

Ambient Ultrafine Particles and Health

Walker K. / Health Effects Institute, Boston, USA

Introduction: In the nearly two decades since toxicologists first posited that ultrafine particles, particles <100 nanometers in diameter, might play a central role in the adverse effects associated with ambient air pollution, a substantial body of work has been sponsored by HEI and other institutions around the world to explore that hypothesis. Where are we now? HEI will address this question in a forthcoming report in its "*Perspective*" series, whose role is to describe and interpret results bearing on important and timely issues for a broad audience interested in environmental health. Preliminary conclusions were presented at the ETH conference.

Investigation: HEI assembled a multidisciplinary, multi-national panel to review the scientific literature and to provide a broad perspective on what is known – and not known – about emissions and exposures to ambient ultrafine particles and associated health impacts drawing on evidence from experimental studies in animals and humans, and from epidemiologic studies. We structured our evaluation of the evidence as responses to three broad questions:

1. Sources, emissions and exposures. To what extent are mobile sources an important contributor to human exposure to ambient ultrafine particles?
2. Do ultrafine particles affect health? What is the evidence from experimental animal and clinical studies?
3. Do ultrafine particles affect human health at environmental concentrations? What is the evidence from epidemiologic studies?

In developing our responses to these questions, we have focused our attention on reviews and studies that offer insight to the specific role of ambient ultrafine particles and how they might differ from larger particles in their human exposures and toxicity when inhaled. We have therefore restricted our focus to combustion-related ultrafine particles and have specifically excluded the extensive literature on engineered nanoparticles. Among health related studies, we have examined primarily those in which inhalation is the primary route of exposure to ultrafine particles and those

where the exposure measurements, if not to ultrafine particles alone, provide an opportunity to evaluate the contribution of ultrafine particles distinct from co-pollutant exposures.

Results: A substantial body of literature has now been published on the sources and generation of ultrafine particles, their spatial and temporal distribution in ambient air, their inhalation and fate in the body, their mechanisms of toxicity and their adverse effects in animals and in humans. The purpose of this HEI *Perspective* on ultrafine particles has been to provide a broad assessment of what has been learned and what remains poorly understood. We asked:

What are the sources, emissions and exposures to ambient ultrafine particles? To what extent do motor vehicles contribute?

The research has clearly shown that while ultrafine particles have multiple sources, in urban areas, particularly in proximity to busy roads, motor vehicle exhaust can be identified as a major source of human exposure. Other sources can be as or more important in specific locations. The overall contributions of secondary organic aerosols to human exposure have

Do ultrafine particles affect health? What is the evidence from experimental studies in animals and humans?

Experimental studies have established the theoretical potential for UFP to accumulate in the body and to translocate beyond the lung. Both animal and human studies provide evidence for respiratory and cardiac effects, and animal exposure studies suggest the possibility of effects on the brain. However, the data do not provide strong evidence that UFP have short-term effects that are dramatically different from those of larger particles. Our ability to draw definitive conclusions – or to make predictions -- about the likelihood for long-term impacts of exposures to ultrafine particles on human health is limited by the near absence of long-term animal exposure studies, and by somewhat inconsistent findings in human chamber and “real world” studies.

Do ultrafine particles affect human health at environmental concentrations? What is the evidence from epidemiologic studies? Epidemiologic studies have provided suggestive, but often inconsistent evidence of adverse effects of short-term exposures to ambient ultrafine particles on acute mortality, acute morbidity, pulmonary and cardiovascular endpoints. The independent effects of ultrafine particles have not been assessed routinely in most studies and where they have, the effects have not been consistently discernible from those of other co-pollutants, including those that are also related to

traffic. No epidemiologic studies of long-term exposures to ambient ultrafine particles have been conducted.

What does this body of toxicologic and epidemiologic evidence collectively tell us about the particular role ultrafine particles may play in the adverse effects of ambient air pollution? Despite the ample reasons for concern about the potential hazards posed by ultrafine particles given their particular biophysical properties, the number of studies in animals or in humans for which adequate measurements of and control for the presence of other particle size fractions and other co-pollutants is quite limited. Consequently, we have incomplete evidence with which to determine whether exposures to ambient levels of ultrafine particles are associated either with unique toxic effects, are more likely to account for the adverse effects that have also been associated with other ambient pollutants, or are simply a marker for exposure to the more complex traffic-related air pollution mixture.

Conclusions: A large body of literature on emissions, exposures, and health effects of ultrafine particles has emerged in the years since investigators first became concerned about the potential adverse effects of exposure to the smallest of airborne particles. That the current database of experimental and epidemiologic studies, as extensive as it is in many ways, does not support strong and consistent conclusions about the independent effects of ultrafine particles on human health does not mean that such effects can be ruled out. The limitations in the evidence base are attributable both to the challenges to comparison and synthesis of existing studies discussed above and to the inherent complexity of the task. Similar kinds of issues have faced ongoing efforts to tease out the health significance of other components of the particulate matter mix (Bell, 2012; Brunekreef, 2010).

