Lessons from Epidemiologic Studies of Ambient Fine and Ultrafine Particles

Douglas W. Dockery

June 26, 2013

17th ETH-Conference on

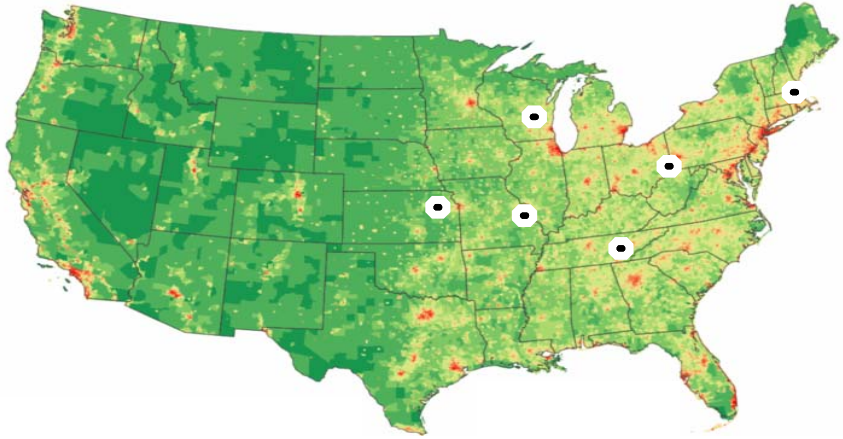
Combustion Generated Nanoparticles

ETH Zürich, Switzerland

HARVARD
SCHOOL OF PUBLIC HEALTH

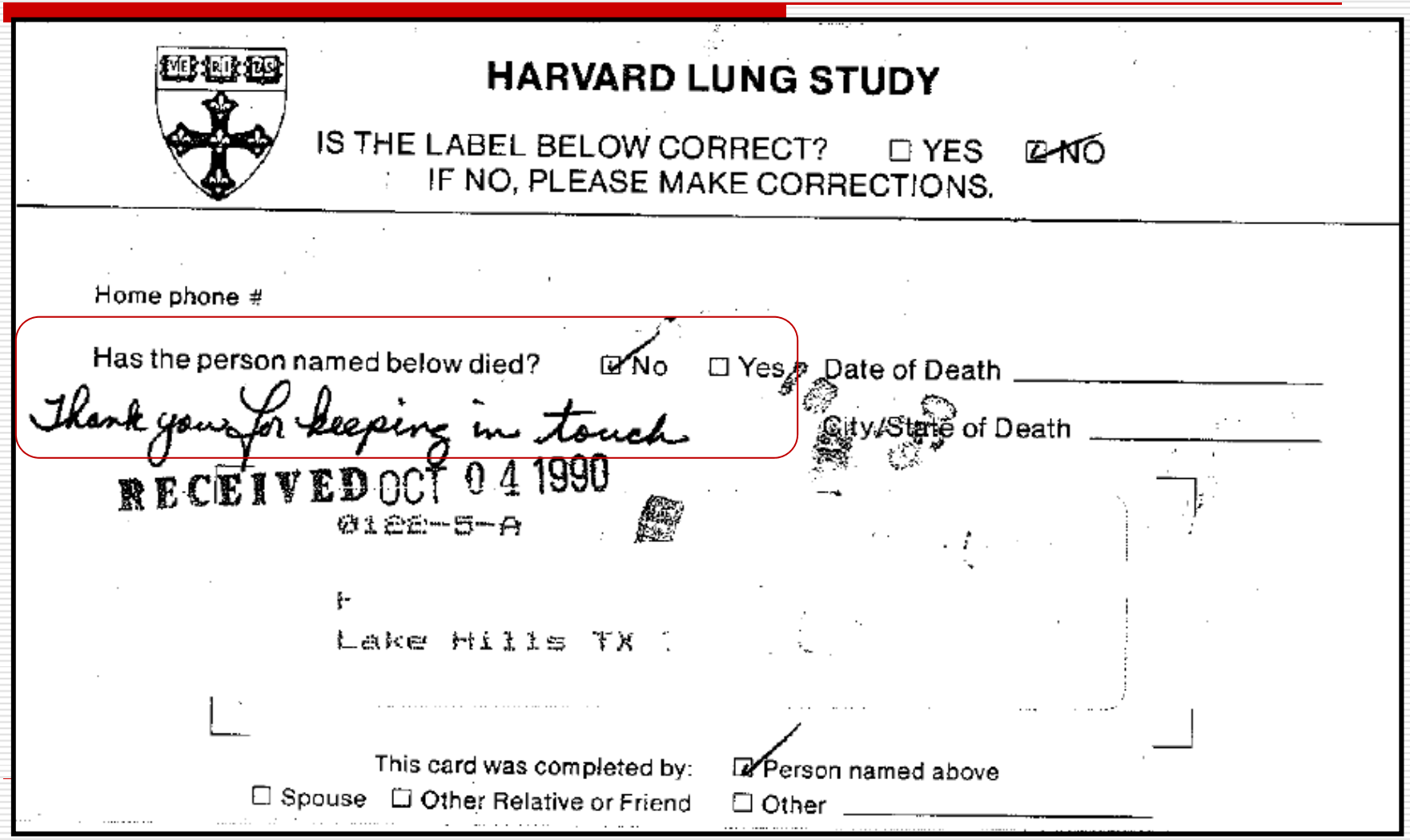
Six Cities Adult Mortality Study

- Random sample of 8411 adults in six cities
  - Dirty: *Steubenville, OH & St. Louis, MI*
  - Moderate: *Watertown, MA & Harriman, TN*
  - Clean: *Topeka, KS & Portage, WI*
- Enrolled 1974-77
- 14-16 years of mortality follow-up



Dockery et al, NEJM 1993;329:1753

Follow-up



HARVARD LUNG STUDY

IS THE LABEL BELOW CORRECT? ☐ YES ☑ NO
IF NO, PLEASE MAKE CORRECTIONS.

