Known and unknown associations and needs for health relevant new metrics

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Structure of the presentation

- Epidemiological methodology for studying air pollutants health effects
- Known associations of various health outcomes and
  - ⇨PM mass measurements by particle size
  - ⇨Traffic and other sources
  - ⇨ Chemical characteristics
- What we would like to know but measurements are inadequate
- Needs and future pathways

Why Epidemiology? Why toxicology?

- Epidemiological studies were the first to provide evidence of health effects of current concentrations of pollutants (start in mid-80s; more in the 90s)
- Evidence was widely doubted; now is widely accepted
- Arguments for doubting – among others- the lack of toxicological evidence/ ignorance about mechanisms
- Since then, toxicological studies have confirmed the effects and have opened new ways for understanding the mechanisms and testing new hypotheses in human population studies
- Still, epidemiology is needed to extend the results to humans under real conditions of exposure and real composition of the population

Time-scale of effects and study design
Short-term effects (same day to, roughly, 2 months)

- Time –series studies with typical time series models or case-crossover analysis
- Panel studies with random effects/mixed models
- Data are daily time series of the exposure metric and daily events/counts of the health outcome
- The data source may be from individual records or aggregated
- Needed: Fine TIME SCALE
- Question: to what extent do we need personal/individualized exposure assessment?

Time-scale of effects and study design

Long-term effects (life-long, or as many years as possible for estimating retrospective exposure)

- Cohort studies (or cross-sectional studies)
- Data for exposure may be individual or ecological; data for health outcome typically individual
- The exposure data must represent LONG-TERM exposure of an individual; this means either that exposure is measured from the beginning and throughout follow-up or there is a valid method to estimate retrospectively.
- Needed: Fine GEOGRAPHICAL SCALE and best to have time-activity patterns for individuals
- Question: to what extent do we need personal/individualized exposure assessment?

Mechanisms through which PM probably cause health effects

- Oxidative stress
- Local inflammatory response
- Systemic inflammatory response
- Changes in the autonomic function
- Coagulation
- Interference with ciliary clearance (results in increased bacterial or viral loads)

- There is evidence that the activation of these mechanisms depends on the physico-chemical characteristics of particles

Sensitive subgroups

- Several groups have been identified in various studies
  - Elderly
  - Children for some outcomes
  - Persons with underlying respiratory or cardiac disease or other chronic conditions (such as diabetes)
  - Persons with specific genetic characteristics (gene-environment interactions)

Is air pollution exposure an important problem for public health?

According to projections from UN, 60% of world's population will reside in urban areas by 2030.

Air pollution is associated with large expenses in medical services, morbidity and is estimated to cause about 800,000 annual premature deaths worldwide (Cohen et al. J Toxicol Environ Health 2005)

WHO (2002) has identified ambient air pollution as high priority in Global Burden of Disease initiative and estimated that air pollution is responsible for 1.4% of all deaths and 0.8% of disability adjusted life years globally.

Health Impact Assessment Within the Clean Air For Europe (CAFÉ) Programme

http://cafe-cba.aeat.com

- For PM exposure, the average loss in life expectancy in 2020 in the EU-25 will be 5.5 months
- About 2.5 million life years will be lost in 2020
- This is equivalent to 271,000 premature deaths
- The morbidity effects include 66,000 serious/cardiac hospital admissions; about 23 million respiratory medication-use days and 200 million restricted activity days

What do we know on effects from studies using PM_{10} or $PM_{2.5}$
(in Europe, we also have similar evidence using the older black smoke measurements)

Percent increase in mortality risk associated with particulate matter (Pope *Inhalation Toxicology* 2007)

Short-term Effects

			Percent Increase in mortality risk (95% CI)	
Study area and types	**Primary sources**	**Exposure increment**	**All cause**	**Cardiovascular/ Cardiopulmonary**
Meta-estimate from single-city studies, Adjusted for publication bias	Anderson et al. (2005)	20 μg/m^3 PM_{10}	1.2 (1.0, 1.4) 1.0 (0.8, 1.2)	
Meta-estimates from COMEAP	COMEAP (2006)	20 μg/m^3 PM_{10} 10 μg/m^3 $PM_{2.5}$		1.8 (1.4, 2.4)[a] 1.4 (0.7,2.2) [a]
U.S. 6 cities	Klemm and Mason (2003)	10 μg/m^3 $PM_{2.5}$	1.2 (0.8, 1.6)	1.3 (0.3,2.4) [c]
California 9 cities	Ostro et al. (2006)	10 μg/m^3 $PM_{2.5}$	0.6 (0.2, 1.0)	0.6 (0.0, 1.1)[a]
U.S. 10 cities	Schwartz (2000, 2003)	20 μg/m^3 PM_{10}	1.3 (1.0, 1.6)	
U.S. 14-city case-crossover	Schwartz (2004)	20 μg/m^3 PM_{10}	0.7 (0.4, 1.0)	
NMMAPS 20-100 U.S. cities	Dominici et al. (2003)	20 μg/m^3 PM_{10}	0.4 (0.2, 0.8)	0.6 (0.3,1.0)[b]
APHEA-2 15-29 European cities	Katsouyanni et al. (2001) Analitis et al. (2006)	20 μg/m^3 PM_{10}	1.2 (0.8, 1.4)	1.5 (0.9,2.1)[a]

