Title: Environmental Health Effects of Combustion-Related Ultrafine Particulate Matter

14th ETH-Conference on Combustion Generated Nanoparticles
August 1st – 4th 2010

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Over the past three decades the focus of environmental aerosol research has progressed from the study of gases to particulate matter (PM), its mass, chemical constituents, and sources. Likewise, the focus of health effects research has transitioned from the respiratory system to the cardiovascular, nervous and reproductive systems. While interest in carcinogenesis and respiratory disease, e.g. asthma, COPD, and allergy persist; new areas of research are emerging. These include the study of the heart, vasculature, fertility, birth outcomes, sleep, human development and neurological effects. Contemporaneously, the body of knowledge of health effects, toxicology and plausible biological mechanisms has grown and informed risk assessment and drove the transition of the PM regulations based on total suspended particles, to PM_{10}, and later to $PM_{2.5}$. Currently, ultrafine PM (nanoparticles) is not regulated, yet vehicle emissions do evoke health effects, and probably contribute to short- and long-term health effects near roadways. Yet, to what extent their health effects are due to combustion-related nanoparticles, secondary aerosols, re-suspended road dusts or other factors near roadways such as noise and stress are not understood fully.

Specific knowledge regarding the health effects of combustion-generated nanoparticles is significantly limited when compared to what is known about $PM_{2.5}$. Integrated information collected from epidemiological studies, small cohort studies, controlled human exposure and animal toxicology studies is accumulating rapidly and appears to link ultrafine PM exposure to pulmonary and systemic inflammation, small changes in blood pressure, heart rhythm, myocardial ischemia, vascular function, and hemostasis and thrombosis. Yet, there are many things we still do not know. For example, do combustion-generated nanoparticles have an inherent biological effect or do they serve as carriers for other toxicants such as organic hydrocarbons or metals? Are their

effects additive or synergistic with other pollutants such as NO_2 or ozone? Do these particles because of their small size and potential to transloce across cell membranes more likely to impact the central nervous system or the unborn? And to what extent does genetic background or epigenetics contribute to the response of an individual?

The mechanisms responsible for the observed biological responses and clinical events attributed to ultrafine PM remain uncertain. When compared to PM of greater mass, ultrafine PM or combustion-generated nanoparticles have greater surface area, thombogenic potency and oxidative potential; have the capability to translocate to other organs; and deposition into the lung is deeper and more efficient. Analogous to our understanding of the mechanisms underlying the effects of $PM_{2.5}$, data generally supports the concept that ultrafine PM increases oxidative stress, mild pulmonary inflammatory responses with subsequent effects on modulation of the autonomic nervous system, systemic inflammation, heart rhythm, endothelial and vascular function, hemostasis and thrombosis. The central role of oxidative stress and inflammation also provide potential explanations for increased vulnerability among some clinical cohorts such as aged adults, and those with diabetes, and pulmonary and cardiovascular disease. Studies point to the possible role of the pulmonary macrophage, and the mast cell in the pathophysiologcial responses to airborne combustion-generated particles.

The time course of physiological responses is also important and suggests that different mechanisms might determine immediate effects when compared to short- or long-term effects. Electrocardiographic changes occur rapidly as do changes in autonomic tone suggesting that pulmonary receptors, and afferent nerves with subsequent loss of sympathetic/parasympathetic balance mediate such effects. Increased spontaneous ectopic beats have been shown to occur in response to traffic-related particles and are likely to be caused by changes in sympathetic/parasympathetic balance, and are associated with changes in cardiac repolarization. Relative increases in NTproBNP in the California Freeway Study as well as other studies showing increases in endothelin-1 and pulmonary pressures suggest that acute changes in pulmonary vasculature might also mediate some cardiac effects and are not due to noise or stress.

Direct recordings of the electrocardiographic QT interval a measure of cardiac repolarization showed that brief inhalation of ultrafine PM from the Chapel Hill, NC airshed increased the variability of the QT interval by approximately 50% for each increment of 10,000 particles/cc (Samet et al. 2009). In this same study D-dimer was increased suggesting that exposure to ultrafine PM increased thrombosis, an effect also present after inhalation of diesel exhaust PM (Lucking et al. 2009). Recent studies continue to implicate traffic-related sources and particle number rather than particle mass as the principal determinant of biological and physiological effects. For example, T-wave alternans developed rapidly during exposure to air pollutants in the Boston, MA airshed and the effect was more strongly associated with black carbon an indicator of traffic rather than $PM_{2.5}$ (Zanobetti et al. 2009). Likewise in the California Freeway study cardiovascular endpoints were more strongly

associated with particle number counts and also polyaromatic hydrocarbons. Direct exposure of subjects with a history of ischemic heart disease to diesel emissions has also been shown to increase electrocardiographic evidence of ischemia (Mills et al. 2007) an effect probably mediated by altered vascular regulation (Barath et al. 2010). Such effects might now provide insight into the observation that the onset of non-fatal myocardial infarction can be related to traffic exposure (Peters et al. NEJM 2004) and that many health effects are influenced by residential proximity to highways.

Demonstration of short-term and probably long-term adverse health effects secondary to exposures to combustion-generated ultrafine PM (nanoparticles) should motivate continued efforts to eliminate these particles from the environment. As demonstrated by the follow-up of the Harvard Six Cities Study improvement in air quality, and in particular a reduction of $PM_{2.5}$ is associated with decreased mortality (Laden et al. 2006). Moreover, a more comprehensive study in the US showed that reductions in $PM_{2.5}$ were associated with a proportional increase in longevity (Pope et al. 2009). Concurrent benefits of PM reduction are also predicted to decrease hospitalizations and health care system utilization among individuals more susceptible to the effects of combustion-generated combustion particles. Such benefits are expected to include improved quality of life and secondary economic benefits of increased productivity and decreased health care expenditures.

