Systematic Review on Long-term Exposure to UFP and Health Effects

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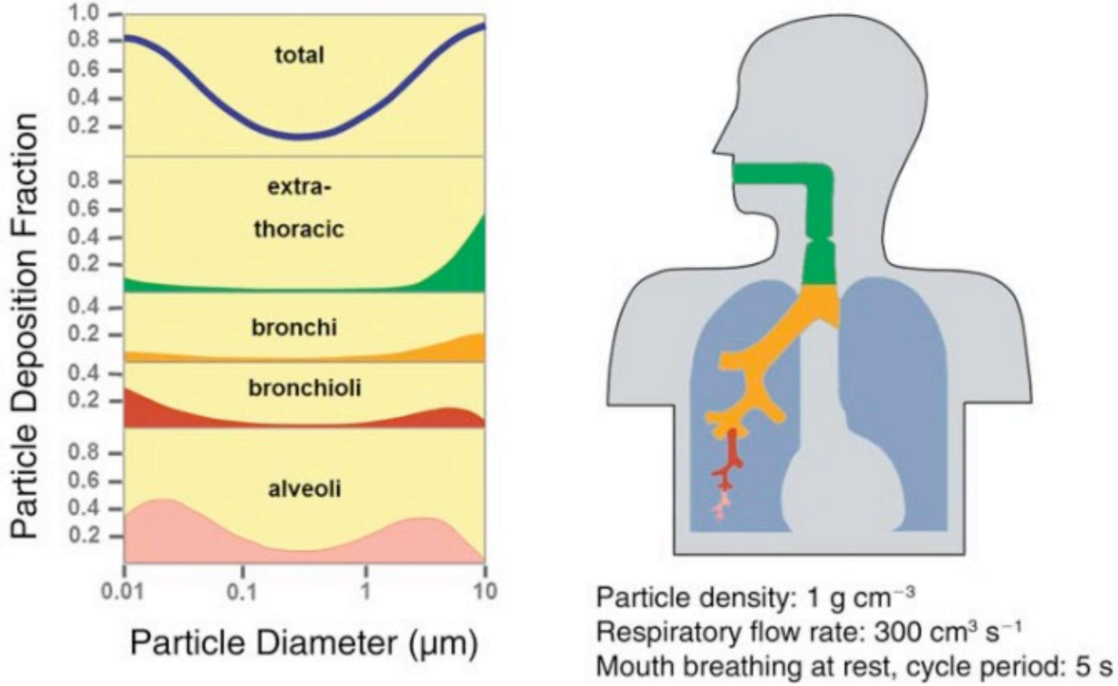
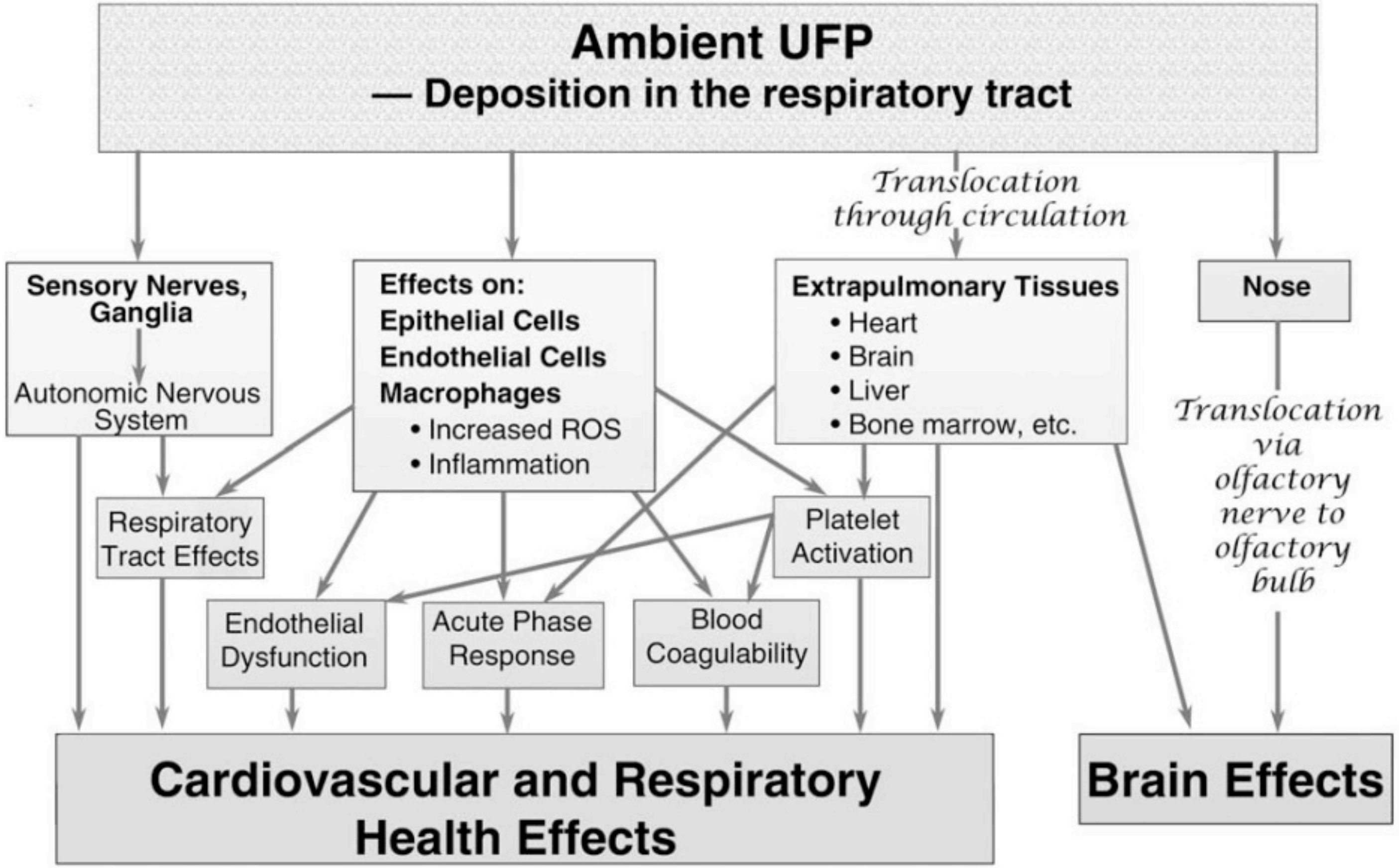
June 13, NPC24 – Zürich, Switzerland