[a]Cardiovascular only [b]Cardiovascular and respiratory deaths combined [c]Ischemic heart disease deaths

Short-term effects of black smoke (BS). Results from the EU APHEA project (data from the 90s)

	Percent increase in mortality risk associated with 10μg/m^3 increase in BS
Mortality	
Total non-accidental (APHEA2, Epidemiology 2001; 12: 521-31)	0.6 (0.3-0.8)
Cardiovascular causes (APHEA2 , Epidemiology 2006;17:230-3)	0.6 (0.4, 0.9)
Respiratory causes (APHEA2 , Epidemiology 2006;17:230-3)	0.8 (0.1, 1.6)

Percent Increase in mortality risk associated with $PM_{2.5}$ (Pope *Inhalation Toxicology* 2007)

Long-term Effects

			Percent Increase in mortality risk (95% CI)	
Study area and types	**Primary sources**	**Exposure increment**	**All cause**	**Cardiovascular/ Cardiopulmonary**
Harvard Six Cities cohort study	Laden et al. (2006)	10 µg/m^3 $PM_{2.5}$	16 (7,26)	28 (13, 44) [a]
ACS, U.S. cohort	Pope et al. (2002)	10 µg/m^3 $PM_{2.5}$	6.2 (1.6, 11)	9.3 (3.3, 16)[b]
ACS, intra-metro Los Angeles cohort	Jerrett et al. (2005)	10 µg/m^3 $PM_{2.5}$	17 (5, 30)	12 (-3,30)[b]

[a]Cardiovascular only [b]Cardiovascular and respiratory deaths combined [c]Ischemic heart disease deaths

Comparison of results from 3 European cohorts on exposure to NO_2 or NO_x for 10 $\mu g/m^3$

	Percent increase in mortality	
	All cause	Cardio-pulmonary
Nafstad (NO_x) 2004	8 (6, 10)	23 (pulm) (13, 35)
Hoek (NO_2) 2002	12 (-2, 33)	27 (0, 78)
Filleul (NO_2) 2005	14 (5, 17)	27 (4, 56)

Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women
(Miller et al. *NEJM* 2008)

Description of the study	
No of subjects	65,893 women
Age	50-79 years
Years of enrollment	1994-98
Follow up	6 years (median)
No of women with CV events	1816
Current smokers	6.1%
$PM_{2.5}$ Individual Exposure (mean $\pm$ SD, range)	13.5$\pm$ 3.7(3.4,8.3)
Citywide $PM_{2.5}$ average exposure	13.5$\pm$ 3.3(4.0,19.3)
Difference between Individual and Citywide average exposure	0$\pm$ 1.6 (-11.5,11.7)

Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women
(Miller et al. *NEJM* 2008)

Estimated Hazard ratios for the Time to the first Cardiovascular Event or Death associated with an Exposure increase of 10 μg/m^3 in the level of $PM_{2.5}$

Outcome	No. of events	Hazard Ratio (95% CI)	
		Between Cities	Within Cities
First Cardiovascular Event			
Any event	1816	1.15 (0.99, 1.32)	1.64 (1.24, 2.18)
Coronary heart disease	1268	1.13 (0.95, 1.35)	1.56 (1.11, 2.19)
Cerebrovascular disease	600	1.20 (0.94, 1.54)	2.08 (1.28, 3.40)
Death from cardiovascular cause			
Any death	261	1.63 (1.10, 2.40)	2.28 (1.10, 4.75)
Coronary heart disease			
Definite diagnosis	80	2.22 (1.06, 4.62)	2.17 (0.60, 7.89)
Possible diagnosis	59	1.20 (0.54, 2.63)	1.57 (0.29, 8.51)
Cerebrovascular disease	122	1.58 (0.90, 2.78)	2.93 (1.03, 8.38)

Results for the effects of gaseous pollutants

- Ozone (especially short-term effects; also recent publications for long-term; important oxidant; important for respiratory effects)
- NO_2 (some evidence that effects may be attributed to NO_2 per se; long discussion of whether it is a proxy of Ultrafines)
- CO (mainly implicated in cardiac effects)
- SO_2 (neglected; last WHO guidelines revised the limit downward; maybe associated with PM chemical aspects)

Heterogeneity of effects provides indirect evidence that some mixtures of PM are more toxic than others

Percent increase in the daily number of deaths associated with an increase of 10μg/m^3 in PM_{10}, by levels of important effect modifiers

(APHEA2, Epidemiology, 2001; 12: 521-31)

Effect modifier	Low*	High*
Average long-term NO_2	0.19	0.80
Average annual temperature	0.29	0.82
Proportion of population >65 years	0.54	0.76

* "Low" effect modifier level is defined as the 25th percentile and "high" as the 75th percentile of the corresponding effect modifier distribution across cities. The actual levels are for NO_2 40 and 70μg/m^3, for temperature 9 and 14^{0}C, for the proportion of persons >65 years 13% and 16% respectively.