References

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Mills NL, Törnqvist H, Gonzalez MC, Vink E, Robinson SD, Söderberg S, Boon NA, Donaldson K, Sandström T, Blomberg A, Newby DE. Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. *N Engl J Med.* 2007 Sep 13;357(11):1075-82.

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Short CV of the Author:

Dr. Wayne Cascio is the Vice-Chairman of the Dept. of Cardiovascular Sciences, and Prof. of Cardiovascular Sciences, and Medicine at East Carolina University in Greenville, NC, USA. He also serves as the Director of Research for the East Carolina Heart Institute. Dr. Cascio received a BA from The John Hopkins University in 1977 and an M.D. degree from the University of Maryland in 1980. Between 1980 and 1986 he served an internal medicine residency and cardiology fellowship at the University of North Carolina, Chapel Hill, NC.

Between 1987 and 1989 Dr. Cascio served as an assistant to Dr. Andre Kléber at the University of Bern where he completed a post-doctoral fellowship in cardiac electrophysiology. His clinical research and teaching activities focus on health care disparities, the environmental health effects of particulate air pollution, electrocardiography, and cardiac electrical signal processing. He serves as a member of the US Environmental Protection Agency's Clean Air Scientific Advisory Committee for Particulate Matter.

Environmental Health Effects of Combustion-Related Ultrafine Particulate Matter

Chris Reuther/EHP, Digital Vision, BrandX Pictures

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14th ETH-Conference on
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Zurich, Switzerland
August 3, 2010

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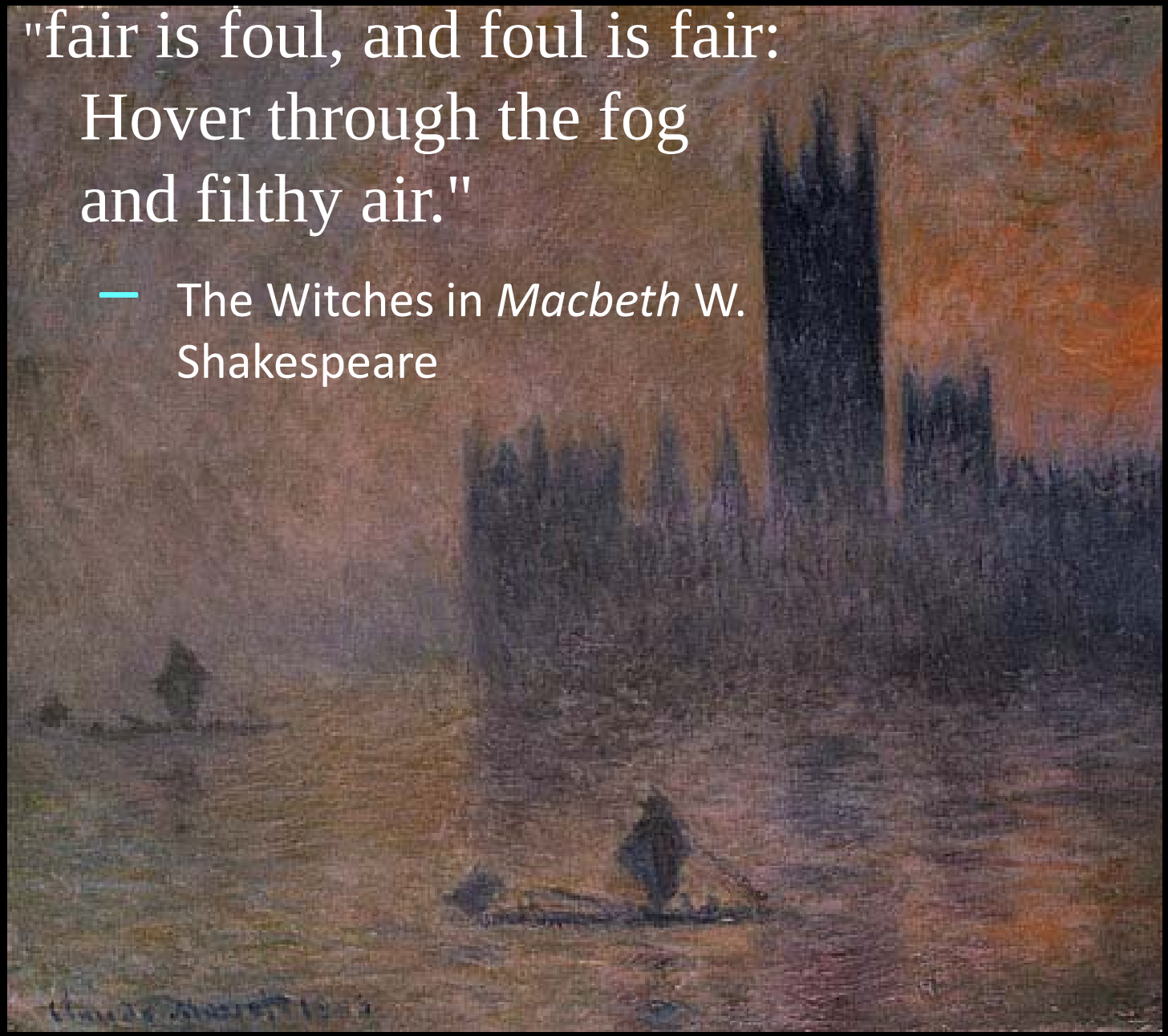
Objectives