The high correlations of ultrafine particles levels with those of other traffic-related emissions in the near road environment, the rapid changes in their composition and size over space and time, and their high degree of spatial variability over even small geographic areas pose special challenges to investigators and policy makers. Future work will need to weigh carefully the value to scientific understanding and to regulatory decisions of continuing to treat ultrafine particles as an individual pollutant versus alternative approaches that focus on limiting exposures to traffic per se.

What is clear is that we have come a long way in the characterization of ultrafine particle emissions, particularly from motor vehicle exhaust. Ongoing changes in motor vehicle engine

technologies, in technology for exhaust aftertreatment, and in the use of new fuels provide some reasons for optimism that emissions of ultrafine particles from new vehicles will decline over time. The ultimate time course of resultant declines in ambient ultrafine particle concentrations will depend on a number of factors beyond the scope of this review, including changes in the size, age, and composition of the vehicle fleet in particular urban areas. All of these changes are still evolving and their implications for emissions of ultrafine particles or their precursors will need ongoing monitoring and evaluation in the years to come.

Ultrafine Particles and Health:

A Health Effects Institute Perspective

Panel:

Mark Frampton, Chair, *U of Rochester, US*

Mike Brauer, *U of British Columbia, Canada*

Mike Kleeman, *UC Davis, US*

Wolfgang Kreyling, *Helmholtz Institute, Germany*

Leon Ntziachristos, *Aristotle University, Greece*

Stefanie Sarnat, *Emory University, US*



Earlier HEI 'Perspectives'

HEI Perspectives

June 2001

Insights from HEI's research programs

AIRBORNE PARTICLES AND HEALTH: HEI EPIDEMIOLOGIC EVIDENCE

HEI Perspectives

April 2002

Insights from HEI's research programs

UNDERSTANDING THE HEALTH EFFECTS OF COMPONENTS OF THE PARTICULATE MATTER MIX: PROGRESS AND NEXT STEPS



Motivation.....

Lancet. 1995 Jan 21;345(8943):176-8.

Particulate air pollution and acute health effects.

Seaton A, MacNee W, Donaldson K, Godden D.

Department of Environmental and Occupational Medicine, University of Aberdeen, UK.

Abstract

Hypothesis: [t]hat ...**ultra-fine particles are** able to provoke alveolar inflammation, with release of mediators capable, in susceptible individuals of causing exacerbations of lung disease and of increasing blood coagulability, thus also **explaining the observed increases in cardiovascular deaths associated with urban pollution episodes.** This is testable both experimentally and epidemiologically.

IS PARTICLE NUMBER THE VILLAIN?

The number of particles is an important and usually unmeasured confounder in studies in which both particle mass and NO₂ are associated with health effects.





RESEARCH REPORT

HEALTH EFFECTS INSTITUTE

Number 96
August 2000

Final Version

Acute Pulmonary Effects of Ultrafine Particles in Rats and Mice

Günter Oberdörster, Jacob N Finkelstein, Carl Johnston, Robert Gelein, Christopher Cox, Raymond Baggs, and Alison C P Elder

...early study finds little evidence of induction of inflammatory responses in susceptible animal models with high exposures to model ultrafines ...

HEALTH EFFECTS INSTITUTE

Number 98
November 2000

Final Version

**Daily Mortality and Fine and Ultrafine Particles in Erfurt, Germany
Part I: Role of Particle Number and Particle Mass**

H-Erich Wichmann, Claudia Spix, Thomas Tuch, Gabriele Wölke, Annette Peters, Joachim Heinrich, Wolfgang G Kreyling, and Joachim Heyder

... first study to investigate associations with mortality of detailed size categories of ultrafine and fine particlessubstantial new evidence of relationship with ultrafines ... But also found similar associations with fine particulates.

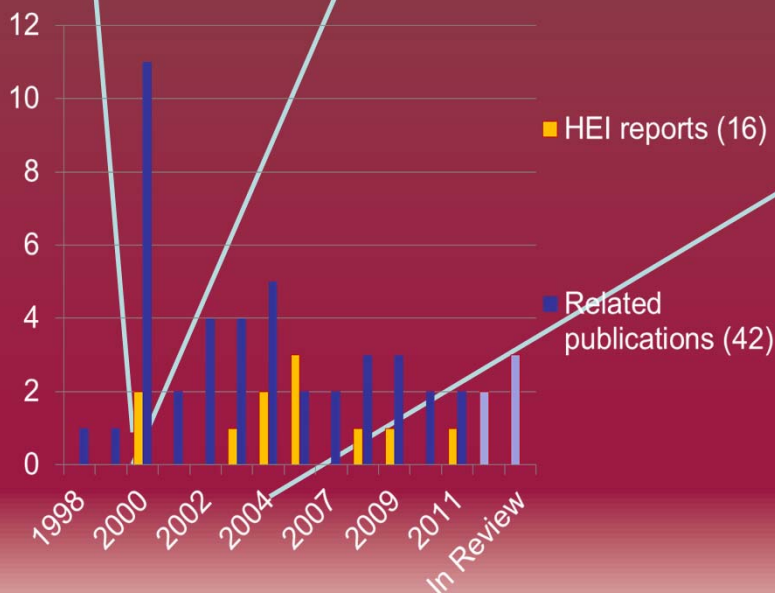
HEALTH EFFECTS INSTITUTE

Number 126
December 2004

Effects of Exposure to Ultrafine Carbon Particles in Healthy Subjects and Subjects with Asthma