Percent increase in the daily number of deaths associated with an increase of 10μg/m^3 in PM_{10} concentrations by region in Europe

(APHEA2, Epidemiology, 2001- data from the 90s)

	Southern European cities	North-western European cities	Central-eastern European cities
Percent increase in number of deaths	0.87	0.73	0.22

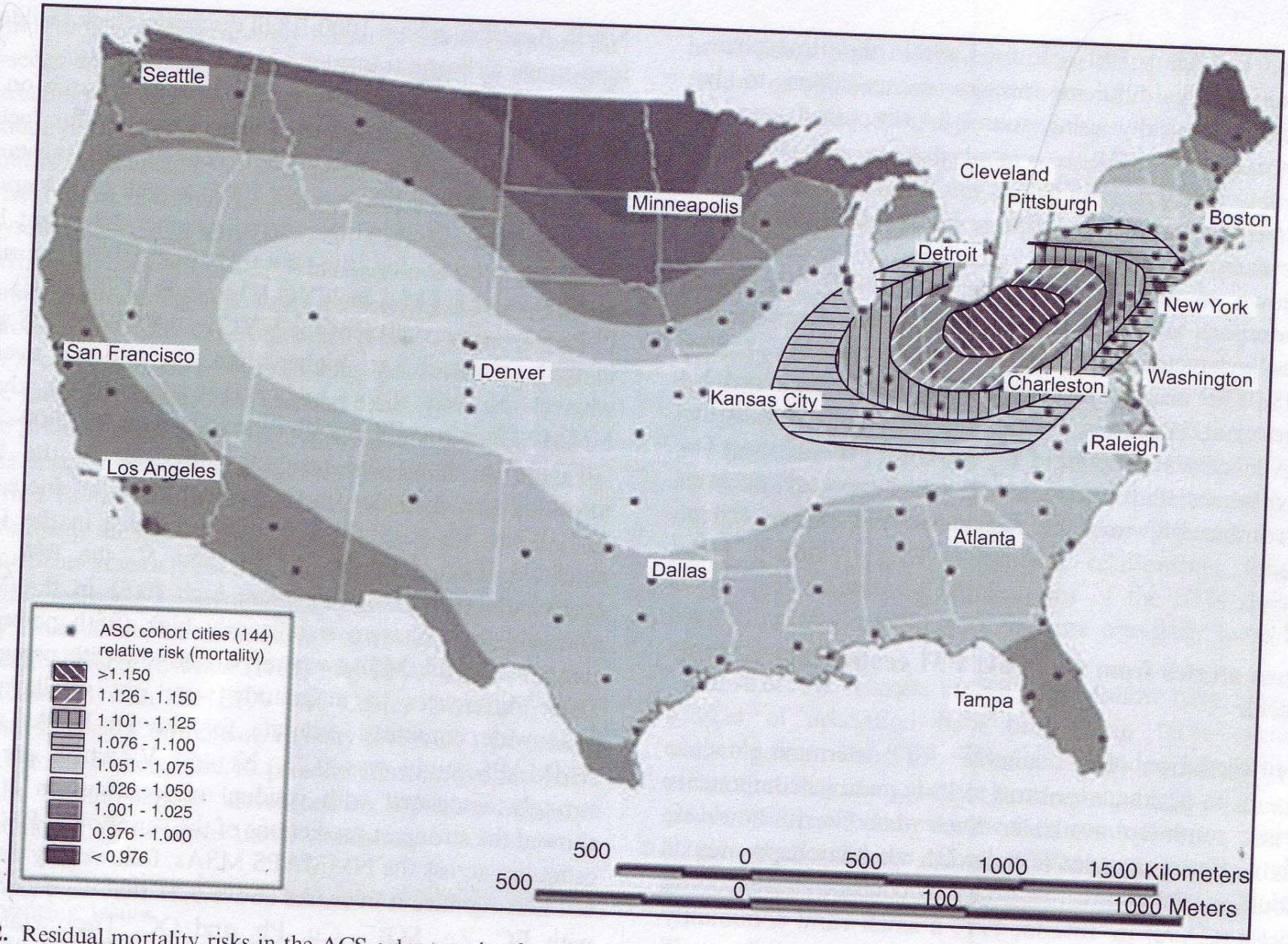


Figure 2. Residual mortality risks in the ACS cohort study after controlling for individual risk factors (adapted from Burnett et al., 2001).

From Lippman 2009; J Exp Sc Environ Epidemiol 19:235

Which size fraction?

- More evidence on what was or is routinely measured, ie . PM_{10}, (BS) and $PM_{2.5}$
- Questions about the specific effects of the coarse fraction and ultrafines (UFP).

Exposure to Ultrafine Particles and health

- There is evidence from epi studies that UFP are associated with health endpoints (e.g. Wichmann 2000- mortality; Penttinen 2001 – lung function; Peng 2008- admissions; Leitte 2010- emergency visits in China)
- The evidence is mainly for short-term health effects.
- UFP are expected to play a role in the observed PM effects as they dominate particle number and surface area concentrations and have a high deposition efficiency in the lung.
- Particle numbers and surface area concentrations are not routinely measured and thus the results available so far are sparse.