Home phone #

Has the person named below died? ☑ No ☐ Yes Date of Death _____

City/State of Death _____

Thank you for keeping in touch

RECEIVED OCT 0 4 1990

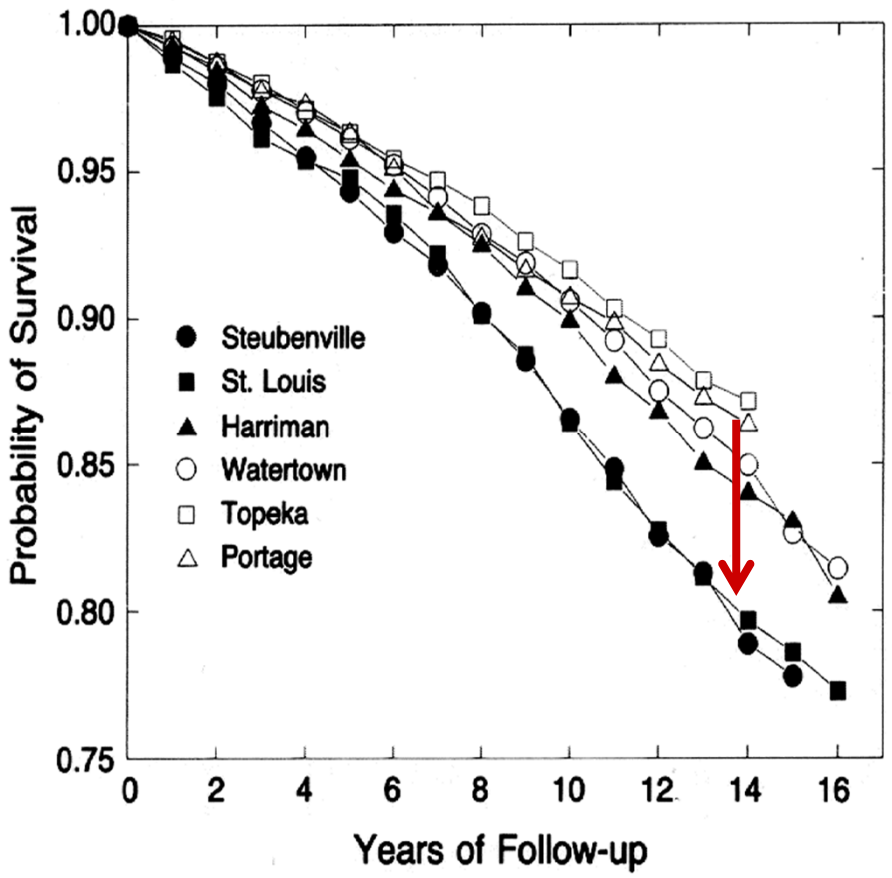
Lake Hills TX

This card was completed by: ☑ Person named above

☐ Spouse ☐ Other Relative or Friend ☐ Other _____

Six Cities Adult Mortality Study

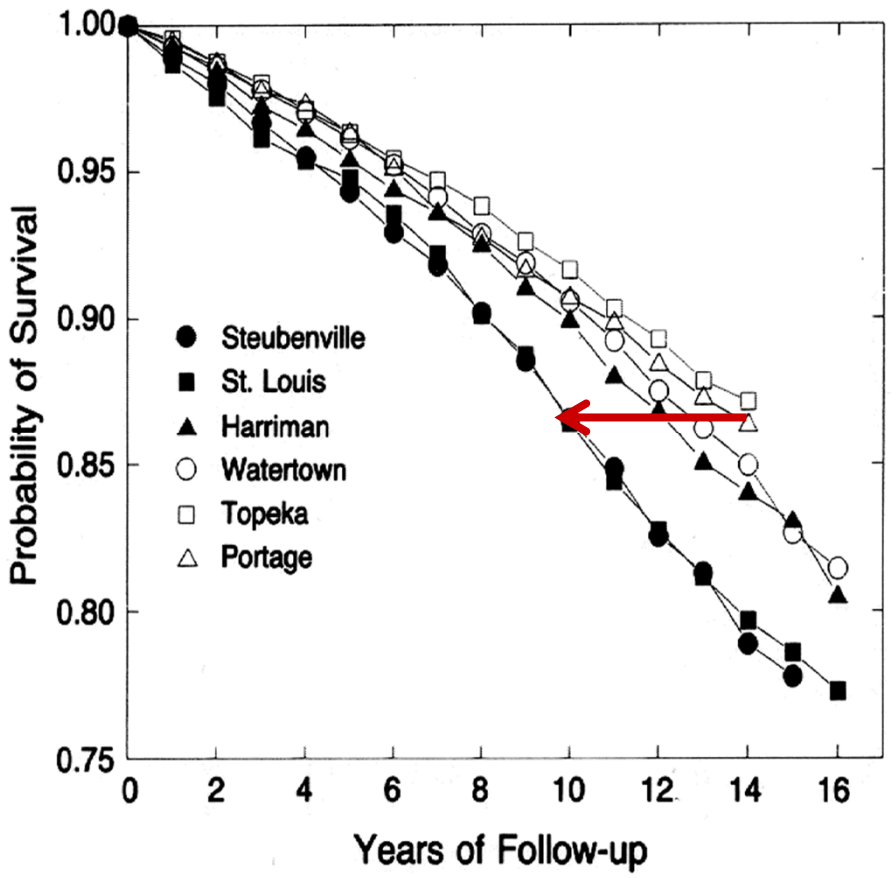
- Random sample of 8411 adults in six cities
  - Dirty: *Steubenville, OH & St. Louis, MI*
  - Moderate: *Watertown, MA & Harriman, TN*
  - Clean: *Topeka, KS & Portage, WI*
- Enrolled 1974-77
- 14-16 years of mortality follow-up



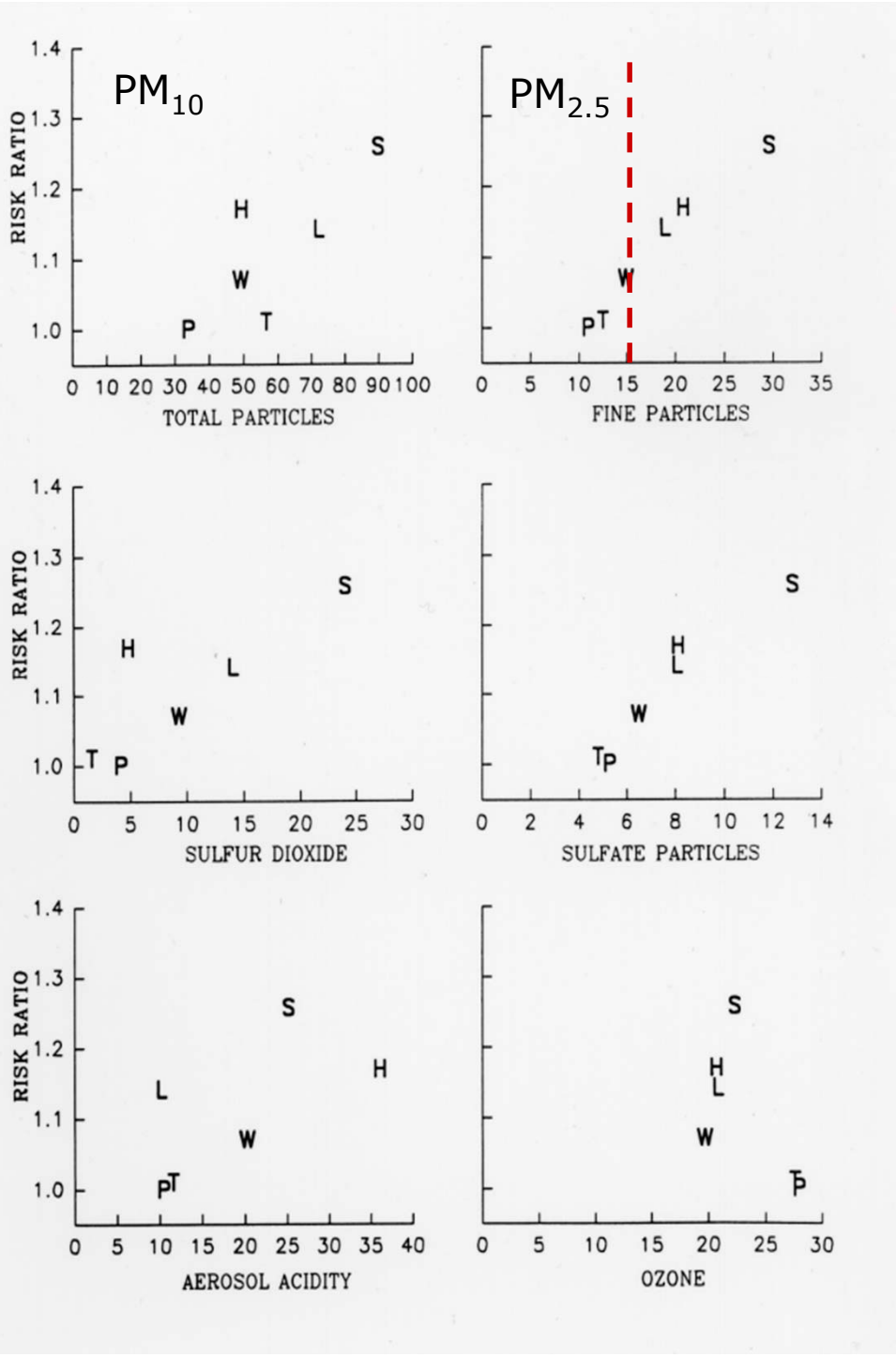
Dockery et al, NEJM 1993;329:1753

Six Cities Adult Mortality Study

- Random sample of 8411 adults in six cities
  - Dirty: *Steubenville, OH & St. Louis, MI*
  - Moderate: *Watertown, MA & Harriman, TN*
  - Clean: *Topeka, KS & Portage, WI*
- Enrolled 1974-77
- 14-16 years of mortality follow-up



