health effects associated with long-term exposure to UFPs

In general, associations were more consistent for mortality and morbidity than for subclinical outcomes, partly due to the wide range of outcomes in the latter. Among the different organ systems and disease groups, cardiovascular diseases (both clinical and subclinical), metabolic diseases (diabetes and diabetes biomarkers), inflammation biomarkers and cancer were most consistently associated with long-term exposure to UFPs. We did not find strong evidence for respiratory outcomes, where most estimates were nonsignificant or diminished in two-pollutant models. Several very recent studies have evaluated the

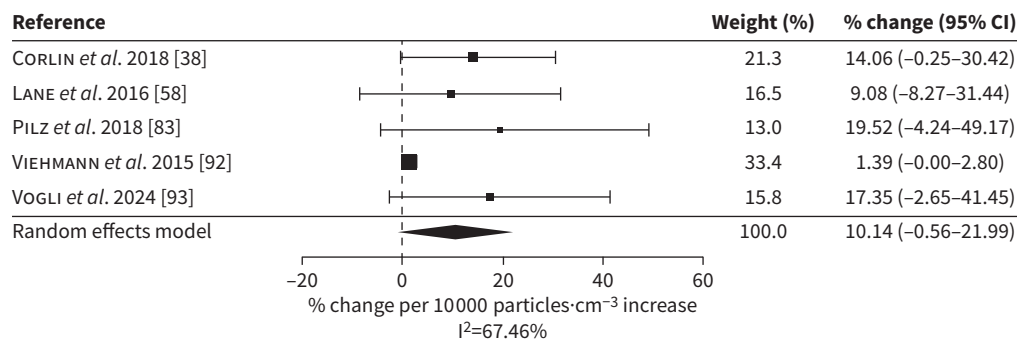


FIGURE 3 Forest plot of random-effects meta-analysis showing individual study and summary estimate of % change and 95% confidence intervals (CIs) in C-reactive protein associated with each 10 000 particles·cm⁻³ increase in long-term exposure to ultrafine particles.

association between long-term exposure to UFPs and neurological and psychiatric outcomes [23, 31, 35, 51, 69, 76, 82, 105]. While these were nonsignificant in studies on psychiatric mortality, positive associations were found with incidence of schizophrenia spectrum disorder, depression and childhood autism.

There are several biological mechanisms behind the adverse health effects of UFP exposure. Exposure to UFPs induces oxidative stress, triggering inflammation, as reflected in our findings, and ultimately increasing the risk of cardiovascular and respiratory diseases [5, 110]. Moreover, UFPs have the ability to deposit deep in the pulmonary alveoli or penetrate biological membranes, from where they can pass into the circulatory system and reach all organs systems, including the brain and nervous system [5, 111]. This systemic translocation of UFPs can lead to endothelial and vascular dysfunction, hypertension, thrombosis and atherosclerosis, and might promote vasoconstriction in the coronary arteries, increasing the risk of stroke, coronary heart disease, heart failure and death [5, 112].

Notably, only about half of all single-pollutant estimates were further adjusted for co-pollutants, limiting the evaluation of independent effects of UFP. Ideally, results should be adjusted for at least PM_{2.5} and NO₂, which are typically moderately correlated with UFPs and may confound UFP health effects estimates [8]. Other relevant exposures include traffic noise and BC or EC. In the available estimates from two-pollutant and multi-pollutant models, only some outcomes, including natural, cardiovascular and lung cancer mortality, as well as cardiovascular disease, hypertension, cancer and diabetes incidence, remained positive after adjustment for NO₂, PM_{2.5} or both, indicating that further research into possible independent effects of UFPs is needed.

TABLE 6 Summary of findings in the studies on pregnancy and birth outcomes

Outcome group	Study	Study outcome	Single-pollutant association (estimate and 95% CI)	Multi-pollutant association
Cardiovascular	ASSIBEY-MENSAH 2019 [28]	Hypertension	OR 1.00 (0.98–1.02) per 4018 pt·cm ⁻³	
Metabolic	ZOU 2022 [107]	Blood glucose levels	% change 4.3 (3.7–4.8) per 5714 pt·cm ⁻³	+
		Gestational diabetes	OR 1.61 (1.35–1.93) per 5714 pt·cm ⁻³	+
Birth outcomes	FANG 2022 [43]	Preterm birth	OR 1.09 (1.03–1.15) per 1000 pt·cm ⁻³	0
	LAURENT 2016 [61]		OR 1.02 (1.02–1.03) per 1.39 µg·m ⁻³ (primary PM _{0.1})	
	RIDDELL 2022 [87]		0 (no estimate for total population)	0
	WING 2020 [98]		OR 1.04 (1.02–1.06) per 9200 pt·cm ⁻³	+
	LAURENT 2014 [59]	Low birth weight	OR 1.03 (1.02–1.03) per 0.43 µg·m ⁻³	
	LAURENT 2016 [60]		OR 1.00 (0.98–1.01) per 6444 pt·cm ⁻³	
	LI 2019 [66]		Absolute change 1.1 (-5.7–7.9) per 1800 pt·cm ⁻³	
	GOIN 2021 [47]	Pre-eclampsia	% change -0.5 (-1.8–0.7) for UFP reduction	
LAVIGNE 2019 [63]	Congenital heart defect	OR 1.02 (0.96–1.08) per 10 864 pt·cm ⁻³		