- Surface area may play an important role in determining the biological activity of UFP as they have an increased potential for biological interaction and absorption of chemical compounds (Oberdoster et al 2005)

- UFP are a better indicator of traffic pollution

Epidemiological Evidence of Effects of Coarse Airborne Particles on Health (Brunekreef & Forsberg ERJ 2005)

- Short-term effects on mortality more associated with $PM_{2.5}$
- For long-term mortality effects no association observed in U.S. cohorts for coarse particles.
- Short-term effects on hospital visits and admissions indicate that the coarse fraction is more important for respiratory endpoints.
- Long-term effects on respiratory endpoints found in one study in China but not in the Children's Health Survey in California.
- The review reflects the problem that most studies use the regulated index, PM_{10}, and not the coarse fraction

Indirect evidence that some mixtures of PM are more toxic than others: proximity to sources; evidence mainly from traffic sources

Exposure to traffic and the onset of Myocardial Infraction

(Peters et al. *NEJM* 2004)

Case crossover in 691 cases with MI and diaries about activities 4 days before

ORs for the onset of Myocardial Infraction (MI) after Time Spent in traffic.

	No. of subjects	Frequency of exposure in case period on day of MI (%)	Odds Ratio (95%CI)	p-Value
Concurrent	585	8.0	1.50 (1.07,2.09)	0.02
1 hr	625	12.1	2.92 (2.22, 3.83)	<0.001
2 hr	634	8.9	2.01 (1.49, 2.72)	<0.001
3 hr	635	5.5	1.15 (0.79, 1.66)	0.47
4 hr	638	5.6	1.27 (0.89, 1.83)	0.19
5 hr	639	6.8	1.64 (1.17, 2.30)	0.004
6hr	640	6.1	1.34 (0.93, 1.92)	0.11

Can we identify Sources of Fine Particles Responsible for Exercise-Induced Ischemia on Days with Elevated Air Pollution? The ULTRA Study

(Lanki et al. EHP 2006)

- Evaluated effects of $PM_{2.5}$ from different sources on exercise-induced ischemia.
- 45 non-smoking subjects with coronary heart disease
- Recorded occurrence of ST segment depressions.

Adjusted ORs between daily source-specific PM2.5 concentrations and occurrence of ST-segment depression (ULTRA study, Lanki et al 2006;EHP 114:655-60)

Source (ave mass g/m^3)	Lag*	OR (95% CI)
Crustal (0.6)	3	1.87 (0.85, 4.09)
Long range transport (6.4)	3	1.06 (0.95, 1.18)
Oil combustion (1.6)	3	1.12 (0.79, 1.58)
Salt (0.9)	3	1.55 (0.83, 2.89)
Local traffic (2.9)	2	1.53 (1.19, 1.97)

* The lag with highest effect estimate is presented

Adjusted (also mutually) ORs between indicator elements of PM2.5 sources and occurrence of ST-segment depression

(ULTRA study, Lanki et al 2006; EHP 114:655-60)

Source indicator	Lag*	OR (95% CI)
Si (crustal)	3	1.95 (0.69, 5.48)
S (long range transport)	3	1.60 (0.73, 3.48)
Ni (Oil combustion)	2	1.15 (0.61, 2.18)
Cl (Salt)	3	1.27 (0.85, 1.91)
ABS (Local traffic)	2	4.46 (1.69, 11.79)

* The lag with highest effect estimate is presented

Mortality Risk Associated with Short-Term Exposure to Traffic Particles and Sulfates.

Maynard et al. (EHP 2007)

Data: 100,000 deaths from all, cardiovascular and respiratory causes for the years 1995-2002 in the Boston area.

Methods: Estimates of exposure to traffic particles were geocoded to the address of the decedent on the day before death and control days, with these estimates derived from a GIS-based exposure model incorporating deterministic covariates, such as traffic density and meteorologic factors, and a smooth function of latitude and longitude.

The associations between daily concentration of black carbon (BC) and sulfates and mortality risk were analyzed using a bidirectional case-crossover design.

Mortality Risk Associated with Short-Term Exposure to Traffic Particles and Sulfates.

Maynard et al (EHP 2007)

Exposure Measure	No. of cases	Percent Increase for IQR increase (95%CI)	P-value
		Univariate models	
GIS-based BC	107,925	2.3 (1.2,3.4)	<0.0001
HSPH sulfate	64,080	1.1 (0.01, 2.0)	0.0169
		Bivariate models	
GIS-based BC	57,029	2.2 (0.16,4.2)	0.0339
HSPH sulfate		0.45 (-0.45, 1.6)	0.2991

Cause specific mortality Risk Associated with Short-Term Exposure to Traffic Particles and Sulfates.

Maynard et al (EHP 2007)

Cause of death	Particle Type	Percent Increase for IQR increase (95%CI)	P-Value
CVD	BC Sulfate	1.5 (-0.4, 3.4) -0.2 (-1.5, 1.0)	0.13 0.72
Stroke	BC Sulfate	4.4 (-0.2, 9.3) 2.0 (-2.4, 6.1)	0.06 0.39
Respiratory	BC Sulfate	3.7 (0.1, 7.4) 2.1 (-1.1, 5.3)	0.04 0.20
Diabetes	BC Sulfate	5.7 (-.17, 13.7) 2.9 (-3.1, 9.5)	0.13 0.36

Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study.