- Review of historical high points of health effects of PM
- General principles of the study of PM's health effects
- Transition from respiratory to cardiovascular endpoints
- General mechanisms and biochemical and physiological responses to PM (fine, and ultrafine)
- What constituents of UF PM cause biological responses
- Summary
- Opportunities for the future

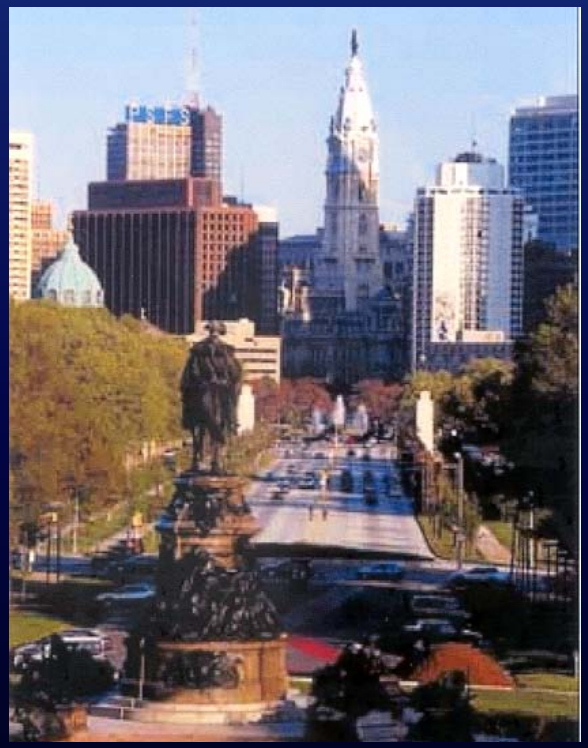


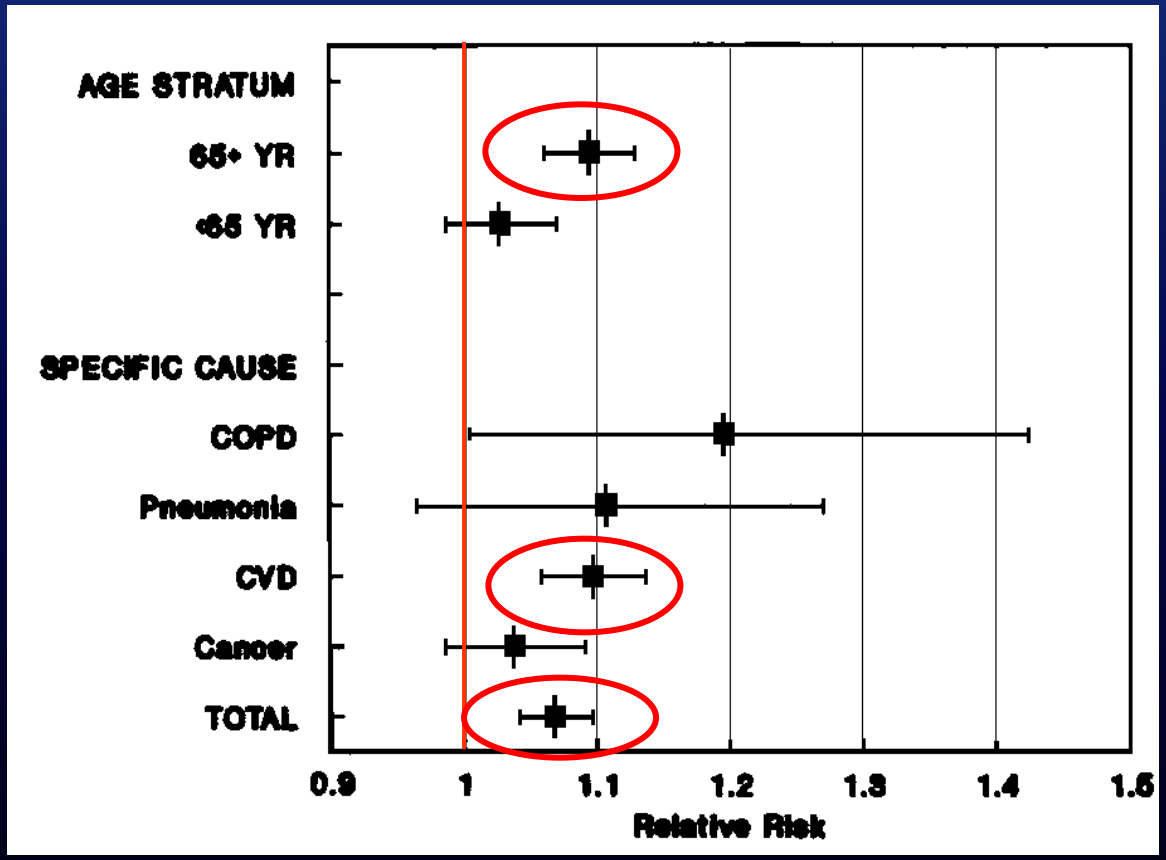
The Houses of Parliament, 1903 - Claude Monet

Donora, PA October 26, 1948

Donora, PA Today

Acute Mortality Associated with Ambient PM Concentration





By the early 1990's, several studies suggested that even moderate levels of air pollution could cause significant health effects.

Schwartz et al., 1992

A New Environmental Health Field is Born

PM Global Public Health Issue

News Focus

Particle air pollution clearly causes substantial deaths and illness, but what makes fine particles so toxic—the size, the chemical compound, or both?