Dockery et al, NEJM 1993;329:1753

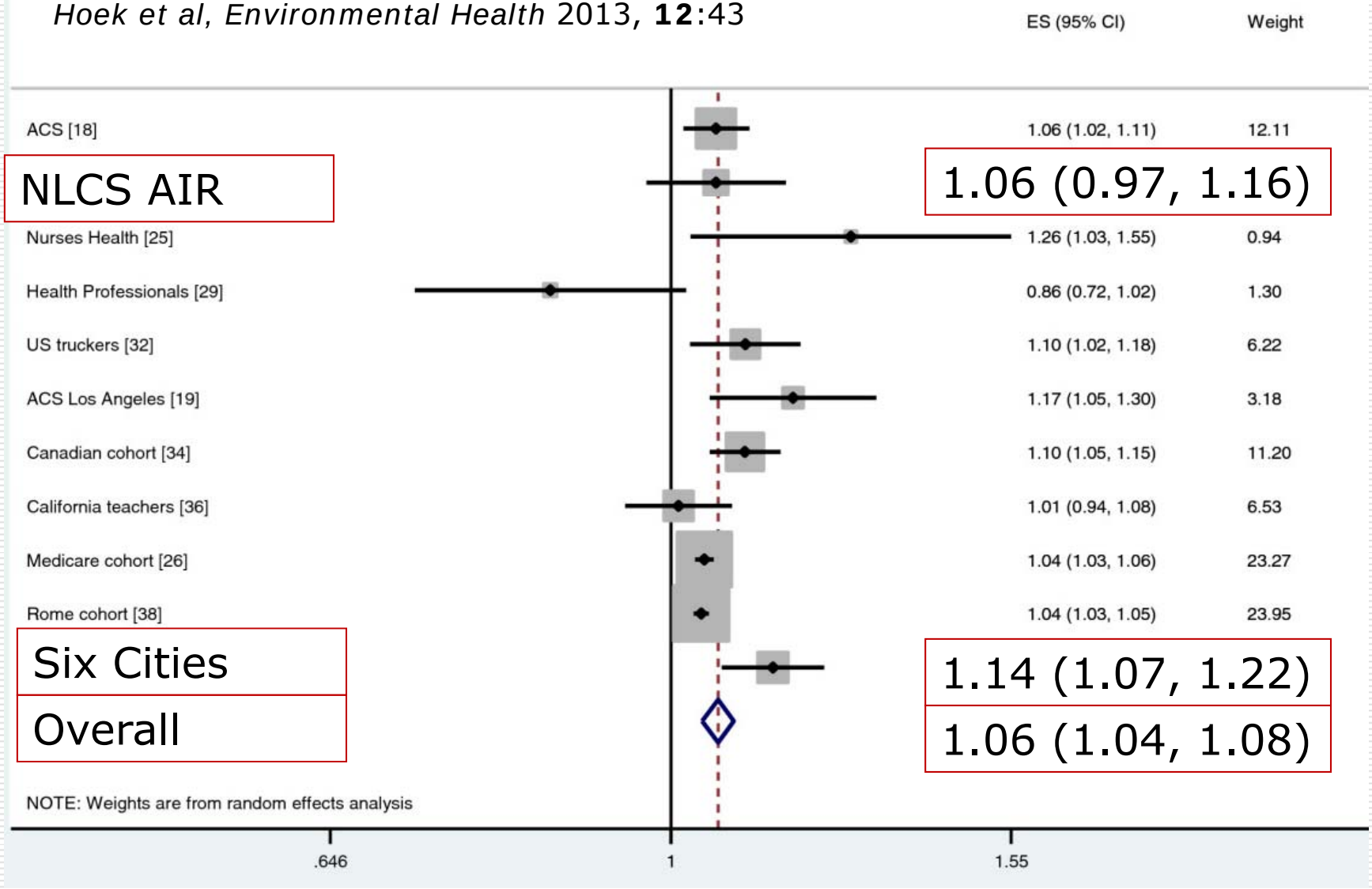

PM10
PM2.5
RISK RATIO
1.4
1.3
1.2
1.1
1.0
S
H
L
W
P
T
0 10 20 30 40 50 60 70 80 90 100
TOTAL PARTICLES
0 5 10 15 20 25 30 35
FINE PARTICLES
0 5 10 15 20 25 30
SULFUR DIOXIDE
0 2 4 6 8 10 12 14
SULFATE PARTICLES
0 5 10 15 20 25 30 35 40
AEROSOL ACIDITY
0 5 10 15 20 25 30
OZONE

Why $PM_{2.5}$?

- Measuring composition by size range
- EPA Dichotomous Sampler
  - Virtual impactor
    - <2.5 μm
    - 2.5 to 10 μm
  - Separate filter samples
    - Elemental Analysis by XRF
  - *Dzubay and Stevens*, Ambient air analysis with dichotomous sampler and x-ray fluorescence spectrometer. *Environ. Sci. Technol.*, 1975: 9; 663

Long-term air pollution exposure and cardio-respiratory mortality: a review

Hoek et al, Environmental Health 2013, **12**:43



Relative risk per 10 μg/m^3 $PM_{2.5}$

NLCS-AIR Study

Long-Term Effects of Traffic-Related Air Pollution on Mortality in a Dutch Cohort

- Long-term exposure (1976-1996) at home address of 120,852 study subjects
  - Black Smoke, NO_2, SO_2, and $PM_{2.5}$
  - Based on regional, urban, and local components
- Indicators of traffic-related air pollution
  - traffic intensity on the nearest road,
  - living near a major road, and
  - sum of traffic intensity in a surrounding 100-m buffer

Beelen et al, Environ Health Perspect. 2008; 116: 196

NLCS-AIR Study

Long-Term Effects of Traffic-Related Air Pollution on Mortality in a Dutch Cohort

- For a 10 μg/m^3 increase in $PM_{2.5}$ concentration, the RR for natural-cause mortality
  - 1.06 (95% CI, 0.97–1.16)

- Traffic intensity on the nearest road was independently associated with mortality.
  - Independent near road air pollution exposure?

Beelen et al, Environ Health Perspect. 2008; 116: 196

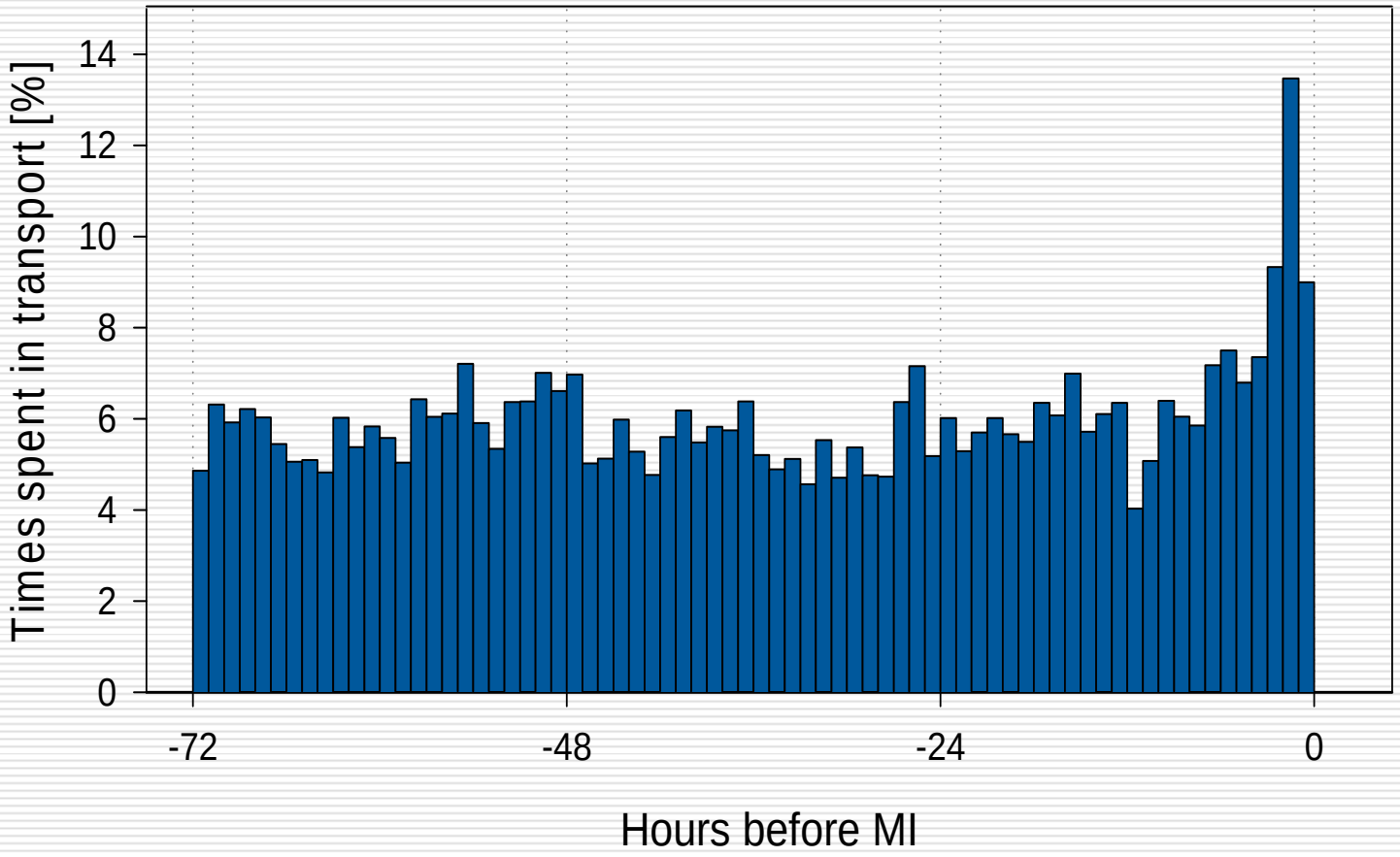
Triggering of myocardial infarctions

HelmholtzZentrum münchen
German Research Center for Environmental Health

- Myocardial infarction survivors age 25 and 74 years based on the KORA Myocardial Infarction Registry, Augsburg, Germany
- Bed-side interview of 1466 cases between 1999 and 2003
- Detailed information on activities 4 days before symptom onset