(Gauderman et al. *Lancet* 2007)

- Results from 3,677 children after 8 years follow up.
- Children living <500m from a freeway had deficits of forced expiratory flow and maximum mid-expiratory flow rate compared with those living >1500m.
- Joint models showed both local exposures to freeways and regional air pollution had detrimental, independent effects on lung function growth.

Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. (Gauderman et al. *Lancet* 2007)

Percent predicted lung function at age 18 years versus residential distance from a freeway.

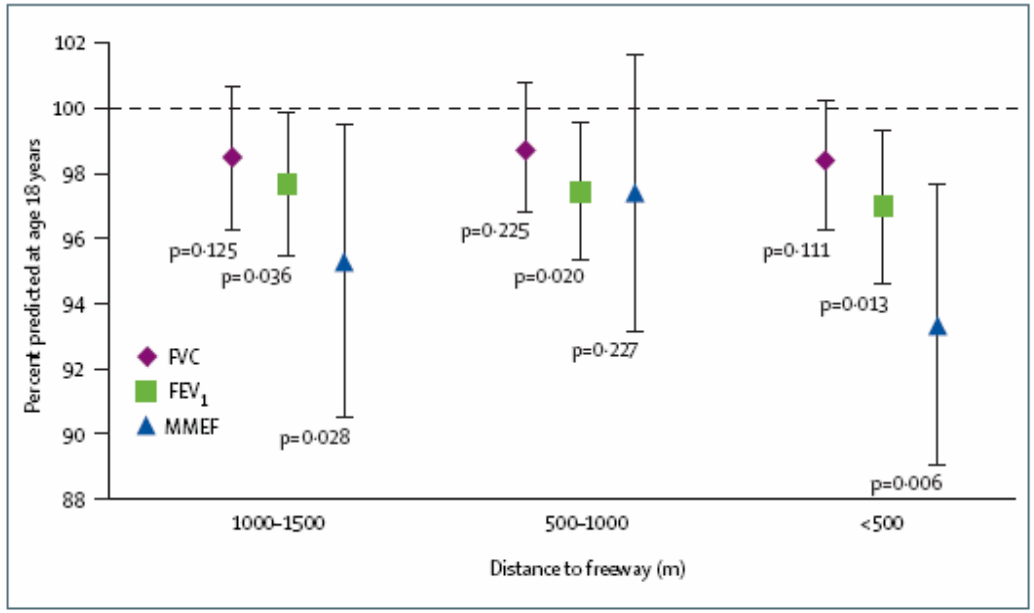


Figure: Percent-predicted lung function at age 18 years versus residential distance from a freeway
The horizontal line at 100% corresponds to the referent group, children living >1500 m from a freeway.

Horizontal line at 100% correspond to referent group, children living >1500m from a freeway.

TRAFFIC RELATED AIR POLLUTION AND INCIDENCE OF CHILDHOOD ASTHMA

The Vesta case-control study (Zmirou et al. JECH 2004)