Background: why UFP?



HEI, 2013

Background: How do UFP act on the body?



HEI, 2013

Background: What makes UFP exposure assessment challenging in epidemiological studies?

1. High spatial variability and temporal variability

→ high degree of exposure missclassification in health studies

2. In traditional models, UFP and related air pollutants (NO_2, black carbon) are often highly correlated

→ teasing apart the UFP effect from co-pollutant effects in health analyses is difficult

→ Which exposure assessment method for UFP have been used?

→ Innovative models present in the literature? Combination of methods?

→ What have others done and how can we transfer these methods to Germany?

KoPilot

Federal Environment Agency – Germany

The Design of a Pilot Study on the Health Effects of Ultrafine Particles

Measuring	Modelling	Epidemiology Systematic review, development of study design
iuta, HSD	TNO, IVU Umwelt GmbH Umweltplanung · Informationssysteme, Ingenieurbüro Janicke Gesellschaft für Umweltphysik	hhu Heinrich Heine Universität Düsseldorf

Objectives

- Present first results from systematic review on long-term health effects of UFP
- Pay specific attention to co-pollutant adjustments in two-pollutant models (NO_2, $PM_{2.5}$)

Methods: Search Strategy

Databases:

PubMed

LUDOK: specialized database on air pollutants and health

Study Period:

01.01.2011 – 01.09.2023 (old + updated search)

Search on 3 concepts:

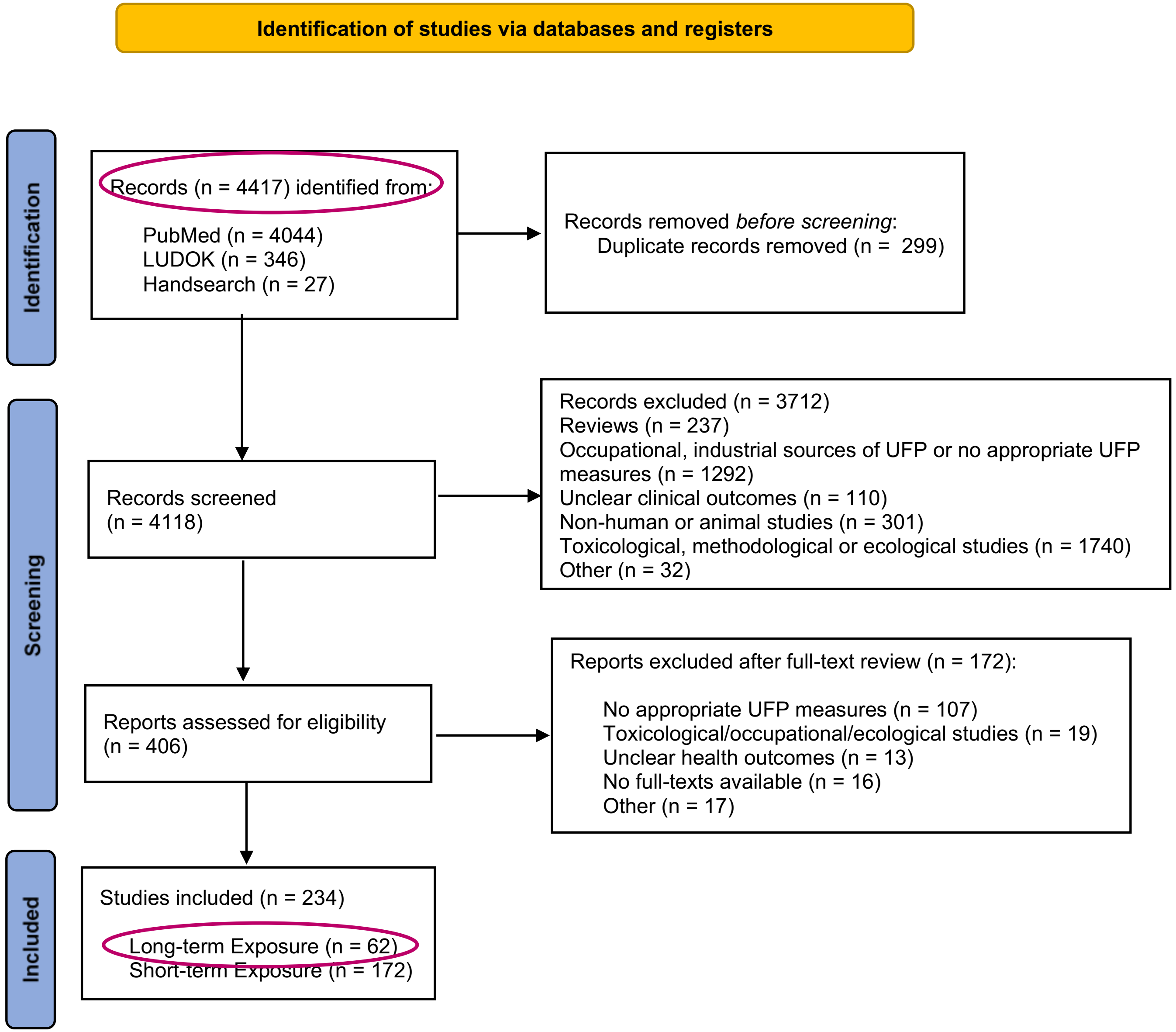
ambient air pollution, ultrafine particles, health and epidemiology

