KØBENHAVNS UNIVERSITET
INSTITUT FOR FOLKESUNDHEDSVIDENSKAB

Health Effects of Ultrafine Particles

A literature review

Scientific Report 2024

Prepared by the Environmental Epidemiology Group

University of Copenhagen

Health Effects of Ultrafine Particles

Marie L. Bergmann
Zorana J. Andersen
Steffen Loft
Youn-Hee Lim

Section of Environmental Health
Department of Public Health
University of Copenhagen

April 2024

Photo on title page: Branislav Nenin

Table of Contents

List of abbreviations

COPD	Chronic obstructive pulmonary disorder
HR	Hazard ratio
IQR	Interquartile range
NO_2	Nitrogen dioxide
PM	Particulate matter (particles)
$PM_{0.1}$	Particulate matter of diameter <0.1 μm
$PM_{2.5}$	Particulate matter of diameter <2.5 μm
PM_{10}	Particulate matter of diameter <10 μm
OR	Odds ratio
PNC	Particle number concentration
RR	Relative risk
UFP	Ultrafine particles
WHO	World Health Organization

Report requested by the City of Copenhagen

København Kommune, Sundheds- og Omsorgsforvaltningen

April 2024

1. Introduction

It is well known that ambient air pollution in the form of particulate matter <2.5 μm ($PM_{2.5}$) can cause adverse health effects such as cardiovascular and respiratory diseases, contributing to approximately four million deaths worldwide every year (1). Recently, there has been increasing research interest in ultrafine particles (UFP), which are the smallest fraction of particulate matter below 0.1 μm, or 100 nm, in diameter. They are small and light, and thus not well represented in the routinely monitored particle mass concentration, but better reflected as particle number concentrations. They also differ from larger particles in terms of their primary sources, which are traffic emissions in urban areas with some contributions from wood stoves, construction work and other combustion processes, and in their short lifespan in the air and large spatial and temporal variation. The health concerns related to UFP are caused by their increased toxicity related to their high surface reactivity and ability to carry large amounts of potentially toxic materials. Additionally, their small size allows them to enter deep into the lungs, blood stream, and be translocated to other organs including the brain and nervous system (2).

Two systematic reviews on the health effects of UFP from 2013 and 2019 found insufficient numbers of studies and inconclusive results (2,3). While there was some evidence of an association between short-term UFP exposure and inflammatory and cardiovascular changes in the body from panel studies, evidence on mortality or the incidence or exacerbation of diseases was scarce. Since the last review, there has been a surge in studies on health effects of UFP, which is why an update of existing reviews is needed.

Studies on the health effects of UFP can be divided into short- and long-term exposure studies. Short-term studies investigate whether changes in daily concentrations of UFP trigger hospital admissions or mortality within a few days of increased exposure. Long-term studies examine the association between UFP exposure over the course of several years and health outcomes. While short-term studies usually combine aggregated health data, such as total daily numbers of deaths in a city, with monitoring data from a single background station, studies on long-term exposure require finer-scale, address-level UFP concentrations in order to detect exposure contrasts between people. An increasing availability of fine-scale spatial UFP models has led

to an increase in the number of long-term UFP studies in recent years. However, exposure assessment remains a challenge in research on the health effects of both short- and long-term UFP exposure. As UFP are not regulated, they are not routinely monitored, and only few cities have monitoring data for extended time series. Moreover, non-standardized measurement equipment and the use of different cut-offs for particle size hamper the comparability of measurements from different locations. For particle size, especially the lower detection limit is crucial, as the smallest particles contribute most in terms of particle number concentration. In fact, particles below 100 nm generally account for 80-90% of the total particle number concentration (4). In line with this, the recent WHO Air Quality Guidelines include a good practice statement on UFP, suggesting a lower limit ≤10 nm with no restriction on the upper limit (5).

Besides road traffic as a major source of UFP in urban areas, airports have received ongoing attention as major emitters of UFP with potential adverse health effects for airport employees and residents in the vicinity. A global modelling study estimated that aviation emissions are responsible for around 16,000 premature deaths globally every year (6). Numerous studies document elevated UFP concentrations in and around airports, and an increasing body of literature is available on the health effects of short-term or long-term exposure to airport-related UFP exposure, both in occupational, experimental, or population-based cohort studies.

In the following chapters, we will provide an overview of the literature on the health effects of short-term, long-term, and airport-related UFP exposure. In doing so, we will summarize the findings of two previous reviews on the short- and long-term health effects of UFP (2,3), and add to these findings by reviewing studies that were published since the last review. For airport-related UFP, we conducted a literature search of studies on exposure patterns, and studies on the short- and long-term health effects in occupational and general population settings.

2. Health effects of short-term exposure

In this chapter, we summarize studies on the association between short-term UFP exposure and morbidity (hospital admissions) and mortality.

We conducted a literature search of epidemiological studies published between January 2017 and September 2023. Additionally, we included studies from a previous review from 2019 that covered studies published in 2011-2017 (2) and a review from 2013 covering studies before 2011 (3). For the current updated literature search, we followed the search strategy, inclusion and exclusion criteria of Ohlwein et al. 2019 (2), and searched the databases PubMed and LUDOK (the Swiss literature database on air pollution and health), using search terms related

to ambient air pollution, ultrafine particles, health, epidemiology, and disease-related keywords, each operationalized with multiple synonyms and combined with "AND"/"OR" operators. We included only studies on mortality or hospital admissions, not those on sub-clinical outcomes or biomarkers.

We found 24 studies on mortality and 31 on hospital admissions associated with short-term UFP exposure. Among the mortality studies, 17 included all-cause natural (non-accidental) mortality, 17 at cardiovascular diseases and 15 at respiratory diseases as outcomes (Table 1). Additionally, some studies examined specific cardiovascular or respiratory diseases such as stroke, ischemic heart disease, coronary disease, or COPD. Among the studies on hospital admissions (including emergency room visits), 10 included cardiovascular, 12 included respiratory diseases, and among the specific diseases, there are studies on stroke, myocardial infarction, heart failure, asthma, COPD, and acute lower or upper respiratory infections. The majority of identified studies are from Europe and North America, with only few studies from Asia and one from South America (Table 1).

2.1 Study designs

Most studies on the health effects of short-term UFP exposure use time series methods (Table 1), where regression models are applied to daily exposure and outcome data, adjusting for time trends and confounders such as the day of the week and meteorological variables (7). Some studies use a case-crossover design with conditional logistic regression, which compares the exposure on the day of an event to exposure levels on other days, typically the same weekdays within the same month and year, thus comparing each case with itself and reducing confounding effects of individuals' characteristics (8). In both designs, results are usually presented as the increase (percentage, odds ratio [OR], or relative risk [RR]) in the daily number of deaths or hospital admissions related to an increase (often the interquartile range) in air pollution concentrations, with 95% confidence intervals (CI). Besides exposure concentrations on the same day as an event, short-term studies usually explore different lagged exposures to account for delayed health effects. These can be single lags up to several days before an event (e.g., 'lag 1', which is the concentration on the previous day) or moving averages of several preceding days' concentrations (e.g., 'lag 0-1', which is the average of the day of an event and the previous day). In order to assess whether the observed associations with UFP are independent from other pollutants' concentrations, many studies (but not all) apply two- or multi-pollutant models, which are adjusted for one or multiple co-pollutants. Commonly, this is done for $PM_{2.5}$ and NO_2, both of which are usually moderately correlated with UFP.

2.2 Exposure assessment

For exposure assessment, most available studies use a central urban background measurement site to reflect day-to-day variations within a study area, typically a single city. While this limits information on spatial variation and local hotspots of UFP, the temporal variation in UFP in different urban locations is usually well reflected in the variation at a background site. Only one study to date has applied a model of daily UFP at a finer resolution.

Another aspect of exposure assessment is the choice of particle size. There is large heterogeneity in size ranges investigated in available short-term studies, with some presenting results for a "stricter" definition of UFP below 100 nm diameter, and others using the whole particle number concentration without an upper limit as a proxy for UFP. In addition, in the absence of standard instruments for UFP measurements, there are differences in the lower cut-off size for particles. While some instruments measure particles as small as 3 nm, others start counting particles at a diameter of 10 or 20 nm. This leads to a limited comparability of measurements from different instruments, as there is large uncertainty in measuring the smallest particles, which contribute most to total particle number concentration. In this review, we only considered studies that used a lower limit ≤20 nm and an upper limit ≥100 nm. The included studies used either UFP below 100 nm, and/or the total particle number concentration (Table 1).

Table 1. Characteristics of short-term exposure studies.