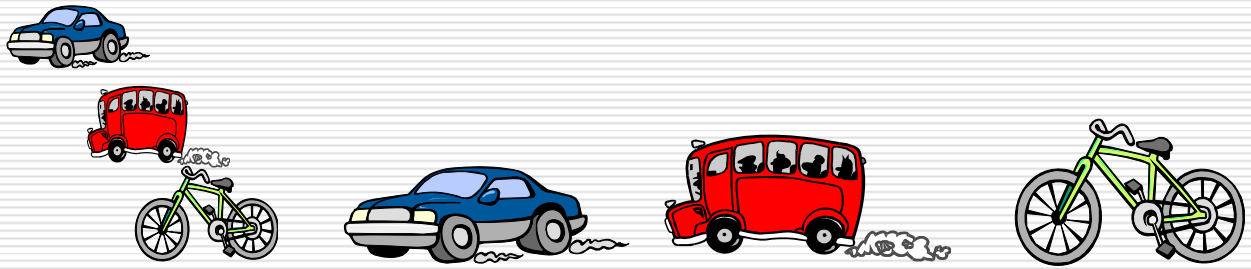
Peters et al. EJPC 2012

Times Spent in Traffic in the Hours before a Heart Attack (N=1466)



Peters et al. EJPC 2012

Times spent in traffic and the triggering of myocardial infarction one hour later



	All	Cars	Bus/Tram	Bicycle
Odds Ratio*	3.2	3.3	2.9	2.6
95% Confidence-interval	2.7 – 3.9	2.7 – 4.1	1.7 – 5.1	1.6 – 4.1

***adjusted for getting up, being outdoors and strenuous exercise**

Peters et al. EJPC 2012

Classification of Causal Associations

Mc

Living Near M

Vasc

Residential Proximity to Freeways and Autism in the CHARGE Study

Heather E. Volk,[1] Irva Hertz-Picciotto,[2] Lora Delwiche,[2] Fred Lurmann,[3] and Rob McConnell[4]

[1]Departments of Preventive Medicine and Pediatrics, Zilkha Neurogenetic Institute, Keck School of Medicine, Children's Hospital Los Angeles, University of Southern California, Los Angeles, California, USA; [2]Department of Public Health Sciences, University of California–Davis, Davis, California, USA; [3]Sonoma Technology Inc., Petaluma, California, USA; [4]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

Background: Little is known about environmental causes and contributing factors for autism. Basic science and epidemiologic research suggest that oxidative stress and inflammation may play a role in disease development. Traffic-related air pollution, a common exposure with established effects on these pathways, contains substances found to have adverse prenatal effects.

Objectives: We examined the association between autism and proximity of residence to freeways and major roadways during pregnancy and near the time of delivery, as a surrogate for air pollution exposure.

Methods: Data were from 304 autism cases and 259 typically developing controls enrolled in the Childhood Autism Risks from Genetics and the Environment (CHARGE) study. The mother's address recorded on the birth certificate and trimester-specific addresses derived from a residential history obtained by questionnaire were geocoded, and measures of distance to freeways and major roads were calculated using ArcGIS software. Logistic regression models compared residential proximity to freeways and major roads for autism cases and typically developing controls.

Results: Adjusting for sociodemographic factors and maternal smoking, maternal residence at the time of delivery was more likely be near a freeway (≤ 309 m) for cases than for controls [odds ratio (OR) = 1.86; 95% confidence interval (CI), 1.04–3.45]. Autism was also associated with residential proximity to a freeway during the third trimester (OR = 2.22; CI, 1.16–4.42). After adjustment for socioeconomic and sociodemographic characteristics, these associations were unchanged. Living near other major roads at birth was not associated with autism.

Conclusions: Living near a freeway was associated with autism. Examination of associations with measured air pollutants is needed.

Key words: autism, epidemiology, gene–environment interaction, roadway proximity, traffic emissions. *Environ Health Perspect* 119:873–877 (2011). doi:10.1289/ehp.1002835 [Online December 2010]

levels. Additionally, autism has been associated with estimated regional concentrations of hazardous air pollutants, including arsenic and nickel, and with diesel PM exposure in early childhood (Windham et al. 2006).

Thus, an emerging literature suggests that near roadways, traffic-related air pollutants, possibly influenced by specific components such as PM or PAHs, affect neurodevelopment. However, the role of timing for this exposure during pregnancy or early life is not clear, nor has the relationship between traffic-related air pollutants and autism been tested. In this study, we examined the relationship between autism and traffic proximity (a marker of traffic-related air pollution) during the prenatal period and at the time of birth.

Materials and Methods

We used data from 304 autism cases and 259 typically developing general-population controls from the Childhood Autism Risks from Genetics and the Environment (CHARGE) study, a population-based case–control study

Risk

ics. The

ed models;

covariates) for

ution) compared with

was approximately linear

ng for background levels of

th versus 90th distance centile in

er in the year before diagnosis).

VT. (*Circulation*. 2009;119:3118-3124

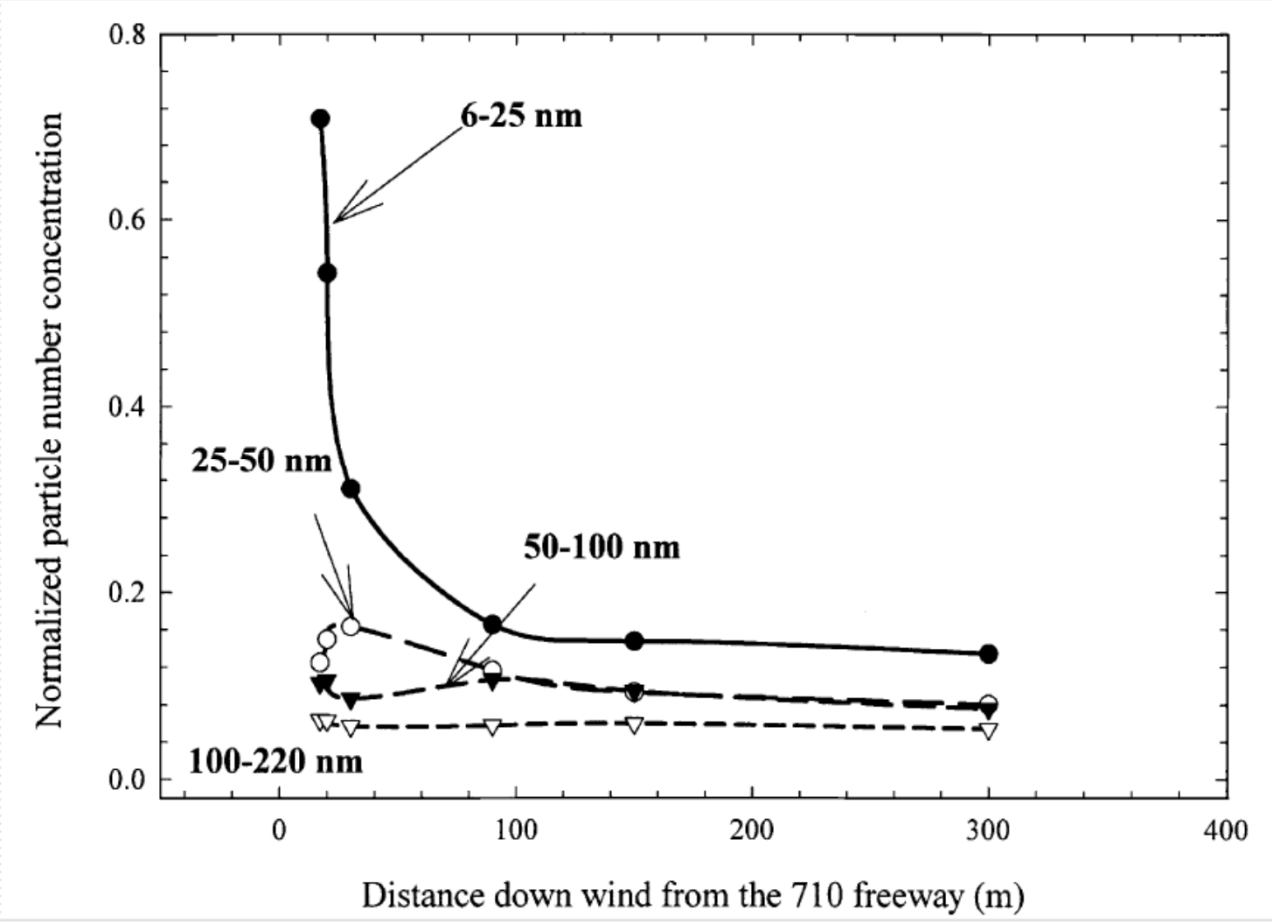
Other H

Birth

Canc

Are these epidemiologic associations with proximity to major roads attributable to ambient ultrafine particles?