Risk of Bias Analysis and Qualitative Analyses

Methods

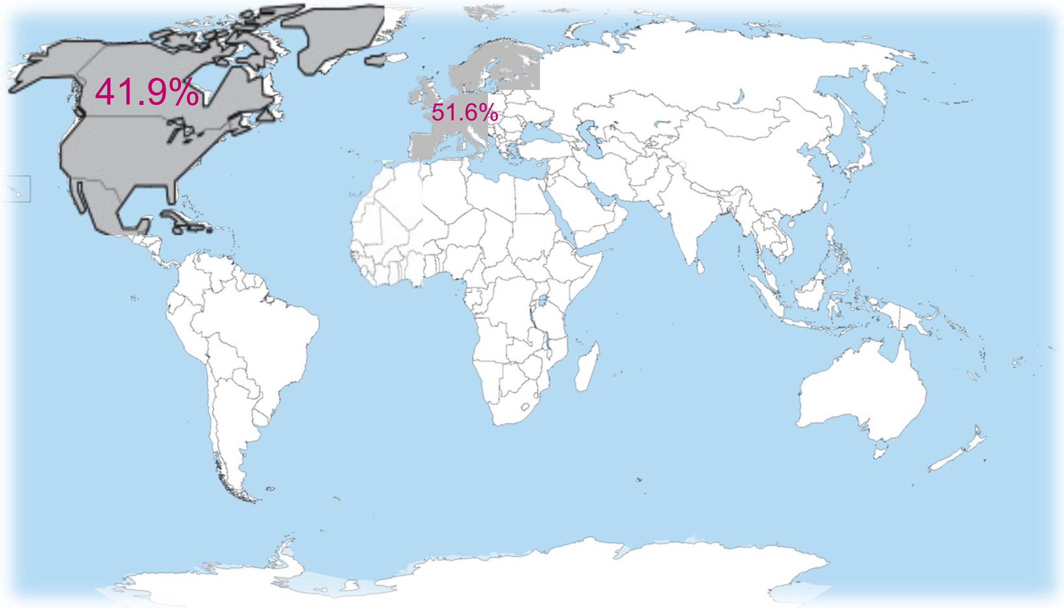
	Inclusion Criteria for studies on UFP
Population	**General, selected or patient population:** All ages Developed and developing areas Urban and rural No geographical restrictions
Exposure	**Long-term Exposure to:** Particle number (PNC) ≤100nm Nucleation-mode particles (NucMP) Aitken-mode particles (AitMP) Quasi-UFP particles (AccMP)