Characteristic	Mortality (n) Total: 24 studies	Hospital admissions (n) Total: 31 studies
Outcome		
All-cause natural	**17**	**0**
All cardiovascular	**17**	**10**
Stroke	3	3
MI	1	7
IHD	2	2
Coronary disease	2	1
Heart failure	1	3
Arrhythmia	1	2
Cerebrovascular disease	1	1
Cardiac arrest	0	1
All respiratory	**15**	**12**
Asthma	0	9
COPD	3	3
Lower/Upper respiratory infections	1	6

Region		
Europe	18	16
North America	0	7
Asia (all from China)	6	7
South America	0	1
Study design		
Time series	23	12
Case-crossover	1	19
Population		
General	22	23
Elderly	2	3
Children	0	5
Exposure assessment		
Central	24	30
Model	0	1
Particle size		
<100 nm	16	22
Total PNC	10	16

2.3 Morbidity

In their review covering studies until 2017, Ohlwein et al. 2019 found limited evidence on the association between short-term UFP exposure and hospital admissions (including emergency room visits), with seven studies available on cardiovascular diseases and six on respiratory diseases. For cardiovascular diseases, most studies found weak, positive associations, but were too heterogeneous to draw overall conclusions. While most studies on respiratory diseases found positive associations with at least one lagged (UFP concentrations on days before a hospital admission) exposure and respiratory diseases, these were robust in only one study (2). In our current, updated search including studies before and after 2017, until September 2023, we identified ten studies on hospital admissions for cardiovascular diseases and twelve for respiratory diseases. In addition, some studies focused on specific diseases such as asthma (n=10), myocardial infarction (n=7), heart failure (n=3), stroke (n=3), chronic obstructive pulmonary disease (COPD; n=3), respiratory infections (n=5), and other respiratory and cardiovascular diseases.

For cardiovascular diseases, a multi-city study of Dresden and Augsburg (Germany), Prague (Czech Republic), Ljubljana (Slovenia), and Chernivtsi (Ukraine) found non-significant associations close to the null (9). Similarly, studies from Helsinki (Finland) (10), Prague (Czech Republic) (11), and two studies in London (UK) (12,13) did not find any associations. Positive, significant associations were found in New York State (0.3% [95% CI: 0.1%, 0.4%]

per 1601 pt/cm^3 increase in UFP, lag 0-3 days) (14) and Beijing, China (7.2% [95% CI: 1.1%, 13.7%] per 9040 pt/cm^3, lag 0-10) (15), but neither study assessed whether these associations were independent from other pollutants. Two studies were conducted in Copenhagen using data from an urban background monitoring station. The first study included UFP data from 2001-2004 and cardiovascular hospital admissions in the elderly (>65 years) and found no association with cardiovascular diseases (16). The second, more recent study with data from 2002-2018, including all hospital admissions in adults (>30 years), found a significant association (OR: 1.02 [95% CI: 1.00, 1.04]) between 2887 pt/cm^3 increases in two-day average UFP (lag 0-1) and cardiovascular hospital admissions (17) that became non-significant after adjustment for $PM_{2.5}$ or NO_2. Among the specific cardiovascular diseases, we found associations with ischemic stroke (18) hospital admissions in adults in Copenhagen. Others found positive associations with arrhythmia among elderly people in Helsinki (10), out-of-hospital cardiac arrest in Helsinki (19), and particularly with different types of myocardial infarction in Augsburg (Germany) (20,21), Rochester (USA) (22), and Shanghai (China) (23,24).

Respiratory diseases were positively, but not significantly associated with UFP in the Lanzinger et al. (2016) multi-city study (4.3% [95% CI: -0.9, 9.8] per 3675 pt/cm^3, lag 0-5), and diminished after $PM_{2.5}$ or NO_2 adjustment. Positive associations were also found in studies from London (13) and Helsinki (10), both of which did not adjust for other pollutants. Another multi-city study combined data from Barcelona (Spain), Copenhagen, Helsinki (Finland), Rome (Italy), and Stockholm (Sweden) for 2001-2011, and found non-significant associations close to null (25). Similarly, no associations were detected in studies from Prague (Czech Republic) (11), and Beijing (China) (26). A study from Chile found strong associations between wood burning-related UFP and respiratory hospitalizations in people older than 65 (15% [95% CI: 5, 25] per 4.73 pt/cm^3, lag 5) (27). In Copenhagen, associations were non-significant and close to the null in the analysis of elderly people (16), and positive in the more recent analysis for adults (OR: 1.04 [95% CI: 1.01, 1.07] per 2513 pt/cm^3, lag 0-4) (17), but diminished after $PM_{2.5}$ or NO_2 adjustment. Among the specific respiratory diseases, we found associations with asthma (17) in adults in Copenhagen, and others found positive associations with pneumonia in elderly people in Helsinki (10).

Some studies restricted their analyses to children and found stronger associations for respiratory diseases than in adults, such as in London (12). Children's hospital admissions specifically for asthma were investigated in a few studies, with inconclusive results (16,28,29), and in a recent study from Copenhagen (currently under review), we found significant, positive

associations in school-aged children (5-14 years), independent from $PM_{2.5}$ or NO_2. Similar associations were also found in studies from Rochester (USA) (30) and Shanghai (China) (31,32). The latter two Chinese studies also found positive associations between UFP and children's emergency department visits or outpatient visits due to bronchitis, upper respiratory infections, and pneumonia, robust to $PM_{2.5}$ or NO_2 adjustment.

2.4 Mortality

We identified 24 studies on short-term UFP exposure and mortality. The number of available studies has increased since the Ohlwein 2019 review, which found four studies on all-cause mortality, six on cardiovascular, and five on respiratory disease mortality, adding to eleven studies from the previous 2013 report, both with inconsistent findings. In our updated search, we found 17 studies on all-cause, 17 on cardiovascular, and 15 on respiratory mortality.

Among the studies on all-cause mortality, most found non-significant associations close to the null, with large heterogeneity in the assessed lag days and particle sizes. Three large, multi-city studies have pooled results from several European cities. Lanzinger et al. (2016b) included between one- and two-year-long time series from Dresden and Augsburg (Germany), Prague (Czech Republic), Ljubljana (Slovenia), and Chernivtsi (Ukraine) in combined analyses, and found no association with all-cause mortality (33). Similarly, Stafoggia et al. (2017) combined data from Helsinki (Finland), Stockholm (Sweden), Copenhagen (Denmark), Ruhr area (Germany), Rome (Italy), Barcelona (Spain), and Athens (Greece), all between 1999 and 2013. They found a weak increase of 0.35% (95% CI: -0.05%, 0.75%) in all-cause mortality per 10,000 pt/cm^3 increase in UFP five to seven days before death (lag 5-7), which disappeared in two-pollutant models (34). Another recent study examined associations of short-term UFP exposure and all-cause mortality in Barcelona (Spain), Helsinki (Finland), London (UK), and Zurich (Switzerland), 2009-2016, and found significant increases of 1.3% (95% CI: 0.07%, 2.5%) per 4012 pt/cm^3 increase in UFP lagged two days in Helsinki, robust to NO_2 adjustment ($PM_{2.5}$ was not assessed), but inconsistent associations in other cities and at other lags (35). Slightly stronger associations were found for primary source UFP in Barcelona (1.63% [95% CI: 0.74%, 2.52%] per 3277 pt/cm^3 at lag 0), not adjusted for $PM_{2.5}$ or NO_2 (36). We have recently studied this association in Copenhagen, using daily data from an urban background station in 2002-2018, and found a suggestive association with an OR of 1.02 (95% CI: 1.00, 1.04) with UFP concentrations on the same day per 3075 pt/cm^3 increase, robust to $PM_{2.5}$ or NO_2 adjustment (17). Lastly, studies from Stockholm (37), the Ruhr area in Germany (38), three German cities (39), and London (12) found no or small and insignificant associations.

For cardiovascular mortality, similar to all-cause mortality, there is heterogeneity in study designs, and findings are inconclusive. In their multi-city studies, both Lanzinger et al. (2016b) and Stafoggia et al. (2017) found insignificant associations close to the null. Rivas et al. (2021) found a significant increase of 3.7% (95% CI: 0.17%, 7.4%) per 5601 pt/cm^3 (lag 1) in Barcelona and 3.8% (95% CI: 0.31, 7.4) per 4735 pt/cm^3 (lag 0) in Zurich, robust to NO_2 adjustment. Positive associations were also found in London (13), Beijing (40,41), and Germany (38), while other studies found non-significant associations close to the null (11,12,37). In our Copenhagen study, we did not find associations with cardiovascular mortality. Among the few studies that focused on specific cardiovascular diseases, there are indications for associations with ischemic heart disease mortality (41), cerebrovascular deaths (40), but not myocardial infarction (20).

For respiratory mortality, some studies found stronger positive associations with short-term UFP exposure with wider confidence intervals, such as in Zurich (9.4% [95% CI: 1.0%, 17.9%] per 4735 pt/cm^3, lag 1), robust to NO_2 adjustment (35), Ruhr area in Germany (4.51% [95% CI: 0.37%, 8.81%] per 4900 pt/cm^3, lag 6) (38), in the Lanzinger et al. multi-city study (9.9% [95% CI: -6.3%, 28.8%] per 2750 pt/cm^3, lag 0-5), robust to NO_2 and $PM_{2.5}$ adjustment, in three German cities (4.46% [95% CI: 1.52%, 7.48%] per 3223 pt/cm^3, lag 5-7) (39), robust to NO_2 and $PM_{2.5}$ adjustment, in Beijing (3.9% [95% CI: -7.3, 16.4%] per 13,000 pt/cm^3, lag 0-4) (42), robust to NO_2 adjustment, and in London (2.3% [95% CI: -0.1%, 4.8%] per 10,166 pt/cm^3, lag 1) (13). Other studies found non-significant associations close to the null (11,12,34). In Copenhagen, we found positive associations with an OR of 1.04 (95% CI: 0.98, 1.11) per 2513 pt/cm^3 increase in five-day average UFP, robust to NO_2 and $PM_{2.5}$ adjustment. Among the specific respiratory diseases, we found positive associations with COPD mortality (17).