Mark W Frampton, Mark J Utell, Wojciech Zareba, Günter Oberdörster, Christopher Cox, Li-Shan Huang, Paul E Morrow, F Eun-Hyung Lee, David Chalupa, Lauren M Frasier, Donna M Speers, and Judith Stewart

...small, but innovative study of controlled exposure to ultrafines and cardiovascular and respiratory responses. "Few conclusive findings, but informative for future designs"



Organization of the review

- ✓ Sources, Emissions and Exposures to UFP. To what extent do motor vehicles contribute?
- ✓ What do experimental studies in animals and humans tell us about UFP and health?
- ✓ What do observational epidemiologic studies tell us ?



Ultimate health question...

- What does the experimental and epidemiologic evidence collectively tell us about the independent health effects of UFP compared with other particle size fractions or with other components of the air pollution mixture?

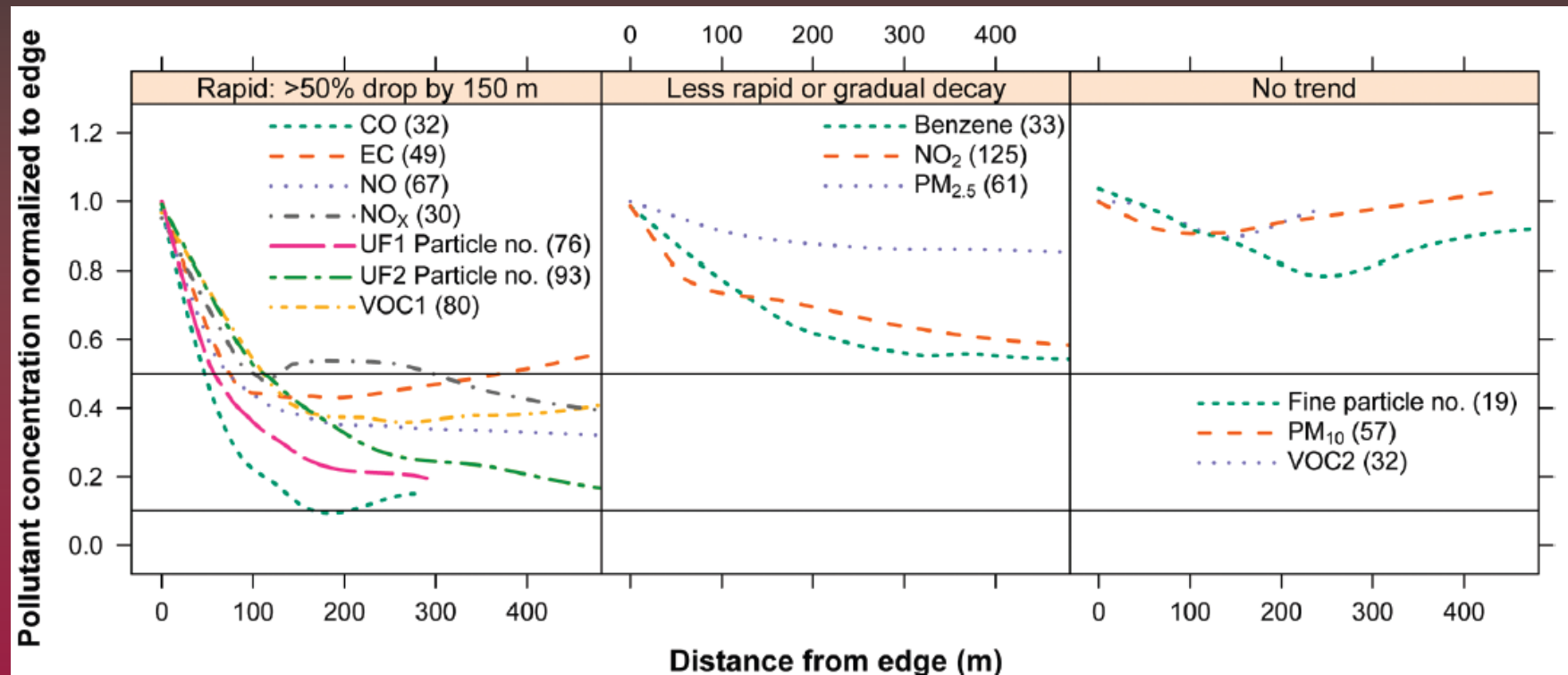


Summary: Sources, Emissions, and Exposures

- In urban areas, particularly near roads, motor vehicles are often the leading source ...
 - Other point sources can be locally important, vary with distance, season
 - Role of secondary processes poorly understood
- On a population basis, characterization of human exposure is limited
 - Few monitors, limited geographically and temporally
 - Multiple metrics across studies (dominated by particle number)
 - Role of indoor exposures, other microenvironments, not widely studied
- Changes in fuels and technology will lead to changes in the absolute and relative contributions from different sources