Normalized PNC versus distance to road



Zhu et al, Atmospheric Environment, 2002;*36; 4323*

HEI Perspectives 3

January 2013

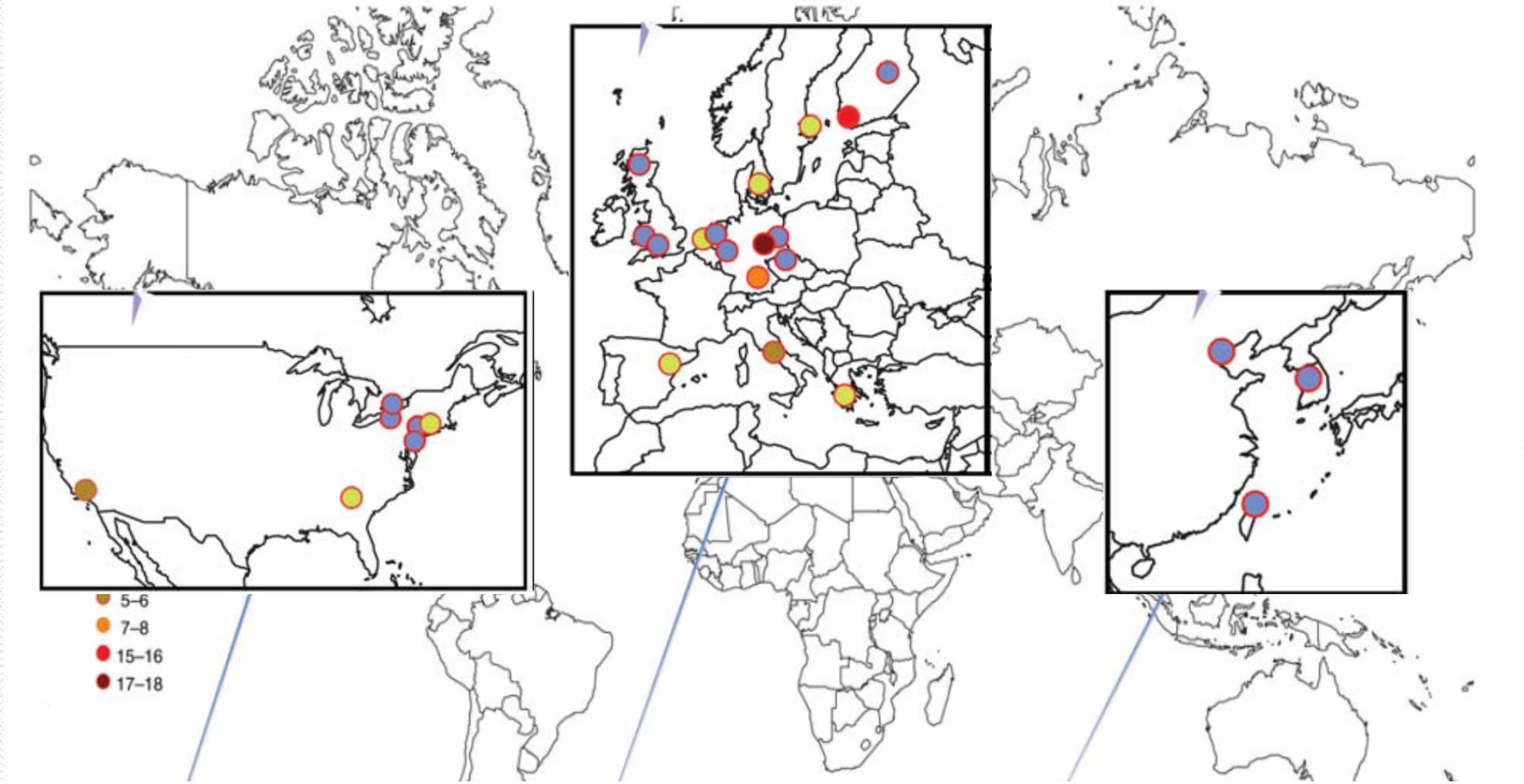
Insights from HEI's research

Understanding the Health Effects of Ambient Ultrafine Particles

HEI Review Panel on Ultrafine Particles

http://www.healtheffects.org/Workshops/Brussels2013/Presentations/Shaikh.pdf

Geographic locations of epidemiologic investigations of the short-term exposures to UFPs



HEI Perspectives 3, 2013

Health effects of particulate air pollution: Review of epidemiological evidence

Ruckerl et al, Inhalation Toxicology, 2011; 23(10): 555–592

Variables	Short-Term Studies	Long-Term Studies
	UFP	UFP
Mortality		
All Cause	1	1
Cardiovascular	1	1
Pullmonary	1	1
Pulmonary Effects		
Lung Function	2	
Lung Function Growth		
Asthma and COPD Exacerbation		
Acute Respiratory Symptoms	1	
Medication Use	1	
Hosptial Admissions		1
Cariovascular Effect		
Hospital Admissions		
ECG-related endpoints		
Autonomic Nervous System	2	
Myocardial substrate/vulnerability	1	
Vascular function		
Blood Pressure	1	
Endothelia Function	1	

3 - Large number of studies
2 - Many studies
1 - Few studies

Variables	Short-Term Studies	Long-Term Studies
	UFP	UFP
Mortality		
All Cause	1	1
Cardiovascular	1	1
Pullmonary	1	1
Pulmonary Effects		
Lung Function	2	
Lung Function Growth		
Asthma and COPD Exacerbation		
Acute Respiratory Symptoms	1	
Medication Use	1	
Hosptial Admissions		1
Cariovascular Effect		
Hospital Admissions		
ECG-related endpoints		
Autonomic Nervous System	2	
Myocardial substrate/vulnerability	1	
Vascular function		
Blood Pressure	1	
Endothelia Function	1	

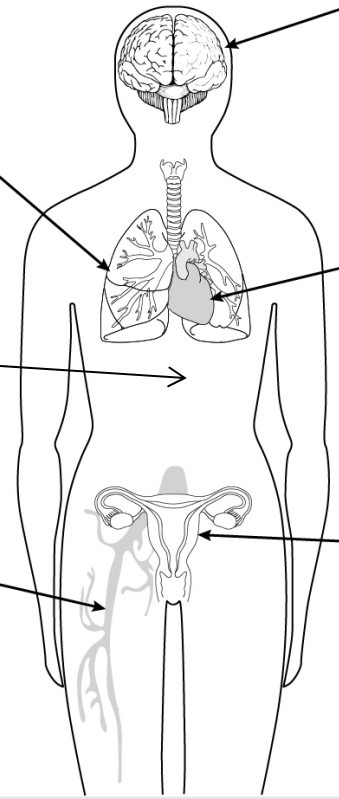
Ruckerl et al, Inhal Tox, 2011; 23: 555

Organs of the human body that can be affected by PM air pollution

- Respiratory mortality
- Respiratory symptoms
- Rhinitis/Pneumonia
- Airway inflammation
- Decreased lung function
- Decreased lung growth
- Lung cancer

- **Metabolic disorders**
- **Diabetes**
- **Liver Disorders**

- Changes in blood pressure
- Endothelial function
- Increased blood coagulation
- Systemic inflammation



- Stroke
- Diseases of the central nervous system

- Cardiovascular mortality
- Cardiovascular hospital admission
- Changes in heart rate variability
- ST-segment depression

- Premature birth
- Decreased birth weight
- Decreased foetal growth
- Intrauterine growth retardation
- Decreased sperm quality