Mounting Evidence Indicts Fine-Particle Pollution

Talk about heart-stopping news: Spending time in traffic may triple some people's risk of having a heart attack an hour later. That's what German researchers reported last October in the *New England Journal of Medicine* (*NEJM*), based on responses from 691 heart attack survivors about their activities in the days before they fell ill. The study seemed to support the notion that tiny air pollution particles from tailpipes, along with stress, could help trigger a heart attack. Yet in another recent study in which volun-

power plants can trigger heart attacks and worsen respiratory disease in vulnerable people, leading to perhaps 60,000 premature deaths a year in the United States. In response, the U.S. Environmental Protection Agency (EPA) in 1997 added new regula-

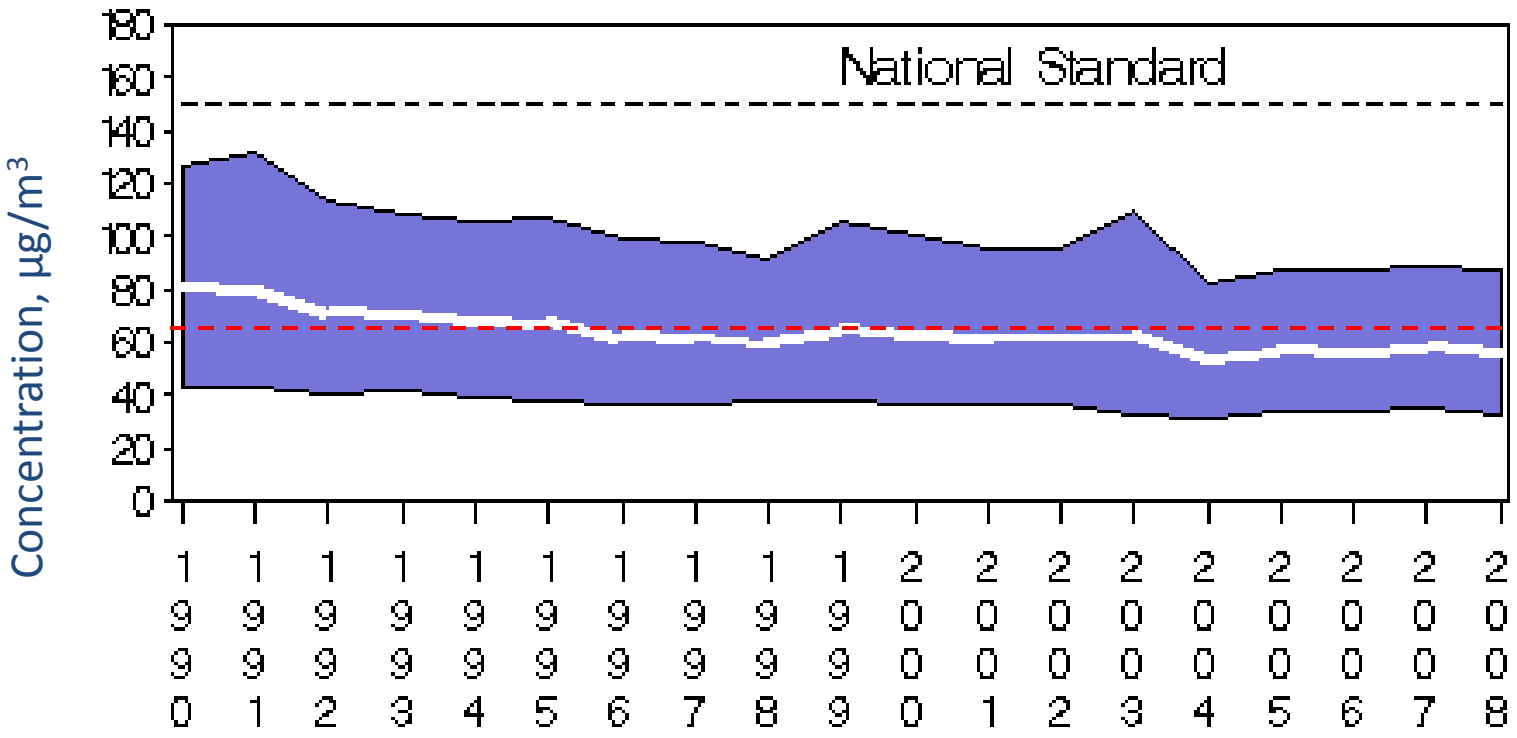
Now the issue is getting another look as EPA faces a December 2005 deadline for revisiting its $PM_{2.5}$ standard. EPA scientists, after reviewing piles of new data implicating $PM_{2.5}$ in health effects, have proposed tightening the 1997 standard to further reduce ambient concentrations of fine particles. Some scientists and industry groups remain skeptical, noting that researchers still haven't pinned down what makes particles dangerous—whether it's mainly size, and that the tiniest particles are most potent; or chemistry,

World Health Organization estimates 3,000,000 people each year die from exposure to air pollutants.