Colours indicate adjustment for +NO₂. +: positive estimate with p<0.05; (+): positive estimate with p≥0.05; 0: estimate is close to the null and p>0.05; (-): negative estimate with p>0.05; -: negative estimate with p<0.05; OR: odds ratio; PM_{0.1}: particulate matter <0.1 µm; pt: particles; UFP: ultrafine particulate.

TABLE 7 Rating of the confidence in the body of evidence on studies on long-term exposure to ultrafine particles (UFPs), using the OHAT method [23]

Outcome	High ++++ Moderate +++ Low ++ 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			Final confidence rating
	Initial confidence rating	RoB	Unexplained inconsistency	Imprecision	Publication bias	Monotonic exposure–response	Consideration of residual confounding	Consistency across populations	
Natural mortality	+++ (n=5) [#] Cohort design (n=4) initially rated as moderate	0 One study at high RoB	-1 High heterogeneity (I ² =77%)	0 Narrow confidence interval	0 Not assessed due to small number of studies	0 Only one study [68] assessed exposure–response curves and found monotonic increases that attenuated at higher concentration	0 Confounding in both directions possible	0 Too few studies to assess consistency	++
C-reactive protein	++ (n=8) [¶] Cross-sectional design initially rated as low	-1 Six studies at high and two at moderate RoB	0 Moderate heterogeneity (I ² =68%)	-1 Wide confidence interval overlapping unity	-1 Indication of publication bias (Egger’s test p=0.005)	1 Two influential studies [57, 58] assessed exposure–response and found monotonic curves	0 Confounding in both directions possible	0 Too few studies to assess consistency	+

Definitions according to Office of Health Assessment and Translation (OHAT) [22]: ++++: 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 in the association between exposure to the substance and the outcome. The true effect may be reflected in the apparent relationship. ++: 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 in the association between exposure to the substance and the outcome. The true effect is highly likely to be different from the apparent relationship. For evidence ratings, high: high confidence in the body of evidence for an association between exposure to the substance and the health outcome(s); moderate: moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome(s); low: 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; no health effect: high confidence in the body of evidence that exposure to the substance is not associated with the health outcome(s); inadequate: insufficient evidence available to assess if the exposure to the substance is associated with the health outcome(s). RoB: risk of bias. [#]: only three studies entered the cohort analysis (assessment was done on all five studies); [¶]: only six studies entered the cohort analysis (assessment was done on all nine studies).

Exposure assessment methods and exposure misclassification

Some of the inconclusive findings may be explained by challenges in exposure assessment that are inherent to UFPs. Related to the large spatial variation of UFPs, exposure misclassification could arise from the use of data from a central or few monitoring stations, models with a coarse resolution, or imprecise assignment of exposure to individuals (e.g. at postal code level). Furthermore, temporal mismatch might have led to exposure misclassification, where one annual mean, estimated in a later year, was assigned to participants' baseline addresses sometimes years earlier. Only a few studies [56, 68, 113] used methods and supplemental data to back-extrapolate the model estimations in time to overcome the lack of air pollution data in earlier years, while in some cases, it has been shown that past spatial variation might be well aligned with measurements taken in later years [114].

The models applied in the studies identified in our review were mostly LUR models or CTMs. The quality of LUR models depends on factors such as the number of monitoring sites and the land-use variables used to build the model. Some older LUR models for UFPs relied on few monitoring stations, limiting their ability to accurately capture the spatial variation of UFPs, while some newer models included more sites. In contrast, CTMs depend on the availability and quality of UFP emission inventories. Notably, more recently developed LUR models from Canada, Germany, the Netherlands, Switzerland and the USA combined stationary and mobile monitoring data, thus increasing the number of measurement sites and reaching better model performance [31, 67, 68, 87]. Furthermore, five studies from Boston, USA, combined spatiotemporal LUR and microscale personal exposures to model time-activity-adjusted exposure [37, 38, 57, 58, 65].