Updated from Peters et al. JOEM 2011

Health effects of particulate air pollution: Review of epidemiological evidence

Ruckerl et al, Inhalation Toxicology, 2011; 23(10): 555–592

Variables	Short-Term Studies		Long-Term Studies	
	$PM_{2.5}$	UFP	$PM_{2.5}$	UFP
Mortality				
All Cause	**3**	1	2	1
Cardiovascular	**3**	1	2	1
Pullmonary	**3**	1	2	1
Pulmonary Effects				
Lung Function	**3**	2	3	
Lung Function Growth			3	
Asthma and COPD Exacerbation				
Acute Respiratory Symptoms	**2**	1		
Medication Use		1		
Hosptial Admissions			2	1
Cariovascular Effect				
Hospital Admissions	**3**		1	
ECG-related endpoints				
Autonomic Nervous System	**3**	2		
Myocardial substrate/vulnerability	**2**	1		
Vascular function				
Blood Pressure	**3**	1		
Endothelia Function	**2**	1		

3 - Large number of studies
2 - Many studies
1 - Few studies

Variables	Short-Term Studies		Long-Term Studies	
	$PM_{2.5}$	UFP	$PM_{2.5}$	UFP
Mortality				
All Cause	**3**	**1**	2	**1**
Cardiovascular	**3**	**1**	2	**1**
Pullmonary	**3**	**1**	2	**1**
Pulmonary Effects				
Lung Function	**3**	**2**	3	
Lung Function Growth			3	
Asthma and COPD Exacerbation				
Acute Respiratory Symptoms	**2**	**1**		
Medication Use		**1**		
Hosptial Admissions			2	**1**
Cariovascular Effect				
Hospital Admissions	**3**		1	
ECG-related endpoints				
Autonomic Nervous System	**3**	**2**		
Myocardial substrate/vulnerability	**2**	**1**		
Vascular function				
Blood Pressure	**3**	**1**		
Endothelia Function	**2**	**1**		

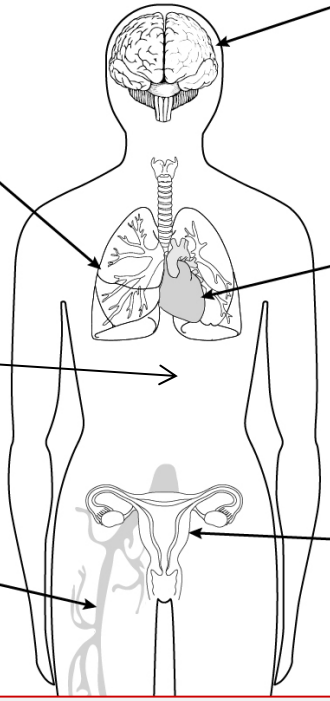
Ruckerl et al, Inhalation Toxicology, 2011; 23: 555

Organs of the human body that can be affected by air pollution

- Respiratory mortality
- Respiratory symptoms
- Rhinitis/Pneumonia
- Airway inflammation
- Decreased lung function
- Decreased lung growth
- Lung cancer

- **Metabolic disorders**
- **Diabetes**
- **Liver Disorders**

- Changes in blood pressure
- Endothelial function
- Increased blood coagulation
- Systemic inflammation



- Stroke
- Diseases of the central nervous system

- Cardiovascular mortality
- Cardiovascular hospital admission
- Changes in heart rate variability
- ST-segment depression

- Premature birth
- Decreased birth weight
- Decreased foetal growth
- Intrauterine growth retardation
- Decreased sperm quality

UFP and acute mortality **not consistently** observed

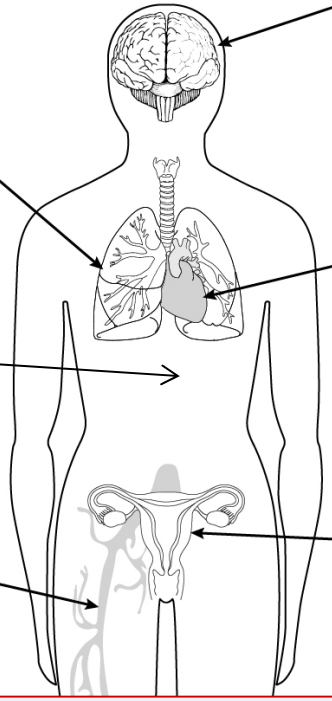
- Weak or no associations in Helsinki and Prague
- Strong associations on Erfurt, London, Rome, and Beijing

Organs of the human body that can be affected by air pollution

- Respiratory mortality
- Respiratory symptoms
- Rhinitis/Pneumonia
- Airway inflammation
- Decreased lung function
- Decreased lung growth
- Lung cancer

- **Metabolic disorders**
- **Diabetes**
- **Liver Disorders**

- Changes in blood pressure
- Endothelial function
- Increased blood coagulation
- Systemic inflammation



- Stroke
- Diseases of the central nervous system

- Cardiovascular mortality
- Cardiovascular hospital admission
- Changes in heart rate variability
- ST-segment depression

- Premature birth
- Decreased birth weight
- Decreased foetal growth
- Intrauterine growth retardation
- Decreased sperm quality

UFP and acute morbidity in 9 locations, 15 studies

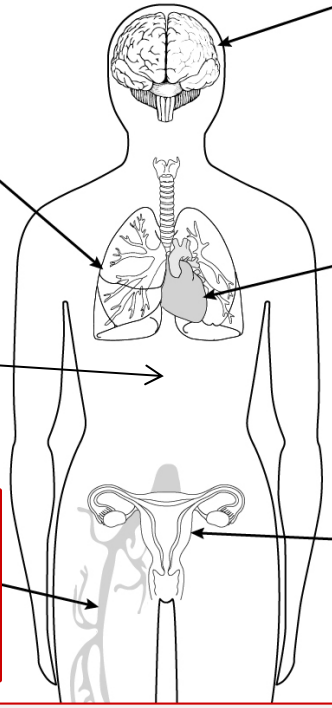
- Hospital admissions, ED visits, Physician visits, Emergency service calls
- **Inconsistent** associations

Organs of the human body that can be affected by air pollution

- Respiratory mortality
- Respiratory symptoms N=7
- Rhinitis/Pneumonia
- Airway inflammation
- Decreased lung function N=9
- Decreased lung growth
- Lung cancer

- **Metabolic disorders**
- **Diabetes**
- **Liver Disorders**

- Changes in blood pressure N=5
- Endothelial function N=2
- Increased blood coagulation N=18
- Systemic inflammation



- Stroke
- Diseases of the central nervous system

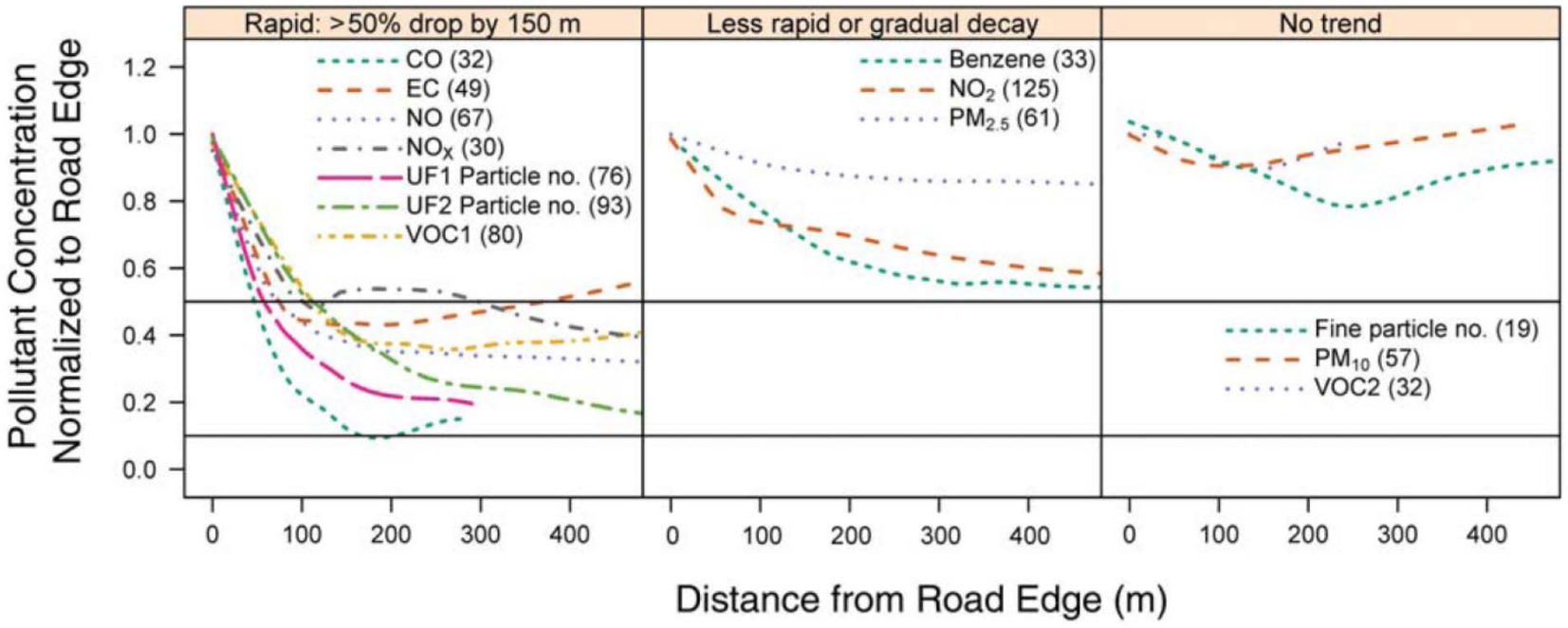
- Cardiovascular mortality
- Cardiovascular hospital admission
- Changes in heart rate variability N=18
- ST-segment depression