PM_{10} Air Quality, 1990 - 2008

(Based on Annual 2nd Maximum 24 - Hour Average)

National US Trend based on 325 Sites

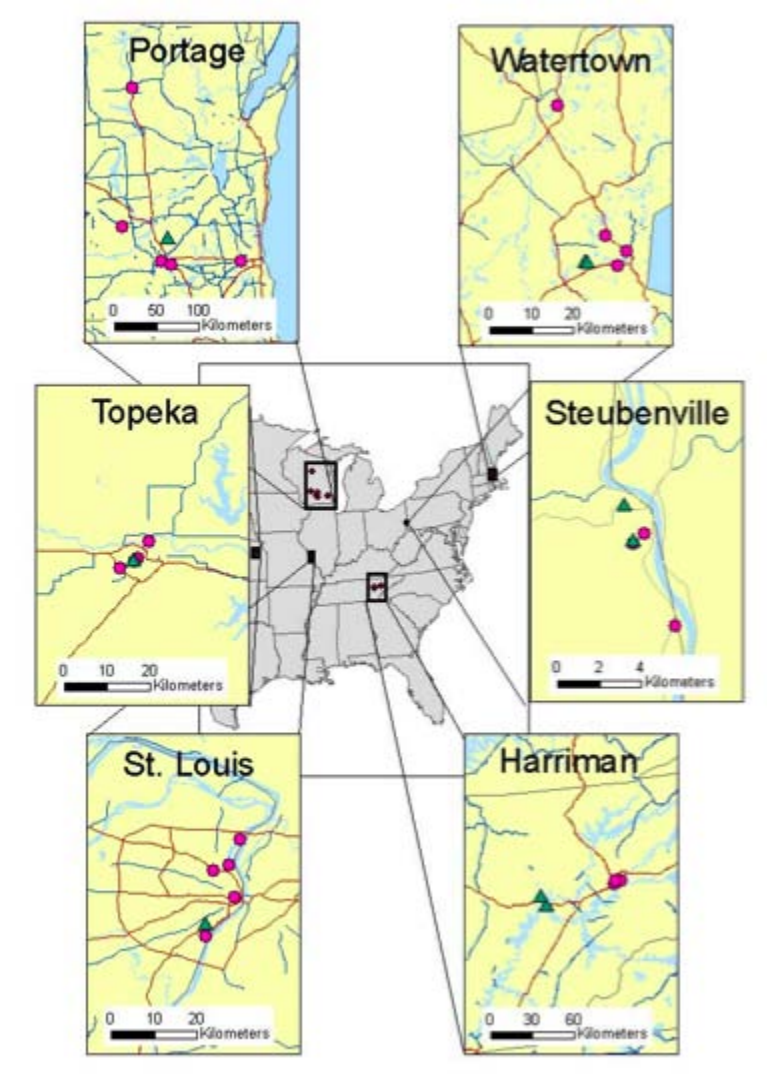


1990 to 2008: 31% decrease in National Average

Does decreasing air particle pollution improve health?

Harvard Six Cities Study

Adjusted Cardiovascular Mortality Rates



Cox Proportional Hazards Model

	Period 1 1974-89
Person Yrs Of follow-up	104,243
Deaths	626
City-specific model	
Portage, WI	1.00
Topeka, KS	1.03
Watertown, MA	1.19
Harriman, TN	1.33
St. Louis, MO	1.21
Steubenville, OH	1.48