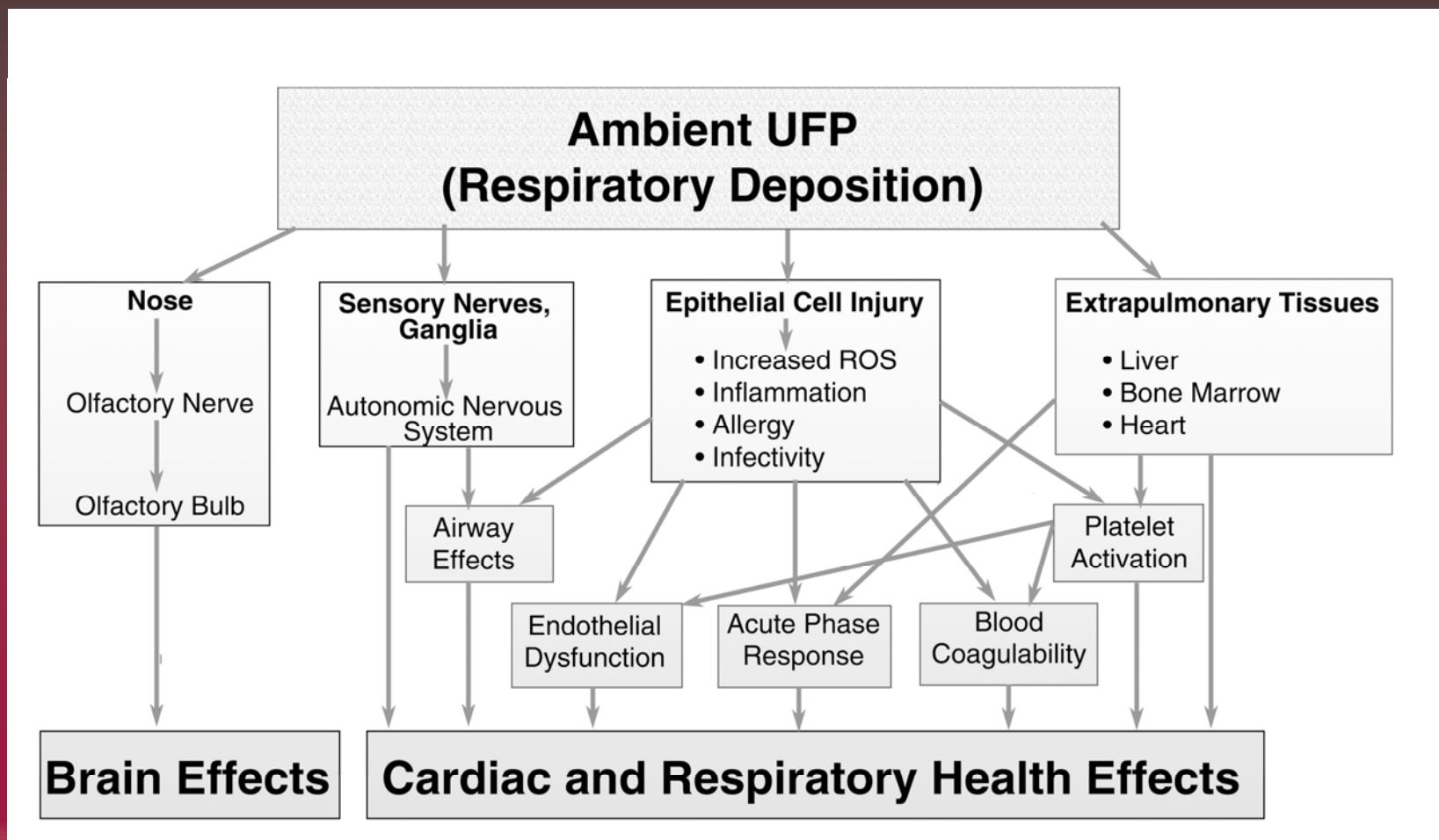
Challenges to studying UFP in the near road environment...



HEI Traffic Report (2010) concluded that no one constituent of the traffic air pollution mix can currently be used as a marker for traffic, including UFP



Not one, but many UFP hypotheses....and many challenges!