For studies on the health effects of UFPs, it is especially important that exposure models are able to distinguish the spatial variation of UFPs from that of other co-pollutants to evaluate whether there are independent effects of UFPs. Notably, our meta-analytic estimates were restricted to single-pollutant estimates owing to the limited availability of multi-pollutant estimates. Out of the five studies on natural mortality, three presented low to moderate correlations (0.10–0.59) of UFPs with $PM_{2.5}$ and found their estimates to be robust to this adjustment [33, 68, 84], while the remaining two studies did not adjust for $PM_{2.5}$. The correlations with NO_2 , assessed in two of five studies, was above 0.8 [33, 84], making it difficult to disentangle the effects of UFPs and NO_2 . Similarly, the same two studies found moderate to high correlation with BC or EC. Among the studies on C-reactive protein, only two performed co-pollutant adjustment, with moderate correlations between UFPs and nitrogen oxides (0.68) [36] and $PM_{2.5}$ (0.34) [92]. This leaves an important research gap on independent health effects of UFPs that should be addressed in future studies using advanced exposure models and multi-pollutant statistical approaches. The development of multi-pollutant statistical approaches remains an active area of research, and many advanced approaches have been developed, particularly for omics analyses and in studies of the exposome [115–117].

Lastly, an area largely unexplored by epidemiology is whether the health effects of UFPs differ between different emission sources and related chemical composition. Different sources were compared in three Danish studies, which found no consistent differences between traffic and non-traffic UFPs [86, 90, 118]. Three studies from California, USA, compared UFPs from six different sources and found significant associations for most sources, with inconsistencies between the three studies [59–61]. However, these studies were hampered by missing emission inventories for UFPs, which increased uncertainty in the exposure model. Moreover, the Californian studies focused on size-fractionated PM emissions, captured as particle mass concentration of $PM_{2.5}$ and $PM_{0.1}$, at a fairly coarse model resolution of 4 km×4 km, which might not have captured UFP variations adequately. Four US studies [32, 35, 98, 100] examined long-term exposure to airport-related UFPs, modelled in CTMs or dispersion models, and found positive associations with outcomes, including preterm birth, autism spectrum disorder in children and brain cancer. In addition to source, particle composition (e.g. metals, organic compounds or polycyclic aromatic hydrocarbons) may also influence the toxicity of UFPs. This was also examined in the Californian studies, with strongest associations for secondary organic aerosols and organic carbon. Caution is warranted when interpreting these results because the exposure model focused on mass concentrations and associations could not be disentangled from the highly correlated composition of $PM_{2.5}$.

As a limitation of our review, we note that the article screening was not done in duplicate, but only 10% of one reviewer's articles were cross-checked by their counterpart, which might have led to subjective exclusion of suitable articles. Furthermore, we note that our decision to conduct meta-analyses if at least four effect estimates were available for an outcome was arbitrary and the number of meta-analyses would increase substantially if we chose a looser threshold of three estimates.

Conclusion

The number of studies on the health effects of long-term exposure to UFPs has increased substantially since the last review in 2019. However, owing to ongoing challenges in assessing long-term exposure to highly variable UFPs, disentangling the effects of co-pollutants, and the limited data available for many health outcomes, the overall evidence for independent effects of long-term UFP exposure remains inadequate to low. The strongest evidence to date pertains to natural mortality and elevated levels of C-reactive protein. Further research, particularly large-scale studies that use advanced exposure modelling for UFPs and co-pollutants, rigorously adjust for co-pollutants and apply multi-pollutant statistical approaches, is necessary to draw more definitive conclusions about the health impacts of UFPs.

Points for clinical practice

- The epidemiological evidence on long-term health effects of UFPs (≤ 100 nm) has grown, with potential adverse effects on a wide range of outcomes.
- Long-term exposure to UFPs is associated with a modest but statistically significant increase in natural mortality, based on current epidemiological evidence.
- There is suggestive evidence for systemic inflammation, as indicated by increased C-reactive protein levels, although findings remain inconclusive.
- Clinicians should be aware that air pollution-related health risks may not be fully captured by current regulatory monitoring, which typically excludes UFPs.
- Vulnerable populations, including patients with pre-existing cardiopulmonary conditions, may be particularly susceptible to the effects of UFP exposure.

Questions for future research

- What are the independent health effects of long-term exposure to UFPs after adjustment for co-pollutants such as $PM_{2.5}$ and NO_2 ?
- How do different UFP sources (e.g. traffic emissions, airports) influence health outcomes across diverse populations?
- What are the most reliable and feasible methods for estimating long-term UFP exposure at the population level?
- Are certain subpopulations (e.g. children, older adults, individuals with underlying disease) more susceptible to health effects of long-term UFP exposure?
- Can interventions targeting UFP reduction demonstrate measurable health benefits, and how do these compare to existing strategies focused on larger particulate matter?

Data availability: Template data collection forms, data extracted from included studies, data used for all analyses, codes and any other materials used in the review will be made available upon request.

Provenance: Submitted article, peer reviewed.

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