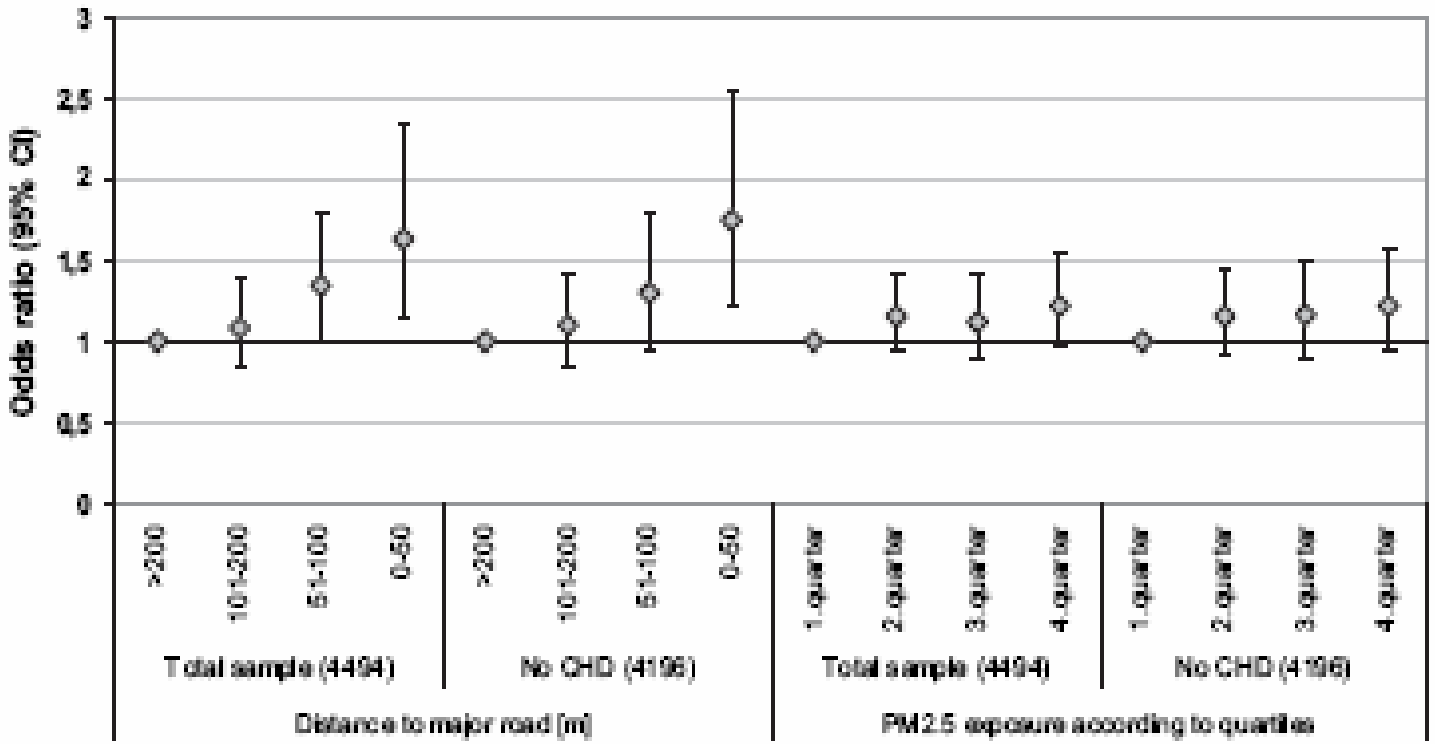
- In five French metropolitan areas 1998-2000. Index of lifelong exposure to traffic exhausts (from info on traffic density close to home and school address since birth)
- Lifelong exposure was not associated with asthma (adjusted for ETS, allergy, other confounders). Associations before the age of 3 were significant OR for tertiles 2 & 3 of exposure index 1.48 (0.7-3.0) and 2.28 (1.1-4.6). Greater for subjects with positive skin prick tests.
- Traffic related pollutants might have contributed to asthma epidemic among children in past decades.

Residential exposure to traffic is associated with coronary atherosclerosis (Hoffmann et al. *Circulation* 2007)

- Associations of long-term residential exposure to traffic and fine particulate matter with the degree of coronary atherosclerosis.
- 4494 participants (age 45 to 74 years) from the German Heinz Nixdorf Recall Study, a population-based, prospective cohort study that started in 2000.
- *Exposure*: distance from residence to major roads and annual $PM_{2.5}$ (GIS assigned)
- *Outcome*: coronary artery calcification (CAC) assessed by electron-beam computed tomography.

Residential Exposure to traffic is associated with coronary atherosclerosis (Hoffmann et al. *Circulation* 2007)

ORs (95%CI) for a CAC score above the age and gender specific 75th centile for the total sample (n=4,494) and for the participants with prior diagnosis of CHD. Adjusted for city, area of residence, age, sex, education, smoking, ETS, physical inactivity, waist to hip ratio, diabetes, blood pressure, lipids.



Residential Exposure to traffic is associated with coronary atherosclerosis

(Hoffmann et al. *Circulation* 2007)

- Participants living within 50, 51-100, and 101- 200 m away from a major road, had ORs of 1.63 (95% CI, 1.14- 2.33), 1.34 (1.00-1.79), 1.08 (0.85-1.39), respectively, for a high CAC (CAC above the age- and gender-specific 75th percentile) compared to participants living >200m away, controlling for individual level risk factors of coronary atherosclerosis

- Reduction in the distance between residence and major road by half was associated with a 7.0% (0.1-14.4) higher CAC.

Other sources which are important for our understanding

- Emissions from diesel cars by type (especially important for Europe)
- Emissions from shipping
- Emissions from air traffic
- Transported particles from Sahara dust (mainly affecting mediterranean countries); Sea salt
- Biological particles (bioallergens)
- Particles from forest fires

- Which chemical characteristics of particles make them more toxic?

Effect modification (e.m.) of the composition of PM2.5 on the % increase in non-accidental mortality (from Franklin et al 2008; Epidemiology 19: 680)

Component	P-value for e.m.	Increase in mortality per 10μg/m3 PM2.5 for an IQ increase in component/PM2.5 mass proportion	Heterog eneity explained (%)
Al	<0.001	0.58	45
As	0.02	0.55	35
Ni	0.01	0.37	41
Si	0.03	0.41	25
NO_3^-	0.07	-0.49	28
SO_4^{2-}	0.01	0.51	33
EC	0.79	0.06	0
OC	0.59	-0.02	4