2.5 Summary

We summarized results from 24 mortality studies and 31 hospital admissions studies, mainly from Europe and North America. For hospital admissions, findings are inconclusive, but suggest associations between UFP and respiratory diseases, particularly among children, and associations with myocardial infarction. Similarly, for mortality, associations are more consistent for respiratory diseases than for all-cause mortality or cardiovascular diseases. Overall, evidence is still too limited to draw firm conclusions, which is partly related to the heterogeneity in study designs due to missing standards for UFP measurements. Moreover, there is limited and inconclusive evidence on whether the effects of UFP are independent from other pollutants.

3. Health effects of long-term exposure

In this chapter, we summarize studies on the association between long-term UFP exposure and morbidity and mortality. We applied the same literature search strategy as described in Chapter 2 and selected all cohort or case-control studies on long-term exposure (i.e. exposure windows of multiple months to years). Due to the low total number of studies, here, unlike for short-term exposures, we also included sub-clinical and biomarker studies, in addition to mortality and incidence of clinical diseases.

We identified 42 studies on long-term UFP health effects in total, which is a substantial increase since the Ohlwein review from 2017, which found six cohort and case-control studies, and the 2013 HEI review, which did not find any. The studies identified in the current review are mainly from Europe (n=23) and North America (n=15), with only two studies from Asia (both China) and none from other locations (Table 2). Most studies focused on morbidity (both clinical and sub-clinical outcomes), and only two on mortality.

3.1 Study designs

The majority of the long-term studies applied cohort study designs, and some case-control designs. Regression models are used to assess the association between an increase in individual-level UFP and health effects. Most studies adjust for individual- and neighborhood-level confounders, such as demographic and socio-economic factors, and some adjust for additional lifestyle and behavioral factors. In addition, most studies apply two- or multi-pollutant models, adjusting for other air pollutants.

3.2 Exposure assessment

The increase in long-term studies is related to an increase in the availability of spatial models of UFP, which provide fine-scale concentrations necessary for conducting cohort or case-control studies. Compared to particle mass ($PM_{2.5}$ and PM_{10}), there are still very few models on UFP, owed to the limited availability of UFP monitoring data. In addition, UFP are characterized by their large spatial variation, with exposure contrasts varying greatly by just few meters distance to sources.

Most of the studies identified in our search applied land-use regression models or hybrid models, and some applied other methods such as chemical transport models or mobile measurements. Several studies are based on models from Toronto (Canada) and the Netherlands (nationwide). Both models are based on mobile monitoring campaigns and land use regression methods, and reach moderate performance in external validation studies (43,44). In Denmark, the “DEHM/UBM/AirGIS” model estimates air pollution at address-level

combining information on the regional background, local background, local traffic composition and intensity, emission factors, meteorology and street and building configuration. The most recent model update includes address-level UFP concentrations since 1979 (45). While there was good correlation with monitoring station data, the model has not been validated by external measurements, and residential background levels might be overestimated.

Table 2. Characteristics of long-term exposure studies.

Characteristic	Mortality (n) Total: 2 studies	Morbidity (n) Total: 40 studies
Outcome		
All-cause natural	**2**	**0**
Cardiovascular		
All cardiovascular	2	2
Diabetes	0	4
Stroke	0	2
MI	0	3
Coronary disease	0	2
Arterial stiffness	0	1
Atherosclerosis	0	2
Congenital defect	0	1
Congestive heart failure	0	2
Hypertension	0	1
Respiratory		
All respiratory	2	0
Asthma	0	4
COPD	0	1
Malignancies		
Prostate cancer	1	1
Breast cancer	0	1
Lung cancer	0	1
Brain tumor	0	1
Other cancer	**0**	1
Sub-clinical/biomarkers	**0**	**9**
Neuro-cognitive outcomes	**0**	**7**
Perinatal outcomes	**0**	**5**
Region		
Europe	1	23
North America	1	15
Asia (all from China)	0	2
Study design		
Cohort	2	36
Case-control	0	4
Population		
General	2	25

Children	0	3
Pregnant women/mother-child pairs	0	9
Other selected population	0	3
Exposure assessment		
Central monitoring	0	4
Land-use regression model	1	19
Hybrid model	0	6
Other	1	11
Particle size		
<100 nm	2	18
Total PNC	0	12
Accumulation mode	0	9
Nucleation mode	0	1

3.3 Morbidity

The incidence of total cardiovascular diseases was positively associated with long-term UFP exposure in one out of two available studies. A Dutch cohort study of ~34,000 people found a hazard ratio (HR) of 1.18 (95% CI: 1.03, 1.34) per 10,000 pt/cm^3 increase in address-level UFP at the year of study enrollment, adjusted for socio-demographic and lifestyle factors, which was robust to adjustment for $PM_{2.5}$ and NO_2 (46). A cohort study from the German Ruhr area used a model of accumulation mode particles, which are larger than particles in the ultrafine range (100-1000 nm), and found no associations between long-term UFP exposure and total cardiovascular diseases (47).

Type 2 diabetes incidence was positively associated with increases in long-term UFP exposure in all four studies. A cohort study from Toronto found a HR of 1.06 (95% CI: 1.05, 1.08) per 9948 pt/cm^3 increase in one-year mean UFP (48). A German cohort study found positive associations between accumulation mode particles (100-1000 nm) and diabetes incidence (RR: 1.29 [95% CI: 1.10, 1.52] per 494 pt/mL) (49). A Danish nationwide study using UFP estimates from the "DEHM/UBM/AirGIS" model found a HR of 1.05 (95% CI: 1.04, 1.06) per 4248 pt/cm^3 increase in five-year mean exposure among all persons living in Denmark for the period 2005-2017, adjusting for individual- and area-level demographic and socioeconomic covariates (50). Lastly, there were indications of a positive association with gestational diabetes in Beijing, China, which used central monitoring to assign exposure during pregnancy (51).

Among other specific cardiovascular diseases, positive, significant associations were found for stroke and larger (accumulation mode) particles in Germany (47), and stroke and UFP in Denmark (52). The Dutch study on cardiovascular outcomes found strong positive associations

for myocardial infarction and heart failure, but not coronary heart disease (46). Myocardial infarction and heart failure were also positively associated with long-term UFP exposure in Toronto, Canada (53). Likewise, a Danish nationwide cohort study using the same methods as described earlier and follow-up from 2005 to 2017 found a HR of 1.04 (95% CI: 1.03, 1.06) of myocardial infarction associated with each 4248 pt/cm^3 increase in five-year mean residential UFP (54). Other studies found non-significant associations with coronary heart disease (47), congenital heart defects (55), arterial stiffness (56), and hypertensive disorders of pregnancy (57). Atherosclerosis was significantly associated with UFP in one study (58), but not in another (59).

Concerning respiratory diseases, studies have examined COPD and asthma incidence. COPD was significantly associated with long-term UFP in a Canadian cohort study (HR: 1.06 [95% CI: 1.05, 1.09]), but diminished after NO_2 adjustment, while asthma was not associated with UFP (60). Similarly, asthma was associated with long-term UFP in a Dutch cohort study of people younger than 20, but was no longer significant after NO_2 or $PM_{2.5}$ adjustment (61). Prenatal UFP exposure was strongly associated with asthma incidence in children in an analysis of 376 mother-child pairs in Boston, USA (OR: 4.28 [95% CI: 1.41, 15.7] per doubling of UFP exposure during pregnancy) (62), independent of NO_2. This confirms a previous Canadian study with similar design, where second-trimester UFP exposure was linked to childhood asthma incidence up to age six in a sample of 160,641 singleton live births (HR: 1.05 [95% CI: 1.01, 1.09] per 10,770 pt/cm^3), adjusted for both NO_2 and $PM_{2.5}$ (63).

Incidence of cancer was associated with long-term UFP exposure in three out of five studies. A Canadian (Toronto) cohort study assessed prenatal and childhood UFP exposure of children, who developed cancer before the age of 14, and found a positive association (HR: 1.13 [95% CI: 1.03, 1.22]) per 10,000 pt/cm^3 increase in the mothers' first trimester exposure, after adjusting for other pollutants and personal and neighborhood-level confounders (64). Two other Canadian studies from Montreal and Toronto focused on post-menopausal breast and lung cancer, but found no significant associations for UFP (60,65). For brain tumor incidence, positive associations (HR: 1.13 [95% CI: 1.03, 1.25] per 10,000 pt/cm^3) were found with residential exposures in a cohort study from Montreal and Toronto (66). Prostate cancer incidence was associated with long term UFP exposure in a case-control study from Montreal (OR: 1.10 [95% CI: 1.01, 1.19]) (67).