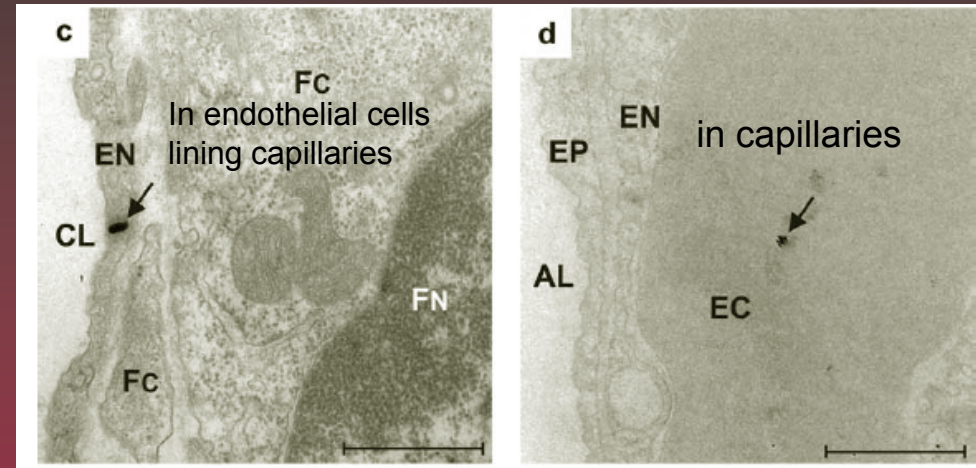
Focused on studies with...

- ✓ Inhalation route of exposure
- ✓ Explicit measure of ultrafine particles
- ✓ Ultrafine particle characteristics
 - particles < 100 nm in diameter
 - ambient origin (CAPs) or of related composition (lab-generated UFCPs)
 - concentrations relevant to ambient
- ✓ Accounting for potential confounding co-pollutants
 - other PM size fractions, gases, etc.



Summary: Experimental studies on UFP Deposition & Disposition

- Reasons for concern:
 - ✓ Increased alveolar deposition + slower clearance = increased accumulation of UFP
 - ✓ UFP enter blood and translocate systemically
 - ✓ UFP enter brain via olfactory nerve
- How much and how important for toxicity?



Geiser et al., EHP 2005



Summary: Experimental Animal Exposure Studies

- Little or no lung inflammation
- Effects more evident with on- and near-road exposures:
 - Allergen responses
 - Cardiovascular responses
 - Heart rate/HRV
 - Progression of atherosclerosis
 - Brain inflammation
- **Caveat:** Mixtures, not just UFP



Summary: Experimental Human Exposure Studies

Health endpoints	Particle types	Impacts?
Airway inflammation	<ul style="list-style-type: none"> • Lab-generated ultrafine carbon particles (UFCP) • Concentrated ambient particles (CAPs) • Controlled ambient air 	<ul style="list-style-type: none"> • Little or none • Little or none • Variable
Lung function (e.g. FEV)	<ul style="list-style-type: none"> • UFCP • CAPs • Controlled ambient air 	<ul style="list-style-type: none"> • None • Variable • Variable
Cardiovascular effects (HRV, cardiac repolarization, coagulation, blood flow)	<ul style="list-style-type: none"> • UFCP • CAPs • Controlled ambient air 	<ul style="list-style-type: none"> • Variable • Variable • Variable



Summary: Observational Epidemiologic Studies

- Reliance on short-term studies
 - Time-series, panel studies
- Single studies, no meta-analyses
- Variable study designs, statistical modeling, UFP metrics, and outcomes
- Suggestive, but inconsistent evidence of adverse effects of short-term exposures to ambient UFP
 - acute morbidity/mortality, pulmonary and cardiovascular endpoints.
- Few studies have shown UFP effects independent of co-pollutants



Overall Conclusions

- Reasons for concern, but 'UFP hypothesis' needs further testing
- Experimental and epidemiologic studies provide suggestive, but not consistent evidence of adverse effects of short-term exposures to ambient UFP
- Currently not strong evidence that effects of short-term exposures to UFP are dramatically different from those of PM_{2.5}



Ongoing Challenges and Opportunities

- Absence of evidence \neq evidence of absence!
- Lack of coordinated studies, consistent or comparable designs, endpoints linked to common pathways
 - Experimental, epidemiology, etc.
 - e.g., UFIREG project (poster)
- Incomplete reporting on all endpoints measured
 - Challenge to comparison and interpretation



Ongoing Challenges and Opportunities

- Many exposure challenges in experimental and epidemiologic studies
 - Uncertainty about the right metric, measurement devices (#, size, surface area, composition, $PM_{0.1}$ mass)
 - Representativeness of lab-generated atmospheres
 - Limited ambient monitoring of UFP
- Changing emissions profiles and implications for exposure



Acknowledgements

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- www.healtheffects.org

THANK YOU!