From Lippman 2009; J Exp Sc Environ Epidemiol 19:235

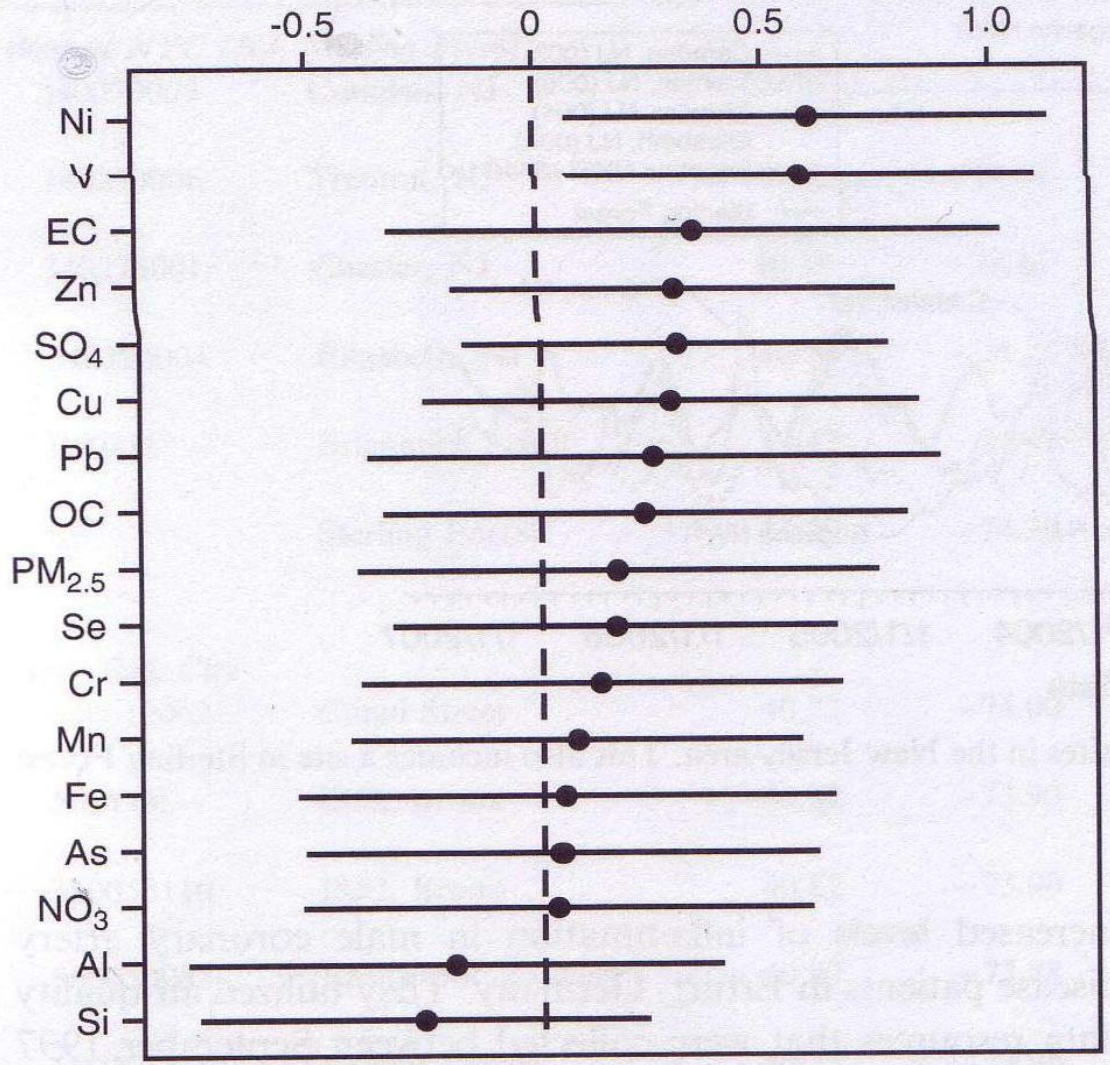


Figure 4. Differences in daily mortality risk coefficients per the 5th to 95th percentile difference in FPM component concentrations across NMMAP MSAs (for the 60 MSAs for which FPM speciation data were available—courtesy *Environ Health Perspect*).