In studies of sub-clinical outcomes and biomarkers, some found positive associations between accumulation mode particles and immune responses (68), blood glucose (69) and other diabetes biomarkers (70), but not with insulin sensitivity (71), inflammation biomarkers (72) or

metabolic syndrome (73). Others found associations with worsened lung function in children that became non-significant after co-pollutant adjustment (74).

Seven studies examined the effects of long-term UFP exposure on neuro-cognitive outcomes, some in children and some in elderly people. In children, studies found an association between outdoor and indoor UFP in schools and impaired cognitive development, measured repeatedly in children in Barcelona, Spain (75,76), and an association between address-level UFP and altered volume of several brain structures in children in Rotterdam, Netherlands (77). In elderly people, a US cohort study with 5646 participants found no associations between residential UFP and cognitive decline (78), while three German studies based on a cohort of ~600 elderly people and accumulation mode particles found significant associations cognitive decline and brain structure (79), with functional connectivity in the brain (80), but not with measures of the default mode network in the brain (81).

Lastly, five studies examined perinatal health. Preterm birth was positively associated with third trimester centrally monitored UFP exposure among 24,001 singleton live births in Beijing, China (82), and with mothers' address at birth in a case-control study with 442,314 cases in California (83). Low birthweight (84,85) or pre-eclampsia (86) were not significantly associated with UFP.

3.4 Mortality

Only two studies examined the association between long-term UFP exposure and mortality. First, >100,000 women from the California Teachers Study Cohort were followed in 2001-2007, and address-level UFP exposure was modelled. Ischemic heart disease mortality was significantly associated with UFP mass (HR: 1.10 [95% CI: 1.02, 1.18]), while cardiovascular mortality was only associated with specific UFP constituents, and no associations were found for all-cause and respiratory mortality. The authors did not assess the independence of UFP from $PM_{2.5}$ or NO_2 effects (87). Second, a Dutch national cohort followed 10.8 million adults above 30 years of age in 2013-2019. Address-level UFP was significantly associated with all-cause mortality (HR: 1.01 [95% CI: 1.01, 1.02]), respiratory mortality (HR: 1.02 [95% CI: 1.01, 1.03]), lung cancer mortality (HR: 1.04 [95% CI: 1.03, 1.05]), and CVD mortality (HR: 1.01 [95% CI: 1.00, 1.01]), of which associations for all-cause and lung cancer mortality were robust to co-pollutant adjustment (88).

3.5 Summary

We found 40 studies on long-term exposure to UFP and morbidity and two on mortality. There was a positive association with diabetes incidence in all available studies, but with only four

studies in total, they were still too few. Similarly, more evidence is needed on total cardiovascular diseases, which were significantly associated with long-term UFP in one out of two studies. Stroke, heart failure and myocardial infarction incidence were also significantly associated with long-term UFP in the available studies, but more evidence is needed. Among the very few studies on respiratory outcomes, the only significant associations were found for prenatal UFP exposure and asthma incidence in children. The few studies on cancer point at possible associations with childhood, prostate and brain tumor incidence. Similarly, for cognitive outcomes, studies were limited, but found adverse effects of long-term UFP on cognitive development in children and cognitive decline in elderly people. Positive associations were also found between UFP exposure during pregnancy and preterm birth. Lastly, only two studies examined mortality, with inconsistent findings. Uncertainty remains regarding whether the health effects of UFP are independent from those of other pollutants with similar sources. This uncertainty arises because not all studies apply two-pollutant models, and in some studies, effects attenuate or become non-significant after adjustment.

4. Health effects of airport-related exposure

This chapter summarizes the health effects of UFP related to airport emissions. First, we briefly describe exposure patterns in and around airports, followed by a summary of studies on the health effects among airport employees, in experimental settings, and among residents living close to airports. Relevant studies were identified through searches in PubMed, with no restriction of publication date, using the following search terms: “ultrafine particles”/”particle number concentration”; “health”/”mortality”/”morbidity”; “airport”/”aviation”.

4.1 Air quality around airports

It is well documented that commercial airport activity adversely affects air quality in and around airports. Jet engine emissions from ascending and descending aircraft, the major source of airport-related air pollution, contain large amounts of volatile organic compounds and particulate matter, especially of the smallest particle size fraction in the ultrafine range below 20 nm in diameter (89). Pollution emitted from aircraft activities has been found to be equally carcinogenic and with similar adverse health effects as diesel particle emissions (90). This causes health concerns for the exposed airport personnel, but also for residents in airport vicinity. Elevated UFP concentrations have been measured at distances as far as 18 km downwind from airports (91), affecting a potentially large number of people.

A substantial number of studies on fixed-site or mobile UFP measurements in and around commercial airports are available from Europe and the US. Those focusing on residential areas

close to airports reported elevated UFP concentrations, such as around the major airports in Los Angeles (91–94), Amsterdam (95), London (96), Zurich (97), and Boston (98). Specifically, UFP concentrations are elevated under the landing approach path (93), and depend on distance to the airport (99), wind direction (95,100), and flight activity (98,99,101).

Some studies evaluated the relative contributions from airport and road traffic emissions to total UFP concentrations, with some finding similar contributions (100,102,103) and some finding higher contributions from airports compared to traffic (92,96).

In Copenhagen, UFP concentrations measured at the apron of Copenhagen Airport were reported to be two to three times higher than those measured at a high-traffic street in the city center (H.C. Andersens Boulevard) in 2012 (104). Another Danish study equipped members of different occupational groups at Copenhagen Airport with mobile monitoring instruments and assessed their UFP exposure, finding seven times higher average concentrations for baggage handlers compared to employees mainly working indoors (105). Another recent study combined mobile monitoring by a Google Street View car with modelling approaches to estimate UFP concentrations for all streets in Copenhagen, Frederiksberg and Tårnby municipalities (106). The resulting exposure map shows clearly elevated UFP concentrations in the residential areas bordering the airport to the west and north, with higher concentrations than in other residential areas in the city.

4.2 Short-term exposure

Short-term studies evaluate whether the exposure to airport-related UFP can trigger health effects or lead to changes in biomarkers of cardiovascular or respiratory health over a course of hours or days. We identified three studies that conducted quasi-experimental studies with healthy or asthmatic volunteers walking (107) or cycling (108,109) in both clean and airport air, taking repeated measurements of biomarkers.

First, in a study around Los Angeles International Airport (LAX), 22 adults with asthma each walked twice, for two hours each time, in public parks inside and outside of a zone impacted by airport-related UFP. Repeated measurements of cardiopulmonary markers showed associations between airport-related UFP and increased systemic inflammation (107).

Second, at Schiphol Airport close to Amsterdam, 21 healthy volunteers were recruited to cycle for five hours each at two to five visits, both in air polluted with airport-related UFP and clean air. Repeated measurements of cardiopulmonary markers showed associations between airport-related UFP and decreased lung function (mainly forced vital capacity [FVC]) and a prolonged corrected QT interval (a cardiovascular marker) (109).

Third, in the same setup with 21 healthy volunteers as in (109), changes in cellular pathway activity were measured in urine. The urinary metabolome was significantly changed after exposure to airport-related UFP, indicating a heightened antioxidant response and altered nitric oxide synthesis (108).

The studies on short-term exposure to airport-related UFP around Schiphol Airport are summarized in a comprehensive report (110). Here, the authors present results of another study on 191 primary school children living close to the airport, who were found to experience more respiratory complaints (shortness of breath and wheezing) and use more medication on days with high exposures. Further sub-studies, additional to the studies described above, found reduced lung function in children and healthy adults after short-term exposure to airport-related UFP, as well as short-term reductions in heart function in healthy adults (110). The authors emphasize that these effects might be stronger in people who already suffer from lung or heart conditions. Furthermore, they conclude that the health effects of UFP emitted at airports are not substantially different from those emitted by road traffic.

4.3 Long-term exposure

Population-based cohort studies of long-term exposure to airport-related UFP and associated health effects are scarce. The only available studies were conducted around Schiphol Airport (111), LAX (112,113), and in all of California (114).

The Dutch studies were summarized in a report including findings on mortality, use of medication, perinatal health and self-reported health as outcomes. Airport-related UFP in 2003-2019 was modelled for a large study population (number differing by sub-study, e.g. ~1.3 million in mortality study) living in an area of 50x55 km around Schiphol Airport. Summarizing the different sub-studies, the authors conclude that there was no indication for associations between long-term exposure to airport-related UFP and general health. For respiratory diseases, adverse effects were only seen for people with pre-existing conditions, while there was suggestive evidence for an association between long-term exposure to airport-related UFP and cardiovascular diseases (i.e., arrhythmia mortality, heart disease medication use, and self-reported heart disease and stroke). Further suggestive evidence was found for an association between long-term exposure to airport-related UFP and perinatal health (i.e. preterm birth, small for gestational age, and congenital anomalies). Evidence regarding the nervous and metabolic system was too inadequate for drawing conclusions (111).