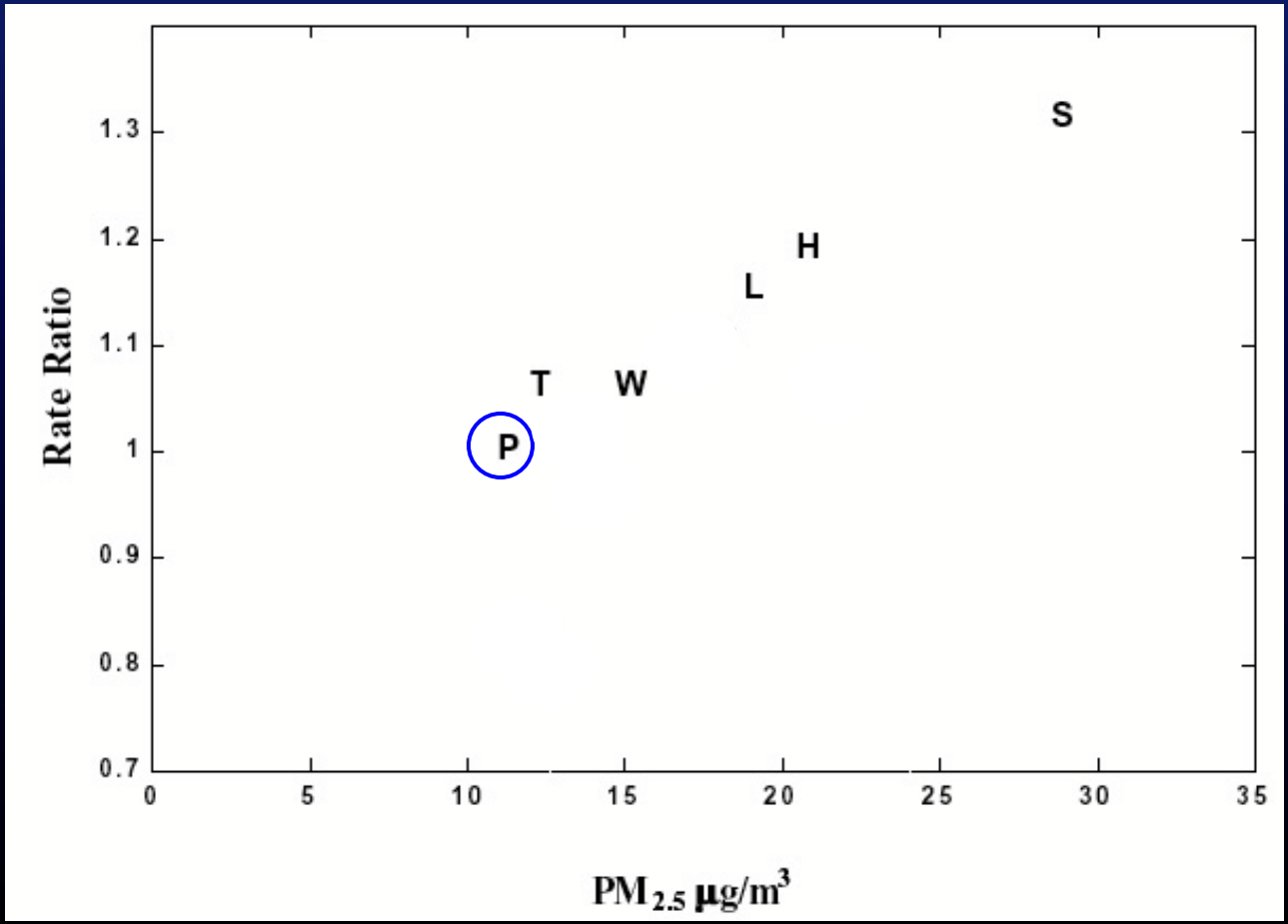
Dockery et al. AJRCCM 2006

Harvard Six Cities Study Follow-up

Estimated adjusted rate ratios for total mortality and $PM_{2.5}$

P - Portage, WI
T - Topeka, KS
W - Watertown, MA
L - St. Louis, MO
H - Harriman, TN
S - Steubenville, OH

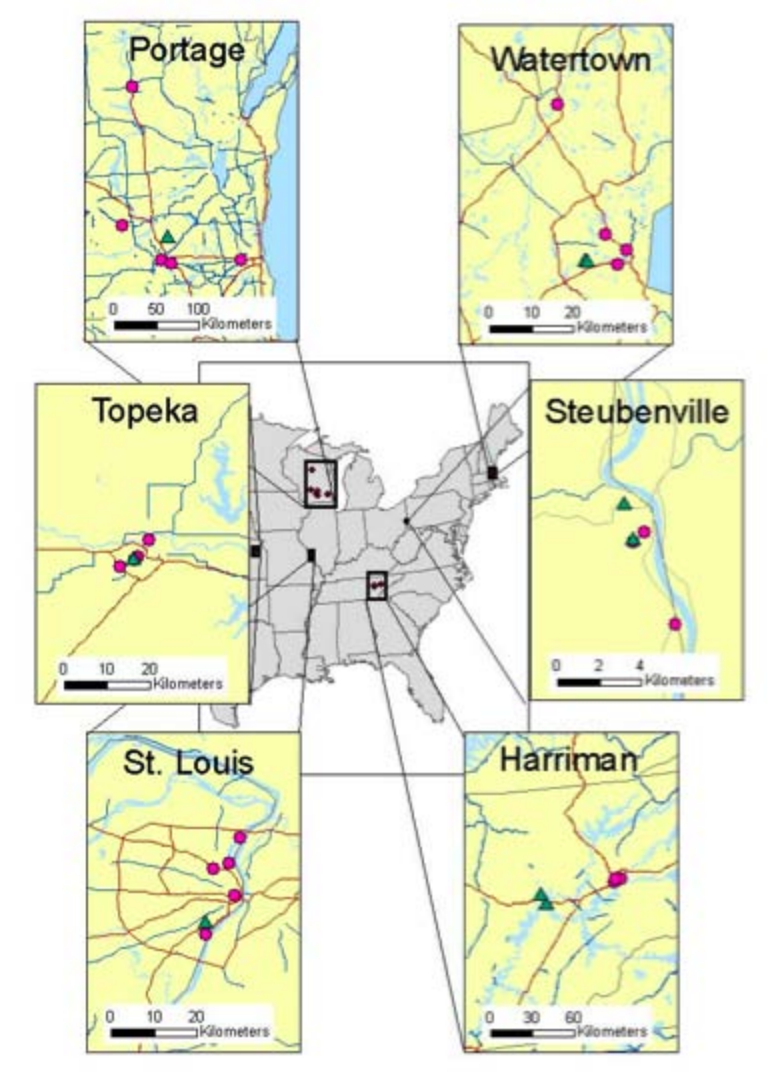
Bold - Period 1
Italics - Period 2



Laden et al. AJRCCM 2006

Harvard Six Cities Study

Adjusted Cardiovascular Mortality Rates



Cox Proportional Hazards Model

	Period 1	Period 2
	1974-89	1990-98
Person Yrs	104,243	54,735
Of follow-up		
Deaths	626	570
	City-specific model	
Portage		1.00
Topeka	1.03	1.00
Watertown	1.19	0.82
Harriman	1.33	1.23
St. Louis	1.21	0.96
Steubenville	1.48	1.21
Period	1.00	0.96