- Premature birth
- Decreased birth weight
- Decreased foetal growth
- Intrauterine growth retardation
- Decreased sperm quality

UFP and acute cardiorespiratory markers- 25 studies

- Largely **inconsistent** associations with NC

Relative Air Pollution vs. Distance to Road



Local regression of road-edge normalized concentrations on distance from the edge of road. Sample size, *n*, is given in parentheses after each pollutant.

Karner et al. Environ Sci Technol 2010; 44:5334

Health effects of particulate air pollution: Review of epidemiological evidence

Ruckerl et al, Inhalation Toxicology, 2011; 23(10): 555–592

Variables	Short-Term Studies				Long-Term Studies			
	$PM_{2.5}$	UFP	BS/BC	EC/OC	$PM_{2.5}$	UFP	BS/BC	EC/OC
Mortality								
All Cause	**3**	**1**	**1**	**1**	2	**1**	2	1
Cardiovascular	**3**	**1**	**1**	**1**	2	**1**	2	1
Pullmonary	**3**	**1**	**1**	**1**	2	**1**	2	1
Pulmonary Effects								
Lung Function	**3**	**2**		**1**	3			
Lung Function Growth					3			
Asthma and COPD Exacerbation								
Acute Respiratory Symptoms	**2**	**1**						
Medication Use		**1**						
Hosptial Admissions					2	**1**		
Cariovascular Effect								
Hospital Admissions	**3**				1			
ECG-related endpoints								
Autonomic Nervous System	**3**	**2**	**1**					
Myocardial substrate/vulnerability	**2**	**1**	**1**					
Vascular function								
Blood Pressure	**3**	**1**	**1**	**1**				
Endothelia Function	**2**	**1**	**1**					

3 - Large number of studies
2 - Many studies
1 - Few studies

Variables	Short-Term Studies				Long-Term Studies			
	$PM_{2.5}$	UFP	BS/BC	EC/OC	$PM_{2.5}$	UFP	BS/BC	EC/OC
Mortality								
All Cause	**3**	**1**	**1**	**1**	2	**1**	2	1
Cardiovascular	**3**	**1**	**1**	**1**	2	**1**	2	1
Pullmonary	**3**	**1**	**1**	**1**	2	**1**	2	1
Pulmonary Effects								
Lung Function	**3**	**2**		**1**	3			
Lung Function Growth					3			
Asthma and COPD Exacerbation								
Acute Respiratory Symptoms	**2**	**1**						
Medication Use		**1**						
Hosptial Admissions					2	**1**		
Cariovascular Effect								
Hospital Admissions	**3**				1			
ECG-related endpoints								
Autonomic Nervous System	**3**	**2**	**1**					
Myocardial substrate/vulner	**2**	**1**	**1**					
Vascular function								
Blood Pressure	**3**	**1**	**1**	**1**				
Endothelia Function	**2**	**1**	**1**					

Ruckerl et al, Inhal Tox, 2011; 23: 555

Evidence from epidemiologic studies

3. Do UFPs affect human health at environmental concentrations? What is the evidence from epidemiologic studies?

No epidemiologic studies of long-term exposures to ambient UFPs have been conducted, as the most common epidemiologic study designs are dependent on spatial contrasts that are far more difficult to characterize for UFPs than for $PM_{2.5}$.

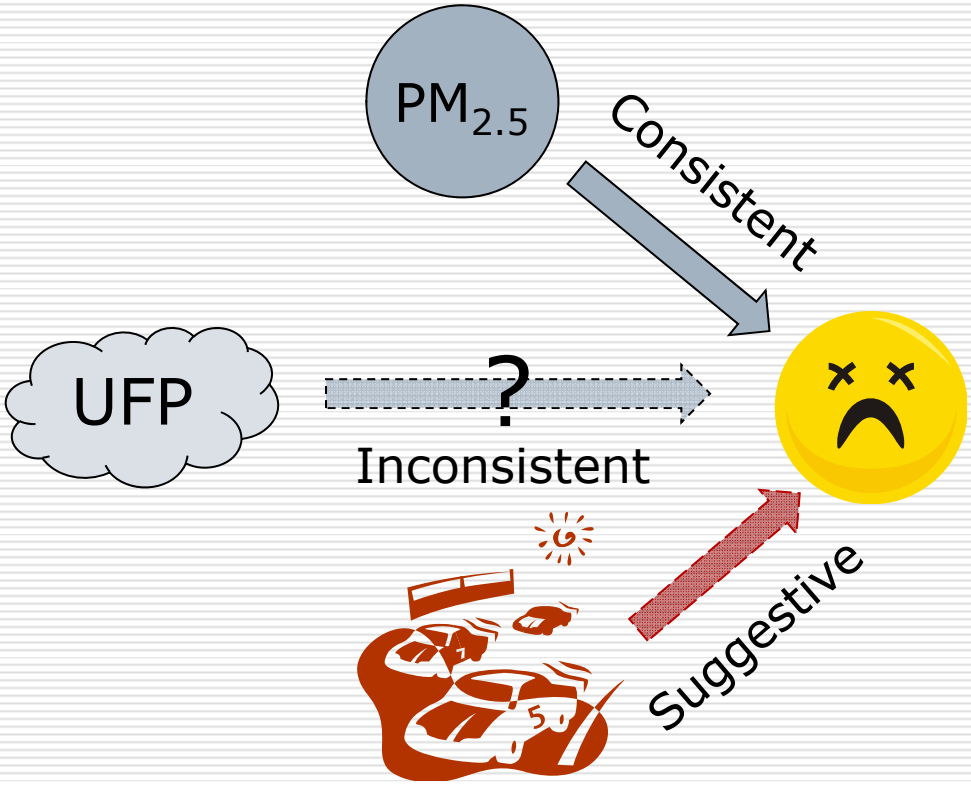
ever, limitations of the current studies are likely to play a role: UFPs have not been assessed routinely in larger epidemiologic studies of air pollution health effects, in part because ambient monitoring of UFPs is not conducted in most locations; UFPs have been defined and measured in different ways; and the greater exposure measurement

Of 42 published articles that cited any significant health associations with UFPs measured as NC, 37 articles also noted significant effects for other particle size fractions or traffic-related pollutants, and 10 articles did not consider any traffic-related gases in the analysis.