The studies around LAX focused on malignant brain cancer and meningioma (112), and preterm birth (113). The former study modelled airport-related UFP for 75,936 residents in an

area of 53x43 km around LAX from date of cohort entry (1993–1996) through the end of 2013. An IQR increase in long-term exposure to airport-related UFP was associated with a HR of 1.12 (95% CI: 0.98, 1.27) with the incidence of malignant brain cancer, after adjusting for sex, race/ethnicity, education, and neighborhood socioeconomic status. No associations were found with meningioma. In the latter study, airport-related UFP exposure was modelled for 174,186 women, who gave birth between 2008 and 2016, living within 15 km from LAX. Using birth records and adjusting for maternal demographic characteristics, exposure to traffic-related air pollution, and airport-related noise, the authors found a significant association between *in utero* exposure to airport-related UFP and preterm birth (OR: 1.04 [95% CI: 1.02, 1.06]).

One study used modelled airport-related UFP exposure for the whole state of California and included 370,723 singletons born in selected hospitals in California between 2001 and 2014. Airport-related UFP exposure was assigned to the mothers' address during pregnancy, and children were followed up for the first five years of their life. An IQR increase in *in utero* airport-related $PM_{0.1}$ exposure was associated with autism spectrum disorder diagnosis with a HR of 1.02 (95% CI: 1.01, 1.03), adjusting for birth year, medical center, maternal age, maternal ethnicity, maternal education, parity, history of comorbidity, income at age one, season of conception, pre-pregnancy diabetes mellitus, pre-pregnancy obesity, and child's sex (114).

4.4 Summary

Studies have shown that short-term exposure to airport-related UFP can have adverse effects on biomarkers related to cardiovascular and respiratory health, such as lung and heart function, and changes in cellular pathway activity. These effects were found in healthy adults, but are likely stronger among people with pre-existing diseases. Moreover, children living close to airports experienced more respiratory complaints on days with high exposures. Long-term studies of cohorts linked to address-level airport-related UFP exposure are very few, but studies found possible associations with cardiovascular diseases, respiratory diseases among people with pre-existing conditions, malignant brain cancer, autism spectrum disorder and perinatal health with only preterm birth found in more than one long-term study.

5. Interpretation and conclusions

This report summarizes the current evidence on health effects of UFP, specifically of short-term exposure, long-term exposure, and airport-related exposure.

Most available studies focus on short-term exposure, examining whether elevated UFP concentrations can trigger mortality or hospital admissions in the course of a few days. These

studies mostly use daily data from urban background monitoring stations and time series of mortality or hospital admissions within a study area around these stations. In addition, numerous studies measure biomarkers and sub-clinical outcomes related to short-term UFP exposure, but a summary of those was beyond the scope of this review. The study designs vary widely, including different measurement instruments and particle size assessments, as well as variations in the evaluation of lagged exposures. Consequently, the available evidence is not conclusive, and results from different studies are not necessarily comparable. Summarizing all studies, the most convincing associations were found for short-term UFP and hospital admissions and mortality due to respiratory diseases, and hospital admissions for myocardial infarction, although documentation of independence from other pollutants has been limited.

Studies on long-term exposure have been emerging increasingly in the last few years, as more and more spatiotemporal models of address-level UFP are being developed. Most of these studies focus on disease incidence and sub-clinical outcomes, and only two on mortality. Associations are generally higher and more significant than for short-term exposure studies. While the overall number of studies is still too small to draw final conclusions, we found most consistent associations for stroke, heart failure and myocardial infarction incidence, some types of cancer incidence, cognitive outcomes in children and elderly people, and preterm birth.

Airport-related UFP raises health concerns for airport workers and residents in airport vicinity. Short-term exposure to airport-related UFP has been shown to affect biomarkers related to cardiovascular and respiratory health, such as lung and heart function, and changes in cellular pathway activity, especially among people with pre-existing diseases. The strongest associations of long-term exposure to airport-related UFP were found with cardiovascular diseases, respiratory diseases among people with pre-existing conditions, and malignant brain cancer.

Exposure assessment remains the most challenging aspect of UFP studies. Short-term studies commonly rely on single monitoring stations for exposure assessment of a whole city. While it has been shown that the daily variations at a single station may adequately reflect variations at other citywide locations, this may be different and should be tested in each individual study area. Crucially, this approach ignores the large spatial variation in UFP concentrations, with hotspots in micro-environments on fine spatial scales. The resulting exposure misclassification may lead to a bias towards the null, which might explain the non-significant or small associations detected in many studies. Similarly, the modelling of residential UFP concentrations for long-term studies is challenging due to the large spatial variation of UFP. While some UFP models reach good prediction performance, they may not adequately reflect

all types of exposure environments. External validation studies are needed to test models in heterogeneous locations, such as different traffic intensities and residential/urban background areas.

Lastly, the available studies are restricted to few geographical locations, with most from Europe and North America. More studies are needed from more diverse locations and settings.

To conclude, we know well from toxicology studies that UFP can harm the body and induce physiological changes related to cardiovascular and respiratory diseases. The body of literature from epidemiological studies on UFP's health effects, related to both short- and long-term exposure, is growing and pointing at adverse effects on mortality and morbidity related to cardiovascular diseases, respiratory diseases, preterm birth, cancer, and cognitive outcomes. These might be even stronger among children or people with pre-existing conditions. There is also a need for studies on UFP and infectious respiratory diseases. Additionally, elevated exposure to UFP in airport vicinity raise health concerns that need to be studied further. In conclusion, epidemiological evidence on UFP health effects is fast growing but is still limited, due to a lack of data, monitoring programs and regulation of UFP. However, available evidence on UFP and health points to serious adverse effects on respiratory and cardiovascular systems, as well as on birth outcomes, metabolic, cognitive diseases and cancer, that suggest need of regulation of UFP and actions for their reduction, in addition to already regulated pollutants. However, more studies are needed on UFP and all major non-communicable diseases, especially those that can separate UFP's health effects from those of other pollutants, both larger particles and traffic-related gasses. This demands more investments in monitoring of UFP and research on their health effects.

Funding

The City of Copenhagen (Københavns Kommune in Danish) has supported the research described in this report.

References

1. Health Effects Institute. State of Global Air 2020. Special Report. Boston, MA: Health Effects Institute; 2020.

2. Ohlwein S, Kappeler R, Kutlar Joss M, Künzli N, Hoffmann B. Health effects of ultrafine particles: a systematic literature review update of epidemiological evidence. Int J Public Health. 2019 May;64(4):547–59.

3. HEI Review Panel on Ultrafine Particles. Understanding the Health Effects of Ambient Ultrafine Particles [Internet]. Boston, MA: Health Effects Institute; 2013 [cited 2020 Dec 4]. (HEI Perspectives 3). Available from: https://www.healtheffects.org/publication/understanding-health-effects-ambient-ultrafine-particles

4. Hofman J, Staelens J, Cordell R, Stroobants C, Zikova N, Hama SML, et al. Ultrafine particles in four European urban environments: Results from a new continuous long-term monitoring network. Atmos Environ. 2016 Jul 1;136:68–81.

5. World Health Organization. WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide [Internet]. World Health Organization; 2021 [cited 2021 Dec 10]. xxi, 273 p. Available from: https://apps.who.int/iris/handle/10665/345329

6. Yim SHL, Lee GL, Lee IH, Allroggen F, Ashok A, Caiazzo F, et al. Global, regional and local health impacts of civil aviation emissions. Environ Res Lett. 2015 Feb;10(3):034001.

7. Bell ML, Samet JM, Dominici F. Time-series studies of particulate matter. Annu Rev Public Health. 2004;25:247–80.

8. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol. 1991 Jan 15;133(2):144–53.

9. Lanzinger S, Schneider A, Breitner S, Stafoggia M, Erzen I, Dostal M, et al. Ultrafine and Fine Particles and Hospital Admissions in Central Europe. Results from the UFIREG Study. Am J Respir Crit Care Med. 2016 Nov 15;194(10):1233–41.

10. Halonen JI, Lanki T, Yli-Tuomi T, Tiittanen P, Kulmala M, Pekkanen J. Particulate air pollution and acute cardiorespiratory hospital admissions and mortality among the elderly. Epidemiol Camb Mass. 2009 Jan;20(1):143–53.

11. Braniš M, Vyškovská J, Malý M, Hovorka J. Association of size-resolved number concentrations of particulate matter with cardiovascular and respiratory hospital admissions and mortality in Prague, Czech Republic. Inhal Toxicol. 2010 Dec;22(sup2):21–8.

12. Samoli E, Atkinson RW, Analitis A, Fuller GW, Beddows D, Green DC, et al. Differential health effects of short-term exposure to source-specific particles in London, U.K. Environ Int. 2016;8.

13. Atkinson RW, Fuller GW, Anderson HR, Harrison RM, Armstrong B. Urban ambient particle metrics and health: a time-series analysis. Epidemiol Camb Mass. 2010 Jul;21(4):501–11.

14. Lin S, Ryan I, Paul S, Deng X, Zhang W, Luo G, et al. Particle surface area, ultrafine particle number concentration, and cardiovascular hospitalizations. Environ Pollut Barking Essex 1987. 2022 Oct 1;310:119795.

15. Liu L, Breitner S, Schneider A, Cyrys J, Brüske I, Franck U, et al. Size-fractioned particulate air pollution and cardiovascular emergency room visits in Beijing, China. Environ Res. 2013 Feb;121:52–63.