PRISMA Flowchart

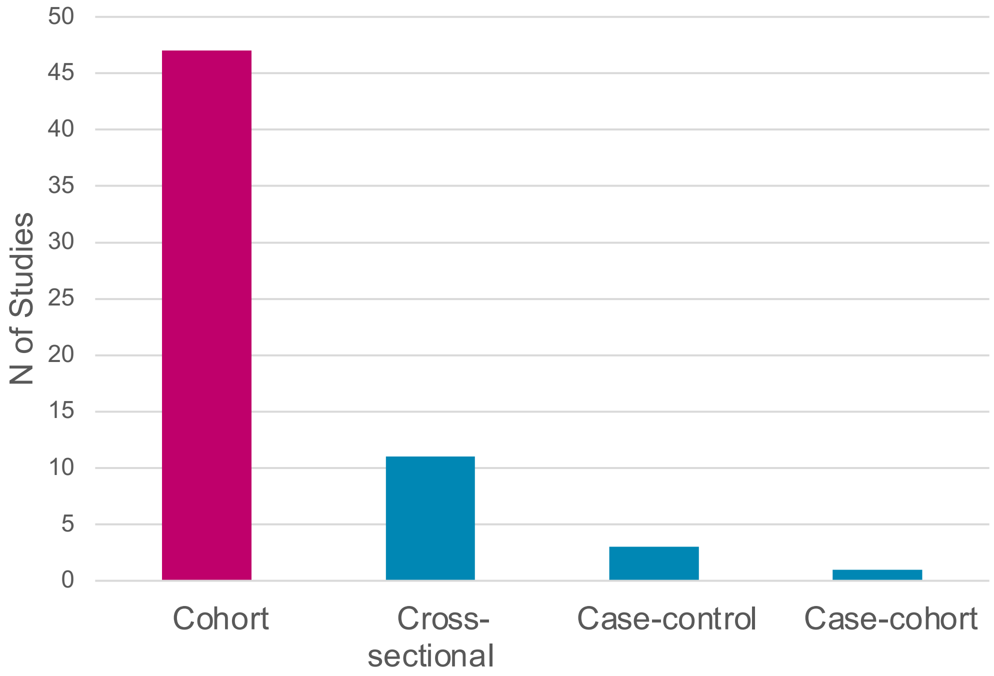


Study Characteristics

Location

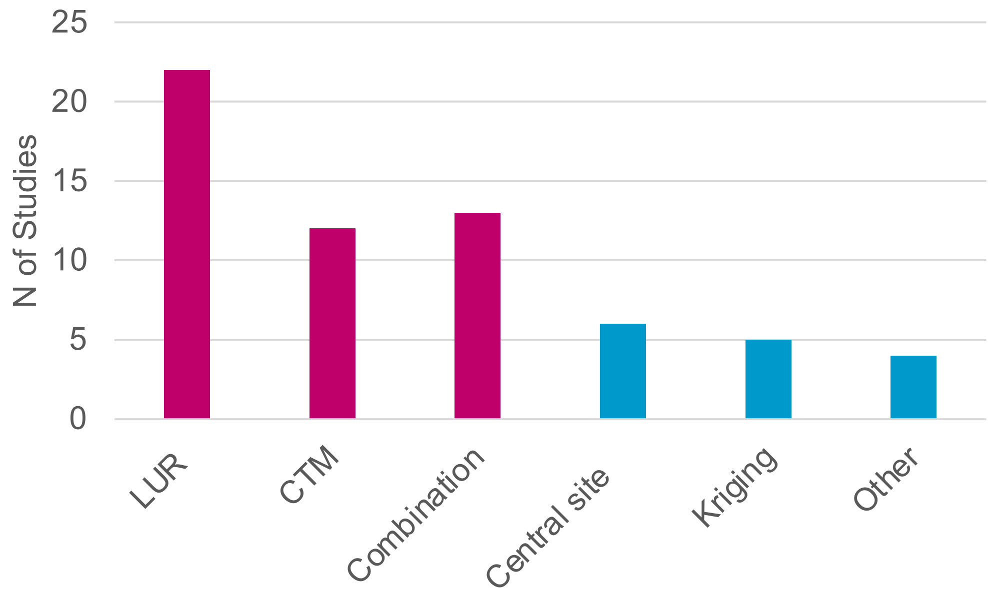


Study Design

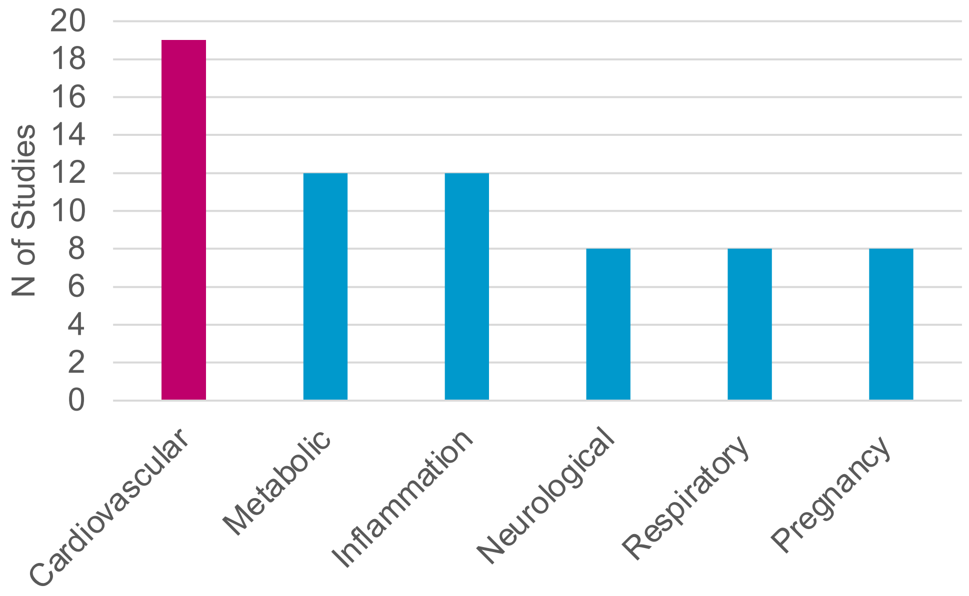


Study Characteristics

Exposure Methods



Organ Systems



Qualitative Results on Cardiovascular Outcomes

Study	All CVD	CVD Mortality	IHD Mortality	Stroke	CHD	MI	Heart Failure	Hypertension Blood Pressure	Pulse Pressure	Atherosclerosis	Congenital Heart Defect
Aguilera et al. 2016											
Assibey-Mensah et al. 2019											
Bai et al. 2018											
Bai et al. 2019											
Bouma et al. 2023											
Corlin et al. 2018											
Corlin et al. 2018											
Downward et al. 2018											
Endes et al. 2017											
Hennig et al. 2020											
Lavigne et al. 2019											
Li Y. et al. 2017											
Ostro et al. 2015											
Peralta et al. 2022											
Poulsen et al. 2023											
Poulsen et al. 2023											
Rodins et al. 2020											

+ Single Pollutant Model + NO_2 + $PM_{2.5}$

+ significant positive; (+) positive not-significant

- negative significant; (-) negative not-significant

0 Null/Unclear

Qualitative Results on Cardiovascular Outcomes

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Assibey-Mensah et al. 2019								0			
Bai et al. 2018								+			
Bai et al. 2019					+	+					
Bouma et al. 2023		+									
Corlin et al. 2018								(+)	(+)		
Corlin et al. 2018								(+)	(+)		
Downward et al. 2018	+			(+)	(+)	(+)	+				
Endes et al. 2017										(+)	
Hennig et al. 2020										0	
Lavigne et al. 2019											0
Li Y. et al. 2017				(+)				(+)			
Ostro et al. 2015		0	+								
Peralta et al. 2022										0	
Poulsen et al. 2023						+					
Poulsen et al. 2023				+							
Rodins et al. 2020	(+)			+	0						