Dockery et al. AJRCCM 2006

Harvard Six Cities Study Follow-up

Estimated adjusted rate ratios for total mortality and $PM_{2.5}$

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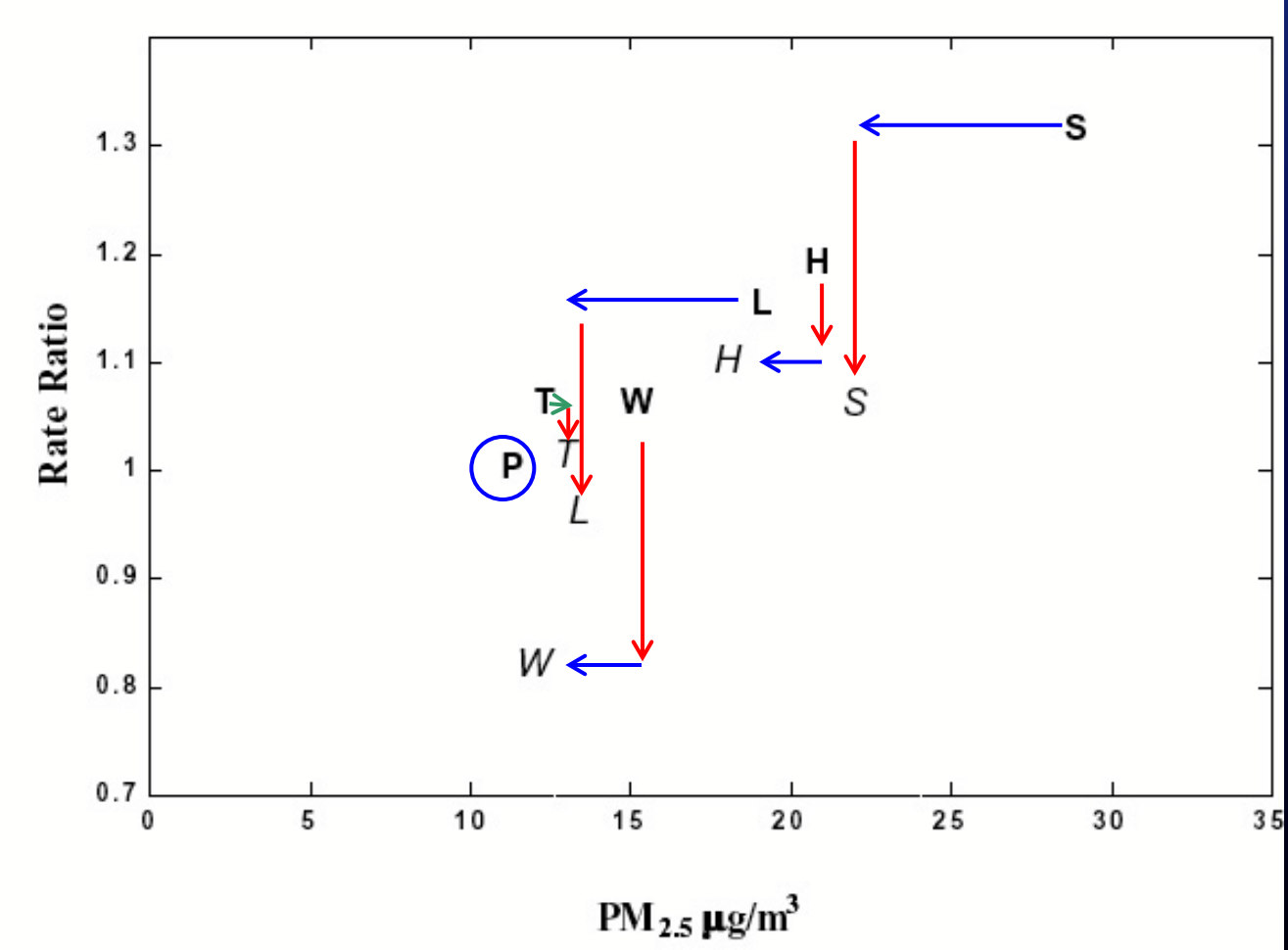
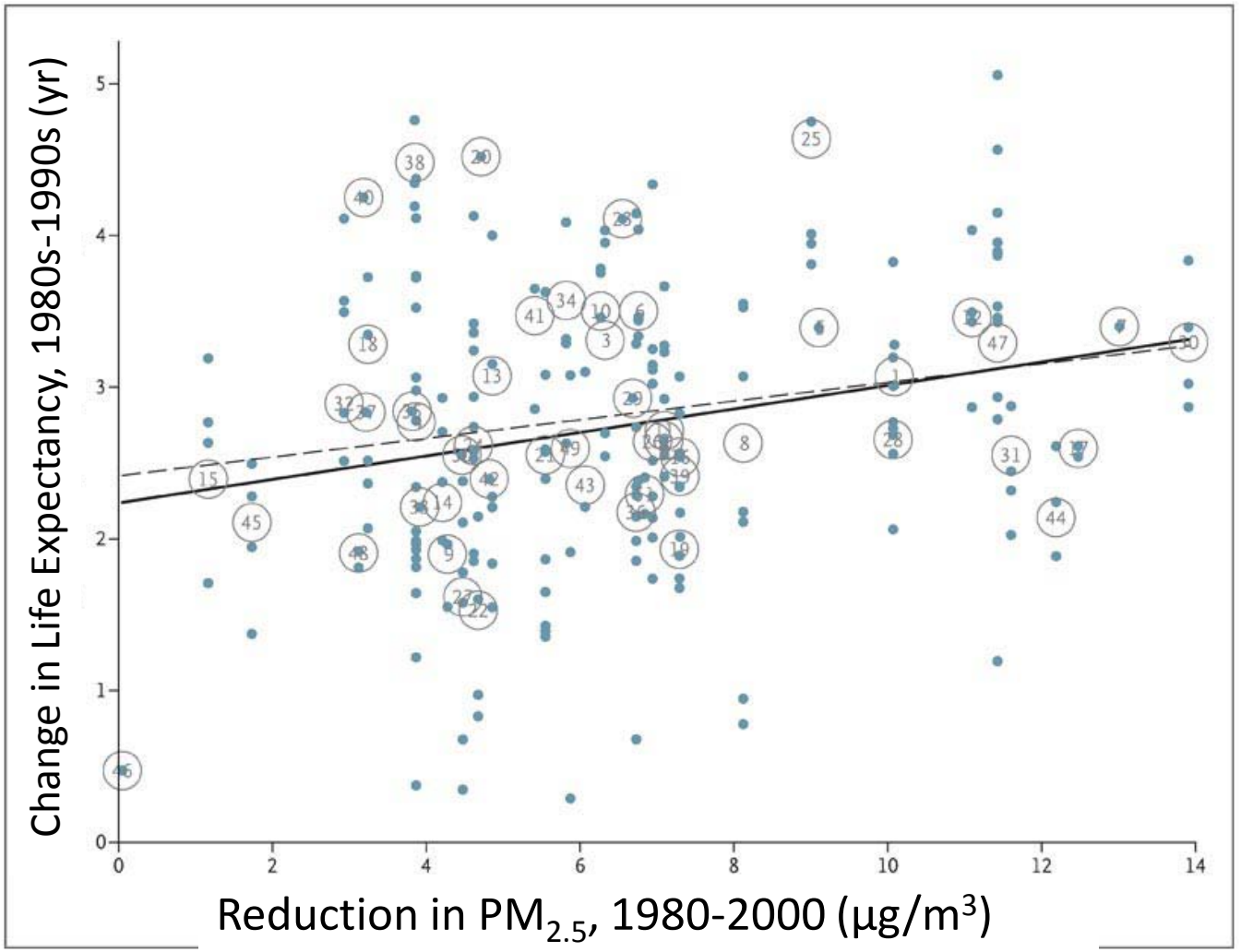