Extra slides

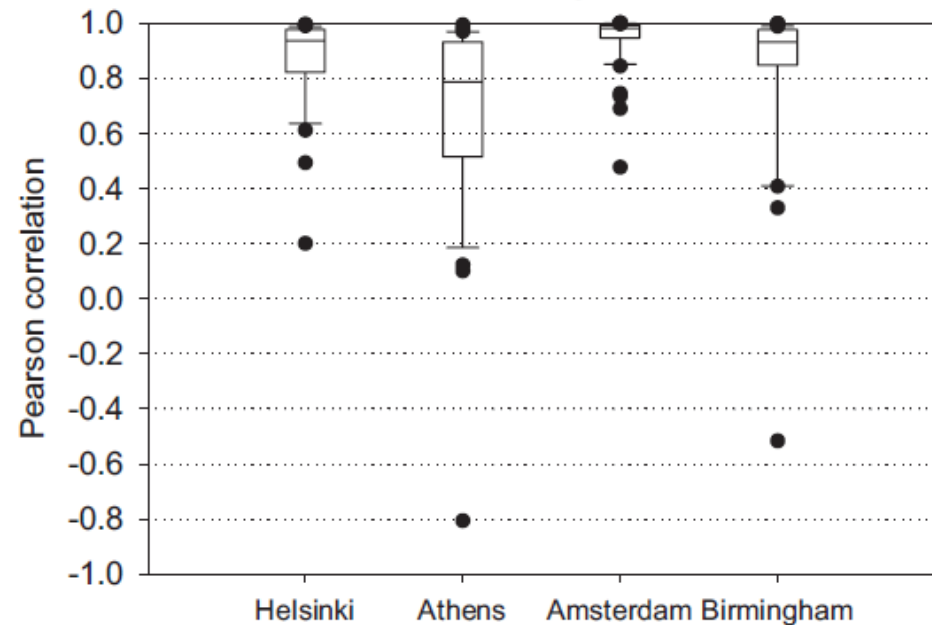
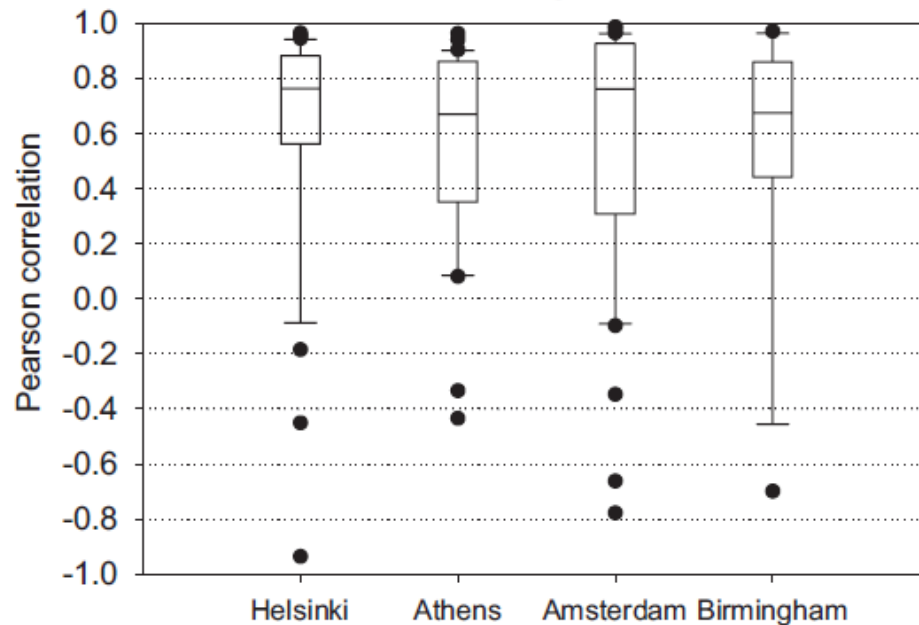


Temporal correlations are better ...

Can rely on central monitors

PNC

PM_{2.5}



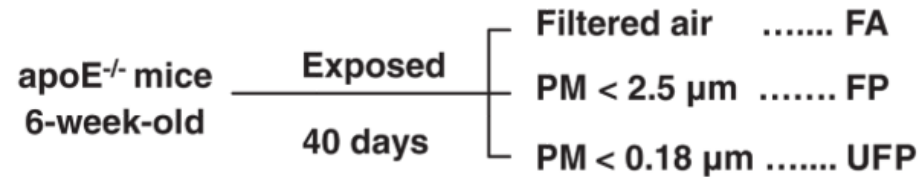
- Median, 75th-25th, 90th-10th percentile ranges of 24-h average concentrations between a central and residential sites