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Bai et al. 2019					+ (+)	+ +					
Bouma et al. 2023		+ (+)									
Corlin et al. 2018								(+)	(+)		
Corlin et al. 2018								(+)	(+)		
Downward et al. 2018	+ +			(+) (+)	(+) (+)	(+) (+)	+ (+)				
Endes et al. 2017										(+)	
Hennig et al. 2020										0	
Lavigne et al. 2019											0
Li Y. et al. 2017				(+)				(+)			
Ostro et al. 2015		0	+								
Peralta et al. 2022										0	
Poulsen et al. 2023						+					
Poulsen et al. 2023				+							
Rodins et al. 2020	(+)			+	0						

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Ostro et al. 2015		0	+ (0)								
Peralta et al. 2022										0	
Poulsen et al. 2023						+					
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Long-term exposure to ambient source-specific particulate matter and its components and incidence of cardiovascular events – The Heinz Nixdorf Recall study

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ARTICLE INFO

Handling editor: Hanna Boogaard

Keywords:
Air pollution
Cardiovascular health
Stroke
Coronary heart disease
Particulate matter
Components
Pollution sources

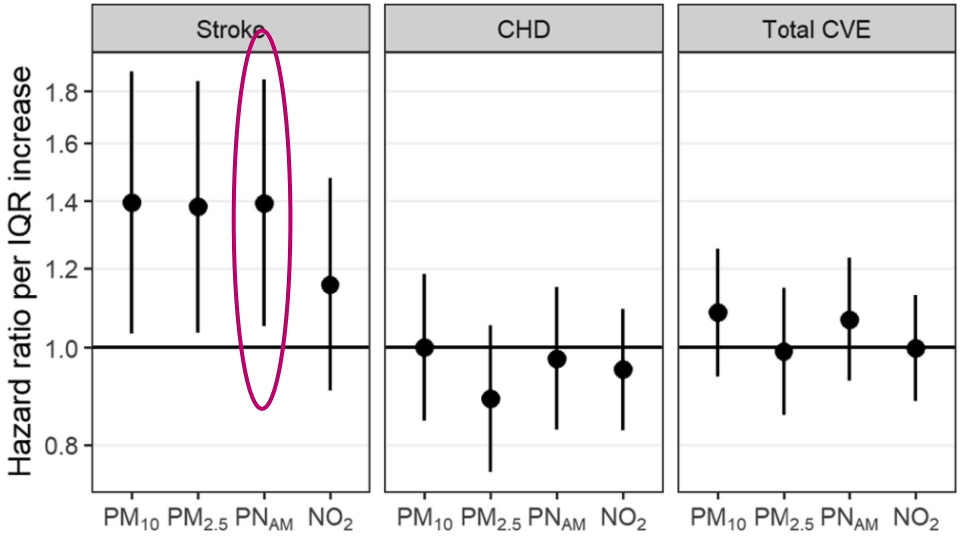
ABSTRACT

Background: Few studies have examined the risk of long-term exposure to source-specific airborne pollutants on incidence of cerebrovascular and cardiovascular events.
Objectives: We aimed to estimate the effect of long-term exposure to source-specific air pollution and particulate matter (PM) components on incidence of stroke, coronary heart disease (CHD), and total cardiovascular events (CVE) in the population-based Heinz Nixdorf Recall study (HNR).
Methods: We used baseline (2000–2003) and 14-year follow-up data of the HNR Study, an ongoing population-based prospective cohort study in Western Germany. Participants' residential mean exposures to NO_2 and total and source-specific PM_{10}, $PM_{2.5}$, accumulation mode particle number concentration (PN_{AM}), and PM components were modelled using a dispersion and chemical transport model. We used Cox regression to evaluate the effect of pollutants (per 1 μg/m^3 increase and per interquartile range – IQR) on risk of stroke and CHD, adjusting

- Cohort Study – Western Germany
- Baseline: 2000-2003 – Follow up: 2015
- Outcome: first occurence of stroke
- Self-reports, physician interviews, medical records

Exposure Assessment Method:

- EURAD CTM
- Multilayer multigrid model system; 1km^2 resolution
- Hourly estimates of PNacc for each grid cell assigned to home addresses
- Multiple-year mean concentration at participants´ addresses



Rodins et al, 2020

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

Air pollution and stroke; effect modification by sociodemographic and environmental factors. A cohort study from Denmark

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ARTICLE INFO

Keywords:
Epidemiology
Cohort study
Stroke
Air pollution
Noise
Green-area

ABSTRACT

Objectives: Air pollution increases the risk of stroke, but the literature on identifying susceptible subgroups of populations is scarce and inconsistent. The aim of this study was to investigate if the association between air pollution and risk of stroke differed by sociodemographic factors, financial stress, comorbid conditions, and residential road traffic noise, population density and green space.
Methods: We assessed long-term exposure to air pollution with ultrafine particles, $PM_{2.5}$, elemental carbon and NO_2 for a cohort of 1,971,246 Danes aged 50–85 years. During follow-up from 2005 to 2017, we identified 83,211 incident stroke cases. We used Cox proportional hazards model (relative risk) and Aalen additive hazards

- Cohort in Denmark
- Baseline: 2005, follow-up: 2017
- Outcome: stroke incident cases
- Source: Danish national patient registry

Exposure Assessment Method:

- DEHM/UBM/AirGis
- Regional background + local 1x1km + mobile
- UFP 10-1000nm
- 5-year average at participants` addresses

0.71 ($PM_{2.5}$ vs EC) to 0.86 (UFP vs NO_2) (Table 2).