16. Andersen ZJ, Wahlin P, Raaschou-Nielsen O, Ketzel M, Scheike T, Loft S. Size distribution and total number concentration of ultrafine and accumulation mode particles and hospital admissions in children and the elderly in Copenhagen, Denmark. Occup Environ Med. 2008 Jul 1;65(7):458–66.

17. Bergmann ML, Andersen ZJ, Massling A, Kindler PA, Loft S, Amini H, et al. Short-term exposure to ultrafine particles and mortality and hospital admissions due to respiratory and cardiovascular diseases in Copenhagen, Denmark. Environ Pollut. 2023 Nov 1;336:122396.

18. Andersen ZJ, Olsen TS, Andersen KK, Loft S, Ketzel M, Raaschou-Nielsen O. Association between short-term exposure to ultrafine particles and hospital admissions for stroke in Copenhagen, Denmark. Eur Heart J. 2010 Aug 1;31(16):2034–40.

19. Rosenthal FS, Kuisma M, Lanki T, Hussein T, Boyd J, Halonen JI, et al. Association of ozone and particulate air pollution with out-of-hospital cardiac arrest in Helsinki, Finland: Evidence for two different etiologies. J Expo Sci Environ Epidemiol. 2013 May;23(3):281–8.

20. Wolf K, Schneider A, Breitner S, Meisinger C, Heier M, Cyrys J, et al. Associations between short-term exposure to particulate matter and ultrafine particles and myocardial infarction in Augsburg, Germany. Int J Hyg Environ Health. 2015 Aug;218(6):535–42.

21. Chen K, Schneider A, Cyrys J, Wolf K, Meisinger C, Heier M, et al. Hourly Exposure to Ultrafine Particle Metrics and the Onset of Myocardial Infarction in Augsburg, Germany. Environ Health Perspect. 2020 Jan;128(1):017003.

22. Yount CS, Utell MJ, Hopke PK, Thurston SW, Lin S, Ling FS, et al. Triggering of ST-elevation myocardial infarction by ultrafine particles in New York: Changes following Tier 3 vehicle introduction. Environ Res. 2023 Jan 1;216:114445.

23. Hu J, Tang M, Zhang X, Ma Y, Li Y, Chen R, et al. Size-fractionated particulate air pollution and myocardial infarction emergency hospitalization in Shanghai, China. Sci Total Environ. 2020 Oct 1;737:140100.

24. Jiang Y, Chen R, Peng W, Luo Y, Chen X, Jiang Q, et al. Hourly Ultrafine Particle Exposure and Acute Myocardial Infarction Onset: An Individual-Level Case-Crossover Study in Shanghai, China, 2015-2020. Environ Sci Technol. 2023 Jan 31;57(4):1701–11.

25. Samoli E, Andersen ZJ, Katsouyanni K, Hennig F, Kuhlbusch TAJ, Bellander T, et al. Exposure to ultrafine particles and respiratory hospitalisations in five European cities. Eur Respir J. 2016 Sep 1;48(3):674–82.

26. Leitte AM, Schlink U, Herbarth O, Wiedensohler A, Pan XC, Hu M, et al. Size-Segregated Particle Number Concentrations and Respiratory Emergency Room Visits in Beijing, China. Environ Health Perspect. 2011 Apr;119(4):508–13.

27. Díaz-Robles LA, Fu JS, Vergara-Fernández A, Etcharren P, Schiappacasse LN, Reed GD, et al. Health risks caused by short term exposure to ultrafine particles generated by residential wood combustion: A case study of Temuco, Chile. Environ Int. 2014 May 1;66:174–81.

28. Halonen JI, Lanki T, Yli-Tuomi T, Kulmala M, Tiittanen P, Pekkanen J. Urban air pollution, and asthma and COPD hospital emergency room visits. Thorax. 2008 Jul 1;63(7):635–41.

29. Iskandar A, Andersen ZJ, Bønnelykke K, Ellermann T, Andersen KK, Bisgaard H. Coarse and fine particles but not ultrafine particles in urban air trigger hospital admission for asthma in children. Thorax. 2012 Mar;67(3):252–7.

30. Evans KA, Halterman JS, Hopke PK, Fagnano M, Rich DQ. Increased ultrafine particles and carbon monoxide concentrations are associated with asthma exacerbation among urban children. Environ Res. 2014 Feb 1;129:11–9.

31. Li H, Liu L, Chen R, Feng R, Zhou Y, Hong J, et al. Size-segregated particle number concentrations and outpatient-department visits for pediatric respiratory diseases in Shanghai, China. Ecotoxicol Environ Saf. 2022 Sep 15;243:113998.

32. Li H, Li X, Zheng H, Liu L, Wu Y, Zhou Y, et al. Ultrafine particulate air pollution and pediatric emergency-department visits for main respiratory diseases in Shanghai, China. Sci Total Environ. 2021 Jun 25;775:145777.

33. Lanzinger S, Schneider A, Breitner S, Stafoggia M, Erzen I, Dostal M, et al. Associations between ultrafine and fine particles and mortality in five central European cities — Results from the UFIREG study. Environ Int. 2016;9.

34. Stafoggia M, Schneider A, Cyrys J, Samoli E, Andersen ZJ, Bedada GB, et al. Association Between Short-term Exposure to Ultrafine Particles and Mortality in Eight European Urban Areas: Epidemiology. 2017 Mar;28(2):172–80.

35. Rivas I, Vicens L, Basagaña X, Tobías A, Katsouyanni K, Walton H, et al. Associations between sources of particle number and mortality in four European cities. Environ Int. 2021 Oct 1;155:106662.

36. Tobías A, Rivas I, Reche C, Alastuey A, Rodríguez S, Fernández-Camacho R, et al. Short-term effects of ultrafine particles on daily mortality by primary vehicle exhaust versus secondary origin in three Spanish cities. Environ Int. 2018 Feb 1;111:144–51.

37. Olstrup H, Johansson C, Forsberg B, Åström C. Association between Mortality and Short-Term Exposure to Particles, Ozone and Nitrogen Dioxide in Stockholm, Sweden. Int J Environ Res Public Health. 2019 Jan;16(6):1028.

38. Hennig F, Quass U, Hellack B, Küpper M, Kuhlbusch TAJ, Stafoggia M, et al. Ultrafine and Fine Particle Number and Surface Area Concentrations and Daily Cause-Specific Mortality in the Ruhr Area, Germany, 2009-2014. Environ Health Perspect. 2018 Feb 15;126(2):027008.

39. Schwarz M, Schneider A, Cyrys J, Bastian S, Breitner S, Peters A. Impact of Ambient Ultrafine Particles on Cause-Specific Mortality in Three German Cities. Am J Respir Crit Care Med. 2023 May 15;207(10):1334–44.

40. Su C, Hampel R, Franck U, Wiedensohler A, Cyrys J, Pan X, et al. Assessing responses of cardiovascular mortality to particulate matter air pollution for pre-, during- and post-2008 Olympics periods. Environ Res. 2015 Oct;142:112–22.

41. Breitner S, Liu L, Cyrys J, Brüske I, Franck U, Schlink U, et al. Sub-micrometer particulate air pollution and cardiovascular mortality in Beijing, China. Sci Total Environ. 2011 Nov;409(24):5196–204.

42. Leitte AM, Schlink U, Herbarth O, Wiedensohler A, Pan XC, Hu M, et al. Associations between size-segregated particle number concentrations and respiratory mortality in Beijing, China. Int J Environ Health Res. 2012 Apr;22(2):119–33.

43. Weichenthal S, Van Ryswyk K, Goldstein A, Shekarrizfard M, Hatzopoulou M. Characterizing the spatial distribution of ambient ultrafine particles in Toronto, Canada: A land use regression model. Environ Pollut. 2016 Jan 1;208:241–8.

44. Kerckhoffs J, Hoek G, Gehring U, Vermeulen R. Modelling nationwide spatial variation of ultrafine particles based on mobile monitoring. Environ Int. 2021 Sep 1;154:106569.

45. Ketzel M, Frohn LM, Christensen JH, Brandt J, Massling A, Andersen C, et al. Modelling ultrafine particle number concentrations at address resolution in Denmark from 1979 to 2018 - Part 2: Local and street scale modelling and evaluation. Atmos Environ. 2021 Nov 1;264:118633.

46. Downward GS, van Nunen EJHM, Kerckhoffs J, Vineis P, Brunekreef B, Boer JMA, et al. Long-Term Exposure to Ultrafine Particles and Incidence of Cardiovascular and Cerebrovascular Disease in a Prospective Study of a Dutch Cohort. Environ Health Perspect. 2018;126(12):127007.

47. Rodins V, Lucht S, Ohlwein S, Hennig F, Soppa V, Erbel R, et al. Long-term exposure to ambient source-specific particulate matter and its components and incidence of cardiovascular events – The Heinz Nixdorf Recall study. Environ Int. 2020 Sep 1;142:105854.

48. Bai L, Chen H, Hatzopoulou M, Jerrett M, Kwong JC, Burnett RT, et al. Exposure to Ambient Ultrafine Particles and Nitrogen Dioxide and Incident Hypertension and Diabetes. Epidemiol Camb Mass. 2018;29(3):323–32.