Mouse model of atherosclerosis: Near-Roadway Concentrated Fine & UF Particles

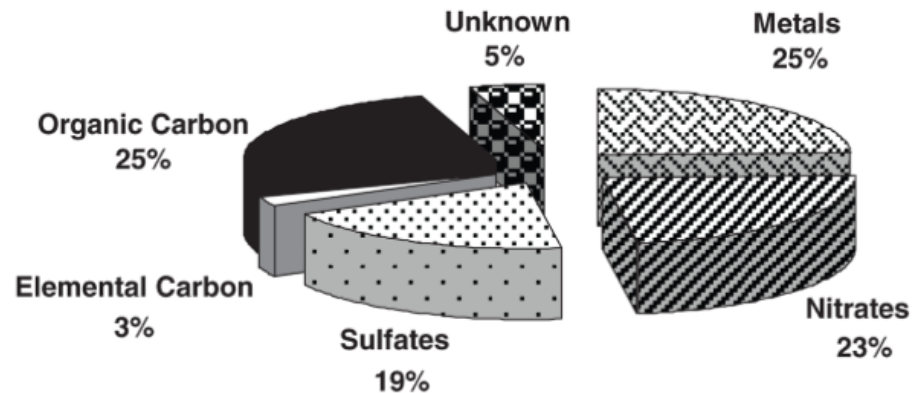
Araujo et al, Circ Res 2008

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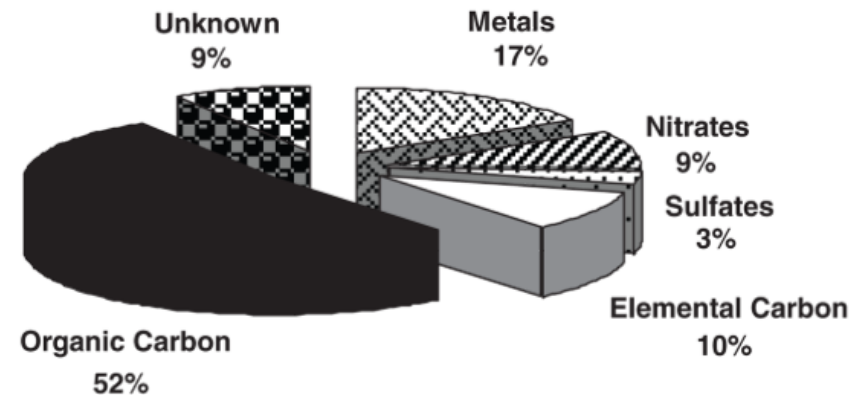
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FP Composition



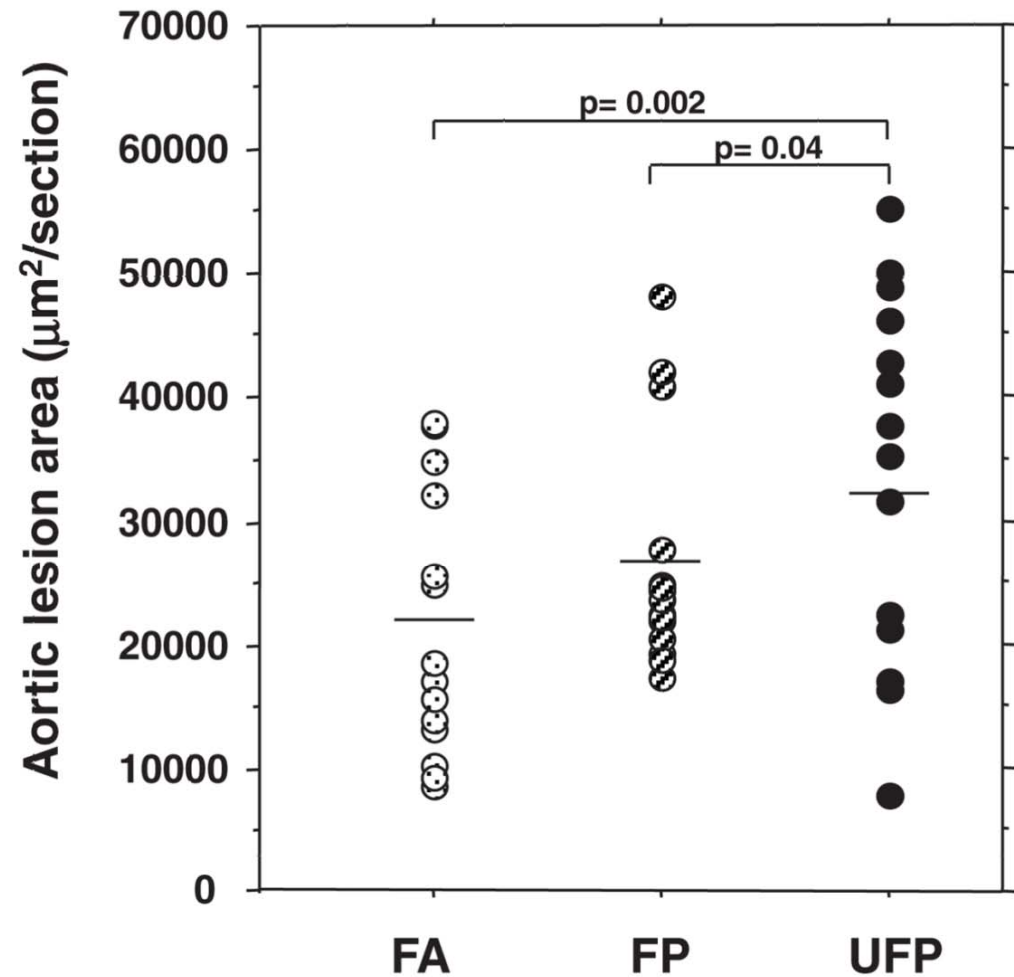
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UFP Composition