Overall, we observed a HR for stroke of 1.28 (95% CI: 1.24–1.33) for 5nullμg/m^3 higher $PM_{2.5}$, 1.12 (95% CI: 1.09–1.15) per 10,000 particles/cm^3, 1.06 (95% CI: 1.04–1.09) per 1nullμg/m^3 of EC and 1.06 (95% CI: 1.04–1.07) per 10nullμg/m^3 NO_2 in models adjusted for age, sex, calendar-year, education, occupational status, civil status, personal income, household income country of origin, and area-level deprivation (percentage of parish population with only mandatory education). Similarly, stroke rate (per 100,000 person-years) differences for the same exposure contrasts were 509 (95% CI: 490–529) for $PM_{2.5}$, 282 (95% CI: 266–298) for UFP, 229 (95% CI: 209–250) for EC, and 120 (95% CI: 112–128) for NO_2.

Poulsen et al, 2023

Research

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP3047.

Long-Term Exposure to Ultrafine Particles and Incidence of Cardiovascular and Cerebrovascular Disease in a Prospective Study of a Dutch Cohort

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[2]MRC-PHE Centre for Environment and Health, Department of Epidemiology and Biostatistics, Imperial College London, St. Mary's Campus, London, UK
[3]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, Netherlands
[4]National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands
[5]Dept. of Civil, Architectural and Environmental Engineering, University of Texas at Austin, USA
[6]Environmental Defense Fund, Washington, DC, USA

Background: There is growing evidence that exposure to ultrafine particles (UFP; particles smaller than 100 nm) may play an underexplored role in the etiology of several illnesses, including cardiovascular disease (CVD).

Objectives: We aimed o investigate the relationship between long-term exposure to ambient UFP and incident cardiovascular and cerebrovascular disease (CVA). As a secondary objective, we sought to compare effect estimates for UFP with those derived for other air pollutants, including estimates from two-pollutant models.

Methods: Using a prospective cohort of 33,831 Dutch residents, we studied the association between long-term exposure to UFP (predicted via land use regression) and incident disease using Cox proportional hazard models. Hazard ratios (HR) for UFP were compared to HRs for more routinely monitored air pollutants, including particulate matter with aerodynamic diameter ≤10 μm (PM_{10}), PM with aerodynamic diameter ≤2.5 ($PM_{2.5}$), and NO_2.

Results: Long-term UFP exposure was associated with an increased risk for all incident CVD [HR = 1.18 per 10,000 particles/cm^3; 95% confidence interval (CI): 1.03, 1.34], myocardial infarction (MI) (HR = 1.34; 95% CI: 1.00, 1.79), and heart failure (HR = 1.76; 95% CI: 1.17, 2.66). Positive associations were also estimated for NO_2 (HR for heart failure = 1.22; 95% CI: 1.01, 1.48 per 20 μg/m^3) and coarse PM (PM_{coarse}; HR for all CVD = 1.21; 95% CI: 1.01, 1.45 per 10 μg/m^3). CVD was not positively associated with $PM_{2.5}$ (HR for all CVD = 0.95; 95% CI: 0.75, 1.28 per 5 μg/m^3). HRs for UFP and CVAs were positive, but not significant. In two-pollutant models (UFP + NO_2 and UFP + PM_{coarse}), positive associations tended to remain for UFP, while HRs for PM_{coarse} and NO_2 generally attenuated towards the null.

Conclusions: These findings strengthen the evidence that UFP exposure plays an important role in cardiovascular health and that risks of ambient air pollution may have been underestimated based on conventional air pollution metrics. https://doi.org/10.1289/EHP3047

- Cohort in the Netherlands (1993-2010)
- Outcome: all incident cerebrovascular diseases
- Source: Dutch Hospital Discharge Diagnosis Database

Exposure Assessment Method:

- Spatial LUR
- UFP 10-1000nm
- 242 monitoring sites (with large contrasts in traffic intensity)
- 30-mins measurements between 9:00 and 16:00; collected 3-times to account for change in seasonality
- Year-mean UFP at baseline address of participant

Table 4. Hazard ratios (95% confidence interval) for the association between annual average air pollutants and cerebrovascular disease incidence.

Pollutants	All incident cerebrovascular disease 1,283 events	Incident ischemic CVA 846 events	Incident hemorrhagic CVA 241 events
Single-pollutant models	—	—	—
$PM_{2.5}$	1.13 (0.69, 1.83)	0.90 (0.49, 1.66)	1.88 (0.66, 5.39)
PM_{coarse}	1.14 (0.80, 1.61)	1.22 (0.79, 1.86)	1.91 (0.90, 4.04)
PM_{10}	1.10 (0.73, 1.68)	1.13 (0.67, 1.89)	1.79 (0.71, 4.52)
UFP	1.11 (0.88, 1.41)	1.07 (0.80, 1.44)	1.48 (0.88, 2.51)
$PM_{2.5}$ absorbance	1.07 (0.82, 1.40)	1.01 (0.72, 1.41)	1.47 (0.81, 2.66)
NO_x	1.03 (0.92, 1.14)	1.04 (0.92, 1.18)	1.15 (0.91, 1.44)
NO_2	1.00 (0.90, 1.11)	1.05 (0.92, 1.19)	1.09 (0.86, 1.37)
Two-pollutant models	—	—	—
UFP + $PM_{2.5}$		—	—
UFP	1.11 (0.83, 1.48)	1.16 (0.81, 1.66)	1.38 (0.72, 2.64)
$PM_{2.5}$	1.00 (0.55, 1.80)	0.76 (0.36, 1.59)	1.29 (0.35, 4.74)
UFP + PM_{coarse}	—	—	—
UFP	1.09 (0.79, 1.52)	0.96 (0.64, 1.43)	1.18 (0.57, 2.44)
PM_{coarse}	1.04 (0.64, 1.68)	1.27 (0.71, 2.29)	1.63 (0.57, 4.63)
UFP + PM_{10}	—	—	—
UFP	1.19 (0.79, 1.78)	1.03 (0.63, 1.71)	1.44 (0.60, 3.48)
PM_{10}	0.87 (0.42, 1.77)	1.08 (0.45, 2.59)	1.07 (0.22, 5.17)
UFP + $PM_{2.5abs}$	—	—	—
UFP	1.19 (0.79, 1.79)	1.19 (0.72, 1.99)	1.42 (0.57, 3.52)
$PM_{2.5abs}$	0.91 (0.57, 1.46)	0.86 (0.48, 1.53)	1.07 (0.38, 3.01)
UFP + NO_x	—	—	—
UFP	1.14 (0.81, 1.59)	1.01 (0.67, 1.52)	1.41 (0.68, 2.93)
NO_x	0.99 (0.85, 1.14)	1.04 (0.87, 1.24)	1.03 (0.75, 1.43)
UFP + NO_2	—	—	—
UFP	1.34 (0.91, 1.98)	0.96 (0.59, 1.57)	1.95 (0.84, 4.53)
NO_2	0.90 (0.76, 1.07)	1.06 (0.86, 1.31)	0.86 (0.59, 1.25)