From Lippman 2009; J Exp Sc Environ Epidemiol 19:235

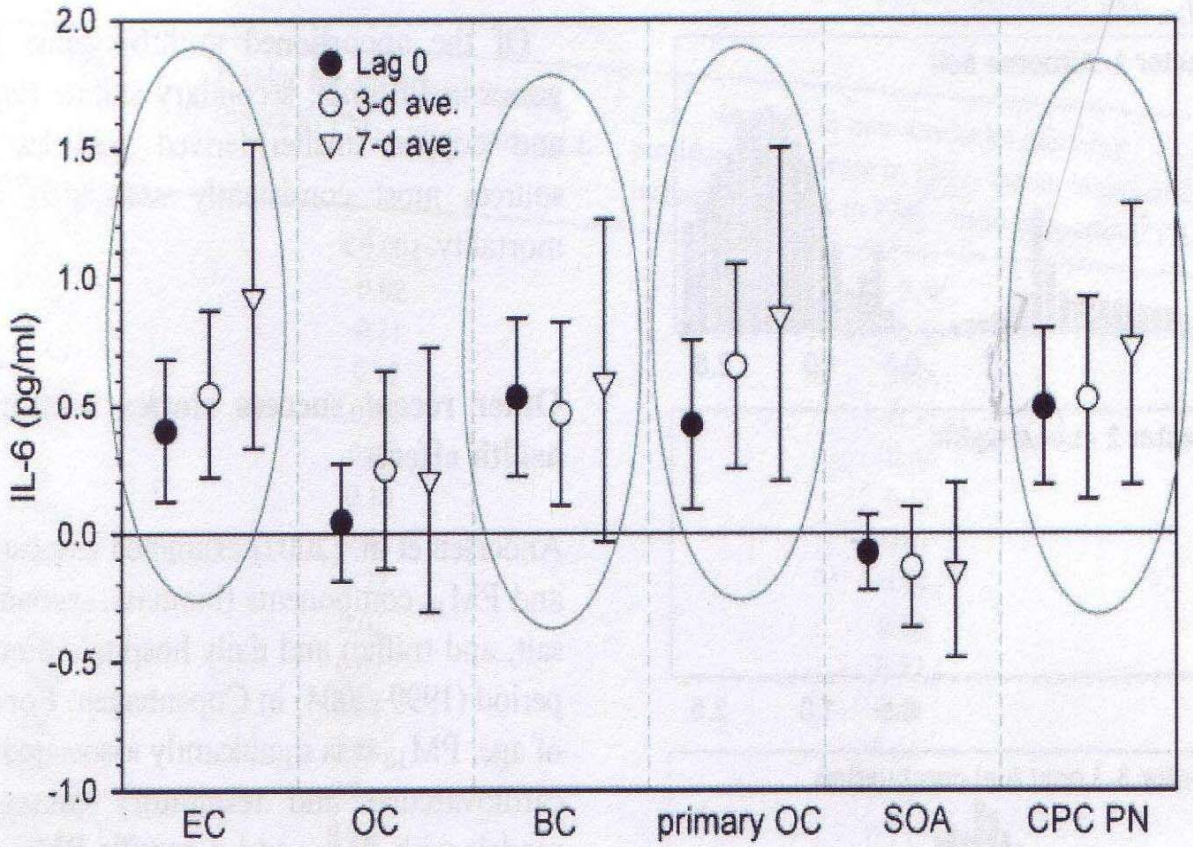


Figure 8. Significant source-related elevations in IL-6 with outdoor carbonaceous aerosols and particle number (per IQR) in the Delfino et al. (2008) study.

From Atkinson et al 2010; Epidemiology 21:501

- Coarse, fine, PM10, particle number concentrations, carbon, sulfate, nitrate, chloride were studied with a time –series approach in London.
- Outcomes were cause specific mortality and hospital admissions.
- Evidence was found that UFP are associated more with cardiovascular outcomes, whilst secondary particles more with respiratory outcomes.

To sum-up: Suggestive evidence but lack of measurements to allow for more conclusive results

- We know that particle mixtures vary according to their toxicity; ie there is spatial and temporal heterogeneity in their effects on health.
- The heterogeneity can, at least to some extent, be explained by special physical and chemical characteristics of the particle composition for specific outcomes.
- A very important problem for human observational studies is posed by the lack of adequate measurements of particle characteristics of relevance.

To sum up: what has been suggested with preliminary evidence or toxicology and requires further investigation

- Size:
  - UFP (short-term effects; cardiovascular; neurological)
  - Coarse (respiratory)
- Source:
  - Transportation (diesel vehicles; shipping)
  - Natural (desert dust; sea salt; vegetation/ bioallergens; forest fires)
- Chemistry:
  - Transition metals (Ni for various short-term effects)
  - Inorganic components (sulfate, nitrate, crustal species, aluminum, silicon…)
  - Carbonaceous particles (OC, EC for various health effects including inflammation)
  - PAHs (potential for carcinogenicity)
- Primary vr Secondary particles
- And …combinations of the above

Single pollutants or mixtures (multi-pollutant approaches)?

- There are arguments about starting to consider the effects of mixtures.
- Thus, it unlikely that one component in the particle mixture is responsible for the health effects, even for one single outcome.
- It is more likely that mixtures with specific characteristics are responsible for specific outcomes
- The mixtures may be defined
  - according to source
  - according to a common mechanism of effect (e.g. their ROS generation potential)
- Gaseous pollutants and bio-allergens and their potential synergy with particles should not be neglected in this approach

Climate change affects the air pollution profile. Some evidence for possible synergy of air pollutants and meteorological/ climatic variables concerning their health effects.

- Understanding the effects of climate change on air pollution
- Investigating joint (synergistic) effects on health
- Reduction of air pollution concentrations is often a co-benefic of mitigation measures for climate change.

For the future: We need good spatial and temporal resolution

- Experimental studies have given and have the potential to produce valuable information but epidemiological studies are needed to consolidate the knowledge gained in real human populations and real exposures.
- For these, relevant measurements with good spatial and temporal resolution are needed.
- For spatial resolution there is accumulation of data for long-term averages within on-going EU projects.
- Temporal resolution is more difficult and expensive but urgently needed, as the first evidence for effects comes from temporal studies (time-series/ panel) and concerns short-term effects.
- Measurements for fixed sites/ mobile sites/ individual (portable)