49. Lucht S, Hennig F, Moebus S, Ohlwein S, Herder C, Kowall B, et al. All-source and source-specific air pollution and 10-year diabetes Incidence: Total effect and mediation analyses in the Heinz Nixdorf recall study. Environ Int. 2020 Mar;136:105493.

50. Sørensen M, Poulsen AH, Hvidtfeldt UA, Frohn LM, Ketzel M, Christensen JH, et al. Exposure to source-specific air pollution and risk for type 2 diabetes: a nationwide study covering Denmark. Int J Epidemiol. 2022 Aug 10;51(4):1219–29.

51. Zou X, Fang J, Yang Y, Wu R, Wang S, Xu H, et al. Maternal exposure to traffic-related ambient particles and risk of gestational diabetes mellitus with isolated fasting hyperglycaemia: A retrospective cohort study in Beijing, China. Int J Hyg Environ Health. 2022 May;242:113973.

52. Poulsen AH, Sørensen M, Hvidtfeldt UA, Brandt J, Frohn LM, Ketzel M, et al. 'Source-specific' air pollution and risk of stroke in Denmark. Int J Epidemiol. 2023 Jun 6;52(3):727–37.

53. Bai L, Weichenthal S, Kwong JC, Burnett RT, Hatzopoulou M, Jerrett M, et al. Associations of Long-Term Exposure to Ultrafine Particles and Nitrogen Dioxide With Increased Incidence of Congestive Heart Failure and Acute Myocardial Infarction. Am J Epidemiol. 2019 01;188(1):151–9.

54. Poulsen AH, Sørensen M, Hvidtfeldt UA, Christensen JH, Brandt J, Frohn LM, et al. Source-Specific Air Pollution Including Ultrafine Particles and Risk of Myocardial Infarction: A Nationwide Cohort Study from Denmark. Environ Health Perspect. 2023 May;131(5):57010.

55. Lavigne E, Lima I, Hatzopoulou M, Van Ryswyk K, Decou ML, Luo W, et al. Spatial variations in ambient ultrafine particle concentrations and risk of congenital heart defects. Environ Int. 2019 Sep 1;130:104953.

56. Endes S, Schaffner E, Caviezel S, Dratva J, Stolz D, Schindler C, et al. Is physical activity a modifier of the association between air pollution and arterial stiffness in older adults: The SAPALDIA cohort study. Int J Hyg Environ Health. 2017 Aug;220(6):1030–8.

57. Assibey-Mensah V, Glantz JC, Hopke PK, Jusko TA, Thevenet-Morrison K, Chalupa D, et al. Ambient wintertime particulate air pollution and hypertensive disorders of pregnancy in Monroe County, New York. Environ Res. 2019 Jan;168:25–31.

58. Aguilera I, Dratva J, Caviezel S, Burdet L, de Groot E, Ducret-Stich RE, et al. Particulate Matter and Subclinical Atherosclerosis: Associations between Different Particle Sizes and Sources with Carotid Intima-Media Thickness in the SAPALDIA Study. Environ Health Perspect. 2016 Nov;124(11):1700–6.

59. Hennig F, Geisel MH, Kälsch H, Lucht S, Mahabadi AA, Moebus S, et al. Air Pollution and Progression of Atherosclerosis in Different Vessel Beds—Results from a Prospective Cohort Study in the Ruhr Area, Germany. Environ Health Perspect. 2020 Oct;128(10):107003.

60. Weichenthal S, Bai L, Hatzopoulou M, Van Ryswyk K, Kwong JC, Jerrett M, et al. Long-term exposure to ambient ultrafine particles and respiratory disease incidence in in Toronto, Canada: a cohort study. Environ Health Glob Access Sci Source. 2017 19;16(1):64.

61. Yu Z, Koppelman GH, Boer JMA, Hoek G, Kerckhoffs J, Vonk JM, et al. Ambient ultrafine particles and asthma onset until age 20: The PIAMA birth cohort. Environ Res. 2022 Nov;214(Pt 1):113770.

62. Wright RJ, Hsu HHL, Chiu YHM, Coull BA, Simon MC, Hudda N, et al. Prenatal Ambient Ultrafine Particle Exposure and Childhood Asthma in the Northeastern United States. Am J Respir Crit Care Med. 2021 Oct 1;204(7):788–96.

63. Lavigne E, Donelle J, Hatzopoulou M, Van Ryswyk K, van Donkelaar A, Martin RV, et al. Spatiotemporal Variations in Ambient Ultrafine Particles and the Incidence of Childhood Asthma. Am J Respir Crit Care Med. 2019 Jun 15;199(12):1487–95.

64. Lavigne E, Lima I, Hatzopoulou M, Van Ryswyk K, van Donkelaar A, Martin RV, et al. Ambient ultrafine particle concentrations and incidence of childhood cancers. Environ Int. 2020 Dec 1;145:106135.

65. Goldberg MS, Labrèche F, Weichenthal S, Lavigne E, Valois MF, Hatzopoulou M, et al. The association between the incidence of postmenopausal breast cancer and concentrations at street-level of nitrogen dioxide and ultrafine particles. Environ Res. 2017 Oct;158:7–15.

66. Weichenthal S, Olaniyan T, Christidis T, Lavigne E, Hatzopoulou M, Van Ryswyk K, et al. Within-city Spatial Variations in Ambient Ultrafine Particle Concentrations and Incident Brain Tumors in Adults. Epidemiol Camb Mass. 2020 Mar;31(2):177–83.

67. Weichenthal S, Lavigne E, Valois MF, Hatzopoulou M, Van Ryswyk K, Shekarrizfard M, et al. Spatial variations in ambient ultrafine particle concentrations and the risk of incident prostate cancer: A case-control study. Environ Res. 2017 Jul;156:374–80.

68. Ohlwein S, Hennig F, Lucht S, Schmidt B, Eisele L, Arendt M, et al. Air Pollution and Polyclonal Elevation of Serum Free Light Chains: An Assessment of Adaptive Immune Responses in the Prospective Heinz Nixdorf Recall Study. Environ Health Perspect. 2021 Feb;129(2):27004.

69. Lucht SA, Hennig F, Matthiessen C, Ohlwein S, Icks A, Moebus S, et al. Air Pollution and Glucose Metabolism: An Analysis in Non-Diabetic Participants of the Heinz Nixdorf Recall Study. Environ Health Perspect. 2018 Apr 3;126(4):047001.

70. Lucht S, Hennig F, Moebus S, Führer-Sakel D, Herder C, Jöckel KH, et al. Air pollution and diabetes-related biomarkers in non-diabetic adults: A pathway to impaired glucose metabolism? Environ Int. 2019 Mar;124:370–92.

71. Zhang S, Mwiberi S, Pickford R, Breitner S, Huth C, Koenig W, et al. Longitudinal associations between ambient air pollution and insulin sensitivity: results from the KORA cohort study. Lancet Planet Health. 2021 Jan 1;5(1):e39–49.

72. Viehmann A, Hertel S, Fuks K, Eisele L, Moebus S, Möhlenkamp S, et al. Long-term residential exposure to urban air pollution, and repeated measures of systemic blood markers of inflammation and coagulation. Occup Environ Med. 2015 Sep;72(9):656–63.

73. Voss S, Schneider A, Huth C, Wolf K, Markevych I, Schwettmann L, et al. ENVINT-D-20-01309: Long-term exposure to air pollution, road traffic noise, residential greenness, and prevalent and incident metabolic syndrome: Results from the population-based KORA F4/FF4 cohort in Augsburg, Germany. Environ Int. 2021 Feb;147:106364.

74. Yu Z, Koppelman GH, Hoek G, Kerckhoffs J, Vonk JM, Vermeulen R, et al. Ultrafine particles, particle components and lung function at age 16 years: The PIAMA birth cohort study. Environ Int. 2021 Dec 1;157:106792.

75. Forns J, Dadvand P, Esnaola M, Alvarez-Pedrerol M, López-Vicente M, Garcia-Esteban R, et al. Longitudinal association between air pollution exposure at school and cognitive development in school children over a period of 3.5 years. Environ Res. 2017 Nov;159:416–21.

76. Sunyer J, Esnaola M, Alvarez-Pedrerol M, Forns J, Rivas I, López-Vicente M, et al. Association between Traffic-Related Air Pollution in Schools and Cognitive Development in Primary School Children: A Prospective Cohort Study. PLOS Med. 2015 Mar 3;12(3):e1001792.

77. Lubczyńska MJ, Muetzel RL, El Marroun H, Hoek G, Kooter IM, Thomson EM, et al. Air pollution exposure during pregnancy and childhood and brain morphology in preadolescents. Environ Res. 2021 Jul 1;198:110446.

78. Gan W, Manning KJ, Cleary EG, Fortinsky RH, Brugge D. Exposure to ultrafine particles and cognitive decline among older people in the United States. Environ Res. 2023 Jun 15;227:115768.

79. Nußbaum R, Lucht S, Jockwitz C, Moebus S, Engel M, Jöckel KH, et al. Associations of Air Pollution and Noise with Local Brain Structure in a Cohort of Older Adults. Environ Health Perspect. 2020 Jun;128(6):67012.