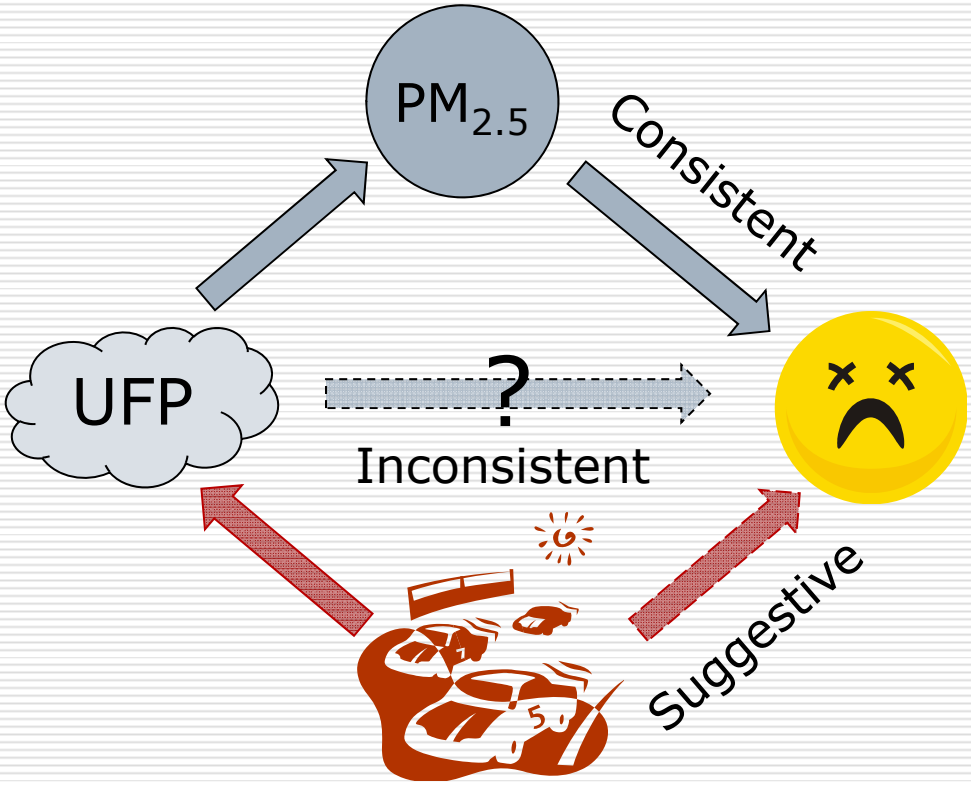
Explanations for inconsistent evidence from epidemiologic studies

- No true underlying association between UFP exposures and adverse effects
- Limitations of current epidemiologic studies
  - Lack of consistent UFP monitoring
  - Spatial variability of UFP exposures
  - Greater exposure misclassification of UFP compared to $PM_{2.5}$

Does this imply that there are not epidemiologic associations with UFP?



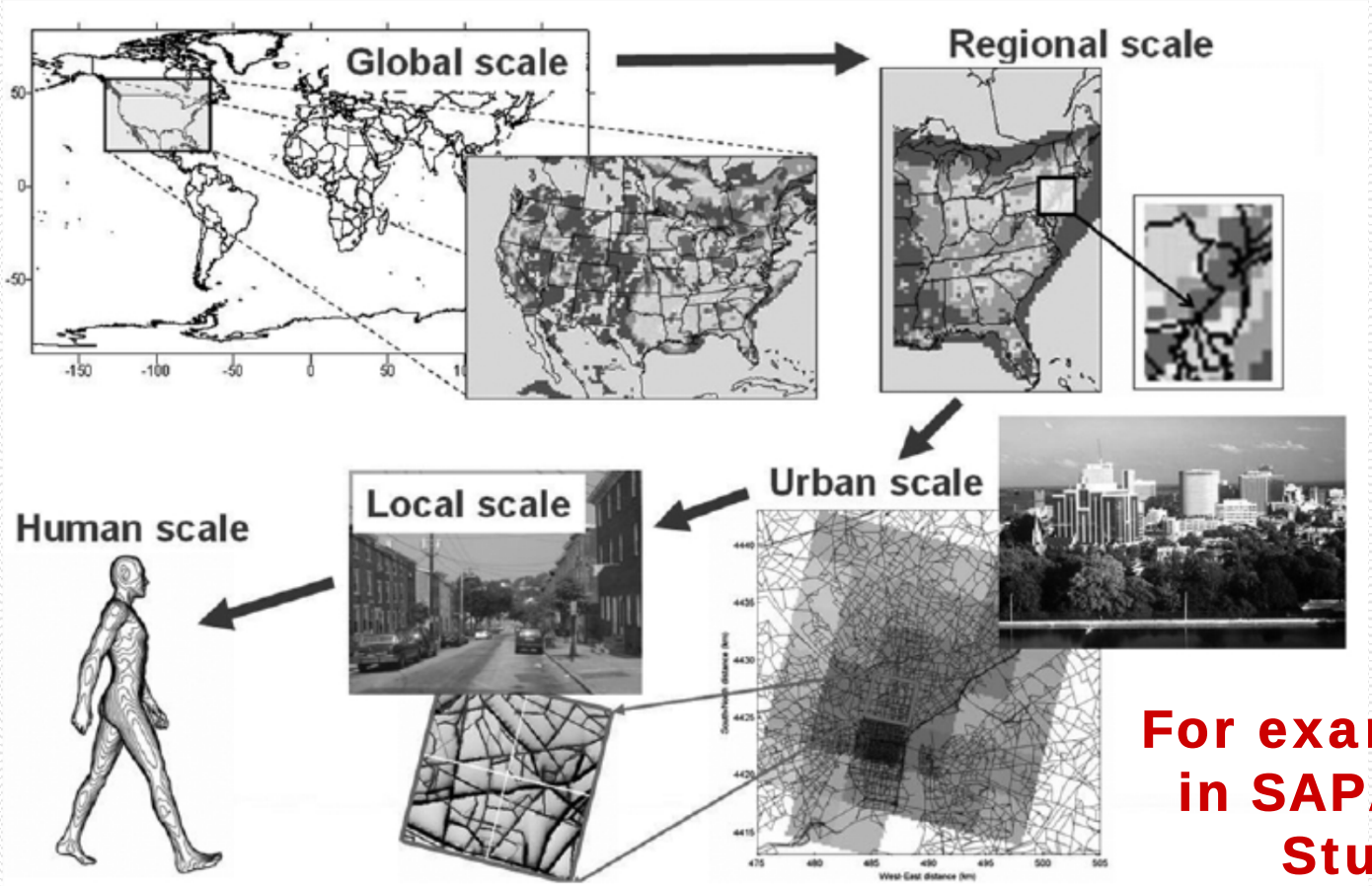
Does this imply that there are not epidemiologic associations with UFP?



Way Forward for Epidemiologic Exposures?

Understanding and quantifying the contribution of combustion nanoparticles to respirable particle ($PM_{2.5}$) exposures.

Way Forward for Epidemiologic Exposures:
Scales used in modeling emissions from traffic

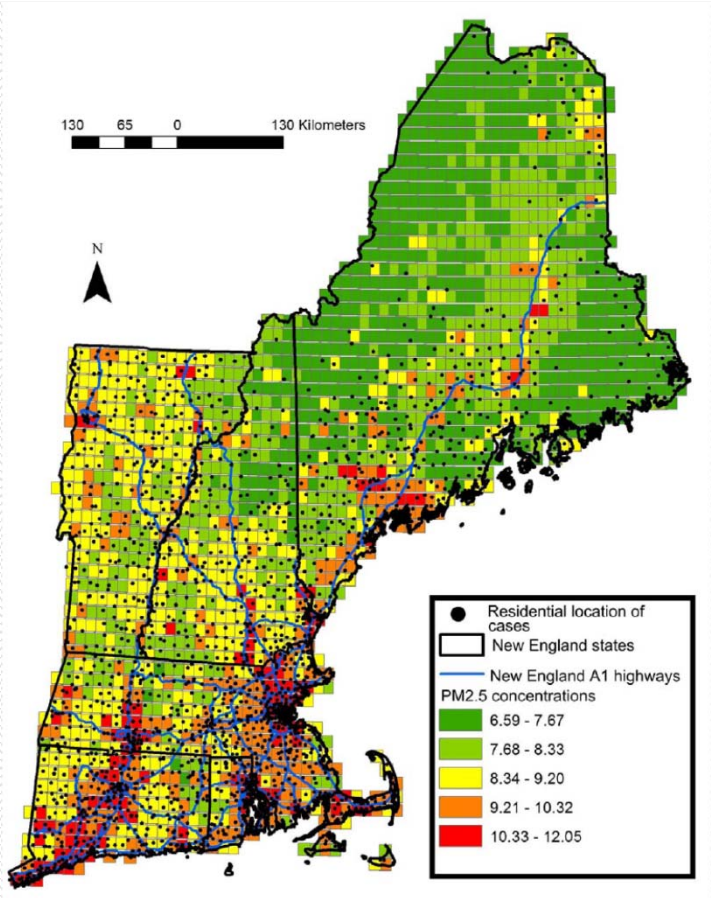


For example as in SAPALDIA Study

Stein et al. Atmos Environ 2007;41:9410

Integrating multiple layers of data

- Ambient Fixed Site Monitoring
- Rotating mobile sites
- Remote Sensing (Satellite)
- Land use regression
- CMAC atmospheric model



Kloog I, et al. PLoS ONE 2012;7: e34664.


Marina Bay, Singapore, Feb 2012
GOOGLE STREET VIEW
Marina Bay, Singapore, June 2013
REUTERS