Note: CVA: cerebrovascular accident; PM, particulate matter; PM_{coarse}, PM between 2.5 and 10 μm; UFP, ultrafine particles <100 nm. All models adjusted for: smoking status (including number of cigarettes and duration of smoking), diet (intake of fruit and vegetables), alcohol consumption, BMI, recruitment year, gender, marital status, education level, and area-level economic status. Hazard ratios (HRs) are presented for the following increments: 5 μg/m^3 for $PM_{2.5}$, 5 μg/m^3 for PM_{coarse}, 10 μg/m^3 for PM_{10} 10,000 particles/cm^3 for UFP, $1 \times 10^{-5} m^{-1}$ for $PM_{2.5}$ absorbance, 20 μg/m^3 for NO_x, and 10 μg/m^3 for NO_2.

Downward et al, 2018

Qualitative Results on Metabolic Outcomes

Study	Diabetes	Metabolic Syndrome	Obesity	HbA1c (Diabetes biomarkers)	IL-1RA (Diabetes biomarkers)	Blood Glucose levels	Adinopectin	Insuline Sensitivity
Bai et al. 2018	+							
de Bont et al. 2019			+					
Li et al. 2017	(-)							
Lucht et al. 2018				+		+		
Lucht et al. 2019					+		(-)	
Lucht et al. 2020	+							
Shin et al. 2020	+							
Sorensen et al. 2022	+							
Voss et al. 2021		0						
Zhang et al. 2021								(+)
Zou et al. 2022	+					+		

+ Single Pollutant Model + NO2 + PM2.5 + PM2.5 and NO2 + CO

+ significant positive; (+) positive not-significant

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Lucht et al. 2020	+							
Shin et al. 2020	+							
Sorensen et al. 2022	+ +							
Voss et al. 2021		0						
Zhang et al. 2021								(+)
Zou et al. 2022	+ +					+ +		

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Zhang et al. 2021								(+)
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Lucht et al. 2019					+ + (+)		(-) (-) (+)	
Lucht et al. 2020	+							
Shin et al. 2020	+							
Sorensen et al. 2022	+ + + +							
Voss et al. 2021		0						
Zhang et al. 2021								(+)
Zou et al. 2022	+ +					+ +		

+ Single Pollutant Model + NO2 + PM2.5 + PM2.5 and NO2 + CO

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0 Null/Unclear

Qualitative Results on Respiratory Outcomes

Study	Respiratory disease mortality	Lung cancer mortality	Asthma	COPD
Bouma et al. 2023	+	+		
Clifford et al. 2018			0	
Lavigne et al. 2019			+	
Weichenthal et al. 2017		0	0	+
Wright et al. 2021			+	
Yu et al. 2022			+	

+ Single Pollutant Model + NO_2 + $PM_{2.5}$ + $PM_{2.5}$ and NO_2

+ significant positive; (+) positive not-significant

- negative significant; (-) negative not-significant

0 Null/Unclear

Qualitative Results on Respiratory Outcomes

Study	Respiratory disease mortality	Lung cancer mortality	Asthma	COPD
Bouma et al. 2023	+ 0	+ +		
Clifford et al. 2018			0	
Lavigne et al. 2019			+ (+)	
Weichenthal et al. 2017		0 0	0 0	+ 0
Wright et al. 2021			+ +	
Yu et al. 2022			+ 0	

+ Single Pollutant Model + NO2 + PM2.5 + PM2.5 and NO2

+ significant positive; (+) positive not-significant

- negative significant; (-) negative not-significant

0 Null/Unclear

Qualitative Results on Respiratory Outcomes

Study	Respiratory disease mortality	Lung cancer mortality	Asthma	COPD
Bouma et al. 2023	+ 0 0	+ + +		
Clifford et al. 2018			0 0	
Lavigne et al. 2019			+ (+) (+) +	
Weichenthal et al. 2017		0 0 0 0	0 0 0 0	+ 0 + 0
Wright et al. 2021			+ +	
Yu et al. 2022			+ 0 (+)	

+ Single Pollutant Model + NO2 + PM2.5 + PM2.5 and NO2

+ significant positive; (+) positive not-significant

- negative significant; (-) negative not-significant

0 Null/Unclear

Qualitative Results on Inflammatory Outcomes

Study	Food allergens	Inhalent allergens	CRP	WCC Platelets	IL-6	Fibrinogens	Free-light Chains	Cancers
Bouma et al. 2023	0	0						
Clifford et al. 2018			+					
Corlin et al. 2018			(+)					
Goldberg et al. 2017								0
Lane et al. 2015			(+)		(+)			
Lane et al. 2016			(+)		(+)	(-)		
Lavigne et al. 2020§								+
Lucht et al. 2019			+			(+)		
Ohlwein et al. 2021							+	
Pilz et al. 2018			(+)					
Viehmann et al. 2015			(+)	(+)		(+)		
Weichenthal et al. 2017								+
Weichenthal et al. 2020								+
Wu et al. 2021								+