Mouse model of Atherosclerosis: Near-Roadway Concentrated Fine & UF Particles

Araujo et al, Circ Res 2008



sub- $0.18 \mu\text{m}$
(particles/ cm^3)

~ 5,000

3.88×10^5

5.59×10^5

HEI

Clear UFP Effect in Some Studies, e.g., on mortality in Erfurt, Germany

(a) Number concentrations of ultrafine particles and total mortality

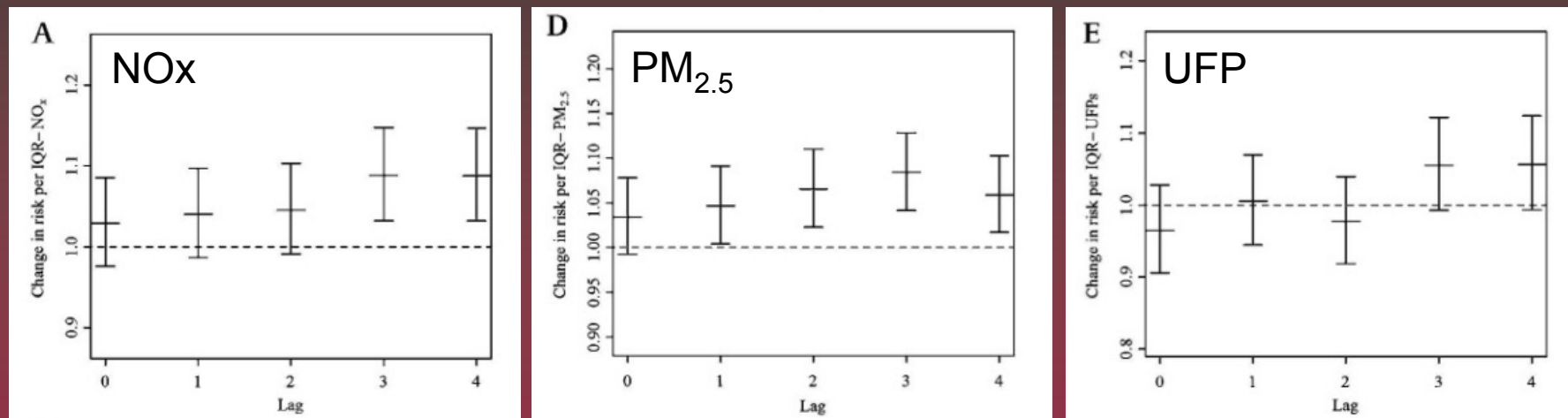
Lag	NC _{0.01-0.1} ^a	NC _{0.01-0.03}	NC _{0.03-0.05}	NC _{0.05-0.1}
0	1.020 (0.993; 1.049)	1.023 (0.995; 1.053)	1.015 (0.990; 1.040)	1.014 (0.990; 1.038)
1	1.001 (0.975; 1.029)	0.999 (0.972; 1.027)	1.008 (0.984; 1.032)	1.009 (0.987; 1.032)
2	0.997 (0.972; 1.023)	0.989 (0.962; 1.016)	1.005 (0.982; 1.029)	1.011 (0.989; 1.033)
3	1.012 (0.986; 1.038)	1.012 (0.985; 1.039)	1.012 (0.990; 1.035)	1.008 (0.986; 1.029)
4	1.029 (1.003; 1.055)*	1.028 (1.002; 1.056)*	1.026 (1.004; 1.049)*	1.019 (0.998; 1.041)
5	1.006 (0.981; 1.032)	1.005 (0.979; 1.032)	1.006 (0.983; 1.028)	1.002 (0.981; 1.023)
pdl ^b	1.042 (1.014; 1.070)*	1.046 (1.017; 1.075)*	1.034 (1.005; 1.064)*	1.026 (0.999; 1.055)*

(c) Mass concentration of particles and total mortality

(e) Gaseous pollutants and total mortality

Lag	NO	NO ₂	CO
0	1.000 (0.988; 1.012)	0.992 (0.962; 1.024)	1.000 (0.977; 1.023)
1	0.996 (0.985; 1.008)	1.007 (0.979; 1.035)	1.002 (0.980; 1.024)
2	1.002 (0.991; 1.014)	1.002 (0.975; 1.030)	1.013 (0.991; 1.035)
3	1.006 (0.994; 1.017)	1.012 (0.985; 1.040)	1.007 (0.986; 1.029)
4	1.004 (0.992; 1.015)	1.007 (0.980; 1.035)	1.012 (0.990; 1.034)
5	0.996 (0.984; 1.008)	0.994 (0.967; 1.021)	0.995 (0.974; 1.017)

UFP Effects Not Distinguishable in other Studies



- e.g., Iskandar et al. (2011) – associations with pediatric asthma hospitalizations in Copenhagen
- Associations observed with NO_x, NO₂, PM₁₀, PM_{2.5}, but not UFP
- Associations with UFP weaker in two-pollutant models