80. Glaubitz L, Stumme J, Lucht S, Moebus S, Schramm S, Jockwitz C, et al. Association between Long-Term Air Pollution, Chronic Traffic Noise, and Resting-State Functional Connectivity in the 1000BRAINS Study. Environ Health Perspect. 2022 Sep 26;130(9):097007.

81. Lucht S, Glaubitz L, Moebus S, Schramm S, Jockwitz C, Caspers S, et al. Long-term air pollution, noise, and structural measures of the Default Mode Network in the brain: Results from the 1000BRAINS cohort. Int J Hyg Environ Health. 2022 Jan 1;239:113867.

82. Fang J, Yang Y, Zou X, Xu H, Wang S, Wu R, et al. Maternal exposures to fine and ultrafine particles and the risk of preterm birth from a retrospective study in Beijing, China. Sci Total Environ. 2022 Mar 15;812:151488.

83. Laurent O, Hu J, Li L, Kleeman MJ, Bartell SM, Cockburn M, et al. A Statewide Nested Case–Control Study of Preterm Birth and Air Pollution by Source and Composition: California, 2001–2008. Environ Health Perspect. 2016 Sep;124(9):1479–86.

84. Li R, Hopke PK, Dozier A, Thurston SW, Thevenet-Morrison K, Croft D, et al. Term birth weight and ambient air pollutant concentrations during pregnancy, among women living in Monroe County, New York. J Expo Sci Environ Epidemiol. 2019;29(4):500–9.

85. Laurent O, Hu J, Li L, Kleeman MJ, Bartell SM, Cockburn M, et al. Low birth weight and air pollution in California: Which sources and components drive the risk? Environ Int. 2016 Jul 1;92–93:471–7.

86. Goin DE, Sudat S, Riddell C, Morello-Frosch R, Apte JS, Glymour MM, et al. Hyperlocalized Measures of Air Pollution and Preeclampsia in Oakland, California. Environ Sci Technol. 2021 Nov 2;55(21):14710–9.

87. Ostro B, Hu J, Goldberg D, Reynolds P, Hertz A, Bernstein L, et al. Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: results from the California Teachers Study Cohort. Environ Health Perspect. 2015 Jun;123(6):549–56.

88. Bouma F, Janssen NA, Wesseling J, van Ratingen S, Strak M, Kerckhoffs J, et al. Long-term exposure to ultrafine particles and natural and cause-specific mortality. Environ Int. 2023 May;175:107960.

89. Riley K, Cook R, Carr E, Manning B. A Systematic Review of The Impact of Commercial Aircraft Activity on Air Quality Near Airports. City Environ Interact. 2021;11.

90. Bendtsen KM, Bengtsen E, Saber AT, Vogel U. A review of health effects associated with exposure to jet engine emissions in and around airports. Environ Health Glob Access Sci Source. 2021 Feb 6;20(1):10.

91. Hudda N, Fruin SA. International Airport Impacts to Air Quality: Size and Related Properties of Large Increases in Ultrafine Particle Number Concentrations. Environ Sci Technol. 2016 Apr 5;50(7):3362–70.

92. Shirmohammadi F, Sowlat MH, Hasheminassab S, Saffari A, Ban-Weiss G, Sioutas C. Emission rates of particle number, mass and black carbon by the Los Angeles International Airport (LAX) and its impact on air quality in Los Angeles. Atmos Environ. 2017 Feb 1;151:82–93.

93. Riley EA, Gould T, Hartin K, Fruin SA, Simpson CD, Yost MG, et al. Ultrafine particle size as a tracer for aircraft turbine emissions. Atmos Environ. 2016 Aug 1;139:20–9.

94. Hudda N, Gould T, Hartin K, Larson TV, Fruin SA. Emissions from an international airport increase particle number concentrations 4-fold at 10 km downwind. Environ Sci Technol. 2014 Jun 17;48(12):6628–35.

95. Keuken MP, Moerman M, Zandveld P, Henzing JS, Hoek G. Total and size-resolved particle number and black carbon concentrations in urban areas near Schiphol airport (the Netherlands). Atmos Environ. 2015 Mar 1;104:132–42.

96. Stacey B, Harrison RM, Pope F. Evaluation of ultrafine particle concentrations and size distributions at London Heathrow Airport. Atmos Environ. 2020 Feb 1;222:117148.

97. Zhang X, Karl M, Zhang L, Wang J. Influence of Aviation Emission on the Particle Number Concentration near Zurich Airport. Environ Sci Technol. 2020 Nov 17;54(22):14161–71.

98. Hudda N, Simon MC, Zamore W, Brugge D, Durant JL. Aviation Emissions Impact Ambient Ultrafine Particle Concentrations in the Greater Boston Area. Environ Sci Technol. 2016 Aug 16;50(16):8514–21.

99. Chung CS, Lane KJ, Black-Ingersoll F, Kolaczyk E, Schollaert C, Li S, et al. Assessing the impact of aircraft arrival on ambient ultrafine particle number concentrations in near-airport communities in Boston, Massachusetts. Environ Res. 2023 May 15;225:115584.

100. Tremper AH, Jephcote C, Gulliver J, Hibbs L, Green DC, Font A, et al. Sources of particle number concentration and noise near London Gatwick Airport. Environ Int. 2022 Mar;161:107092.

101. Hsu HH, Adamkiewicz G, Houseman EA, Zarubiak D, Spengler JD, Levy JI. Contributions of aircraft arrivals and departures to ultrafine particle counts near Los Angeles International Airport. Sci Total Environ. 2013 Feb 1;444:347–55.

102. Austin E, Xiang J, Gould TR, Shirai JH, Yun S, Yost MG, et al. Distinct Ultrafine Particle Profiles Associated with Aircraft and Roadway Traffic. Environ Sci Technol. 2021 Mar 2;55(5):2847–58.

103. Masiol M, Vu TV, Beddows DCS, Harrison RM. Source apportionment of wide range particle size spectra and black carbon collected at the airport of Venice (Italy). Atmos Environ. 2016 Aug 1;139:56–74.

104. Ellermann T, Massling A, Løfstrøm P, Winther M, Nøjgaard J, Ketzel M. Assessment of the air quality at the apron of Copenhagen Airport Kastrup in relation to the working environment. 2012;(Technical report from DCE – Danish Centre for Environment and Energy No. 15):51.

105. Møller KL, Thygesen LC, Schipperijn J, Loft S, Bonde JP, Mikkelsen S, et al. Occupational Exposure to Ultrafine Particles among Airport Employees - Combining Personal Monitoring and Global Positioning System. PLOS ONE. 2014 Sep 9;9(9):e106671.

106. Kerckhoffs J, Khan J, Hoek G, Yuan Z, Hertel O, Ketzel M, et al. Hyperlocal variation of nitrogen dioxide, black carbon, and ultrafine particles measured with Google Street View cars in Amsterdam and Copenhagen. Environ Int. 2022 Dec 1;170:107575.

107. Habre R, Zhou H, Eckel SP, Enebish T, Fruin S, Bastain T, et al. Short-term effects of airport-associated ultrafine particle exposure on lung function and inflammation in adults with asthma. Environ Int. 2018 Sep 1;118:48–59.

108. Selley L, Lammers A, Le Guennec A, Pirhadi M, Sioutas C, Janssen N, et al. Alterations to the urinary metabolome following semi-controlled short exposures to ultrafine particles at a major airport. Int J Hyg Environ Health. 2021 Aug;237:113803.

109. Lammers A, Janssen N a. H, Boere AJF, Berger M, Longo C, Vijverberg SJH, et al. Effects of short-term exposures to ultrafine particles near an airport in healthy subjects. Environ Int. 2020 Aug;141:105779.

110. Janssen NAH, Lammer M, Maitland-Van De Zee AH, Van De Zee S, Keuken R, Blom M, et al. Onderzoek naar de gezondheidseffecten van kortdurende blootstelling aan ultrafijn stof rond Schiphol. 2019 [cited 2024 Jan 4]; Available from: https://rivm.openrepository.com/handle/10029/623133

111. Janssen N, Hoekstra J, Houthuijs D, Jacobs J, Nicolaie A, Strak M. Effects of long-term exposure to ultrafine particles from aviation around Schiphol Airport [Internet].

Rijksinstituut voor Volksgezondheid en Milieu RIVM; 2022 [cited 2023 Dec 4]. Available from: https://rivm.openrepository.com/handle/10029/625854

112. Wu AH, Fruin S, Larson TV, Tseng CC, Wu J, Yang J, et al. Association between Airport-Related Ultrafine Particles and Risk of Malignant Brain Cancer: A Multiethnic Cohort Study. Cancer Res. 2021 Aug 15;81(16):4360–9.

113. Wing SE, Larson TV, Hudda N, Boonyarattaphan S, Fruin S, Ritz B. Preterm Birth among Infants Exposed to in Utero Ultrafine Particles from Aircraft Emissions. Environ Health Perspect. 2020 Apr;128(4):047002.

114. Carter SA, Rahman MM, Lin JC, Chow T, Yu X, Martinez MP, et al. Maternal exposure to aircraft emitted ultrafine particles during pregnancy and likelihood of ASD in children. Environ Int. 2023 Aug;178:108061.