+ Single Pollutant Model + NO_2 + $PM_{2.5}$ + $PM_{2.5}$ and NO_2 + CO

+ significant positive; (+) positive not-significant

- negative significant; (-) negative not-significant

0 Null/Unclear

Qualitative Results on Inflammatory Outcomes

Study	Food allergens	Inhalent allergens	CRP	WCC Platelets	IL-6	Fibrinogens	Free-light Chains	Cancers
Bouma et al. 2023	0 0	0 0						
Clifford et al. 2018			+					
Corlin et al. 2018			(+)					
Goldberg et al. 2017								0
Lane et al. 2015			(+)		(+)			
Lane et al. 2016			(+)		(+)	(-)		
Lavigne et al. 2020§								+ +
Lucht et al. 2019			+			(+)		
Ohlwein et al. 2021							+ +	
Pilz et al. 2018			(+)					
Viehmann et al. 2015			(+)	(+)		(+)		
Weichenthal et al. 2017								+ +
Weichenthal et al. 2020								+ +
Wu et al. 2021								+ (+)

+ Single Pollutant Model + NO2 + PM2.5 + PM2.5 and NO2 + CO

+ significant positive; (+) positive not-significant

- negative significant; (-) negative not-significant

0 Null/Unclear

Qualitative Results on Inflammatory Outcomes

Study	Food allergens	Inhalent allergens	CRP	WCC Platelets	IL-6	Fibrinogens	Free-light Chains	Cancers
Bouma et al. 2023	0 0 0	0 0 0						
Clifford et al. 2018			+ +					
Corlin et al. 2018			(+)					
Goldberg et al. 2017								0
Lane et al. 2015			(+)		(+)			
Lane et al. 2016			(+)		(+)	(-)		
Lavigne et al. 2020§								+ + +
Lucht et al. 2019			+			(+)		
Ohlwein et al. 2021							+ + +	
Pilz et al. 2018			(+) +					
Viehmann et al. 2015			(+)	(+)		(+)		
Weichenthal et al. 2017								+ +
Weichenthal et al. 2020								+ + + +
Wu et al. 2021								+ (+) + (+)

+ Single Pollutant Model + NO2 + PM2.5 + PM2.5 and NO2 + CO

+ significant positive; (+) positive not-significant

- negative significant; (-) negative not-significant

0 Null/Unclear

Summary

- Positive associations:
  - Cardiovascular outcomes (i.e. stroke, hypertension)
  - Metabolic outcomes (i.e. diabetes, diabetes biomarkers)
  - Inflammatory outcomes (i.e. CRP, cancers)
- Unclear associations:
  - Respiratory outcomes (i.e. asthma, lung cancer mortality)
  - Neurological outcomes (i.e. cognitive development)
  - Pregnancy outcomes (i.e. low birth weight)

Conclusions

- Substantial increase in the number of epi studies on long-term UFP and health
- Diverse outcomes, still sparse evidence for most of the specific diseases (exception diabetes, with 6 studies)
- Most studies use LUR models or combinations of various exposure assessment methods, few used time-activity data
- Half of the studies adjusted for co-pollutants (i.e. NO_2 and $PM_{2.5}$) with mostly robust results

- Recommendations for future research:
  - More studies with multi-pollutant analyses needed to draw definitive conclusions
  - Usefulness of "extended" models using personal time-activity data still unclear
  - Vast majority of studies were conducted in relatively clean environments. What about the rest?

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KoPilot

Design and piloting of UFP exposure assessment methods for health studies

Overarching aim

- Improving the investigation of health effects of long-term UFP exposure - accurate and valid assessment of UFP exposure in the general population including their temporal and spatial variability

Objectives

- Systematic literature review for UFP and health effects (update of Ohlwein et al. 2019)
- Conducting a measurement campaign to examine spatial and temporal distribution
- Piloting a combination of 3 UFP models with different spatial resolution (hybrid) on a sub-city level and validation with measurements
- Developing a study protocol for a cohort study on long-term health effects of UFP in an urban area

Qualitative Results on Neurological Outcomes

Study	Cognitive Development (Working Memory)	Cognitive decline	Functional connectivity	DSPN	Brain Volume	Cortical thickness	Cognitive Domains	Cognitive Function	Area-Specific Grey-Matter Thickness
Forns et al. 2017	-								
Gan et al. 2023		0							
Glaubitz et al. 2022			(+)						
Herder et al. 2020				(+)					
Lubczyńska et al. 2021					0 0 0				
Lucht et al. 2022						0			
Nußbaum et al. 2020	0						(-)	(-)	(-)(-)0
Sunyer et al. 2015	(-)						+		

+ Single Pollutant Model + NO2 + PM2.5

+ significant positive; (+) positive not-significant

- negative significant; (-) negative not-significant

0 Null/Unclear

Qualitative Results on Pregnancy Outcomes

Study	Preterm birth	Pre-eclampsia	Birthweight z-scores	Low birth weight
Fang et al. 2022	+ +0 0			
Goin et al. 2021		((+))		
Laine et al. 2020			0 00 0	
Laurent et al. 2014				++
Laurent et al. 2016a				00
Laurent et al. 2016b	00			
Li, R et al. 2019				00
Ridell et al. 2022	++00			

+ Single Pollutant Model + NO_2 + PM2.5 + CO

+ significant positive; (+) positive not-significant

- negative significant; (-) negative not-significant

0 Null/Unclear