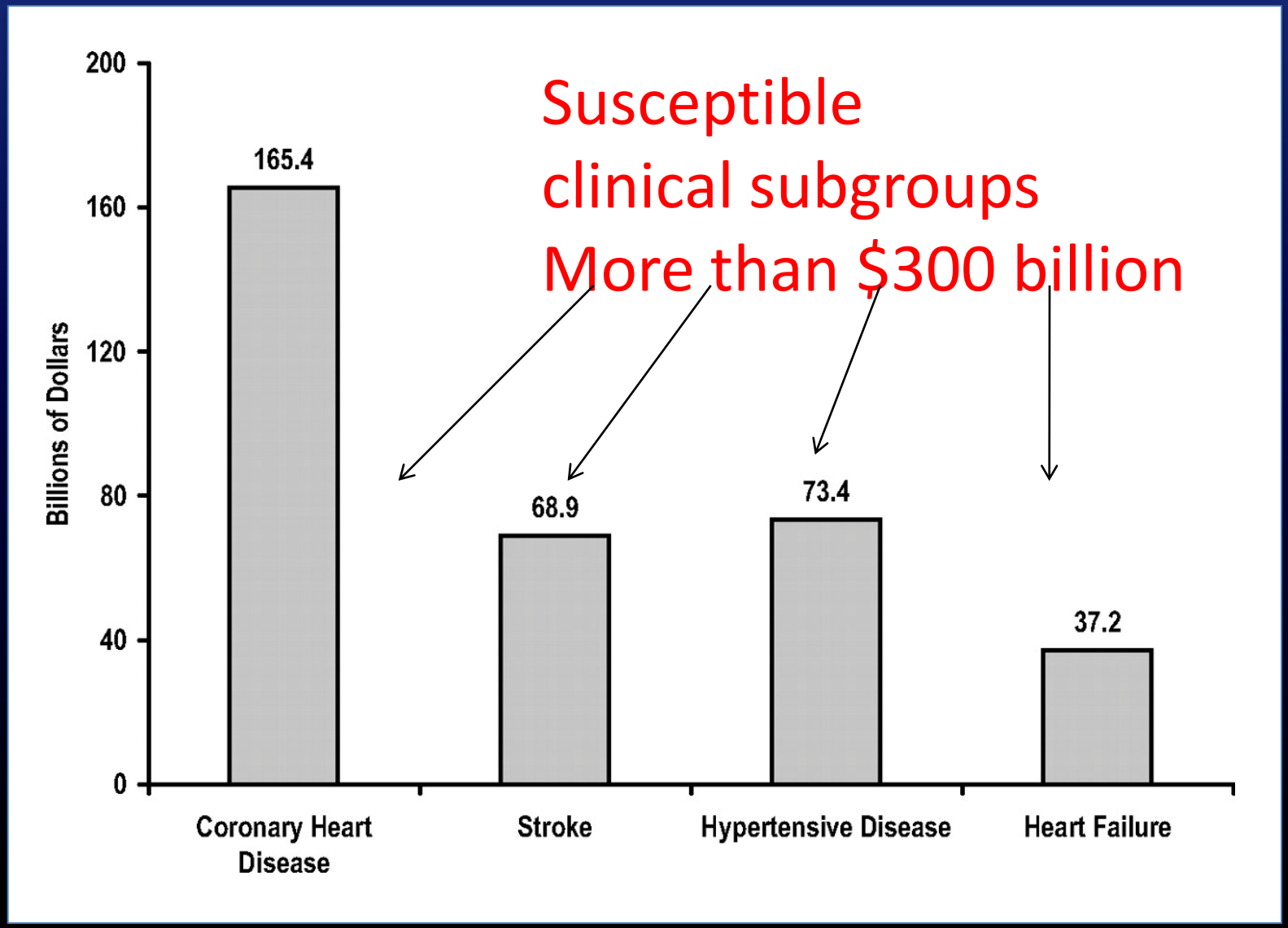
Laden et al. AJRCCM 2006

Lower Air Pollution - Increased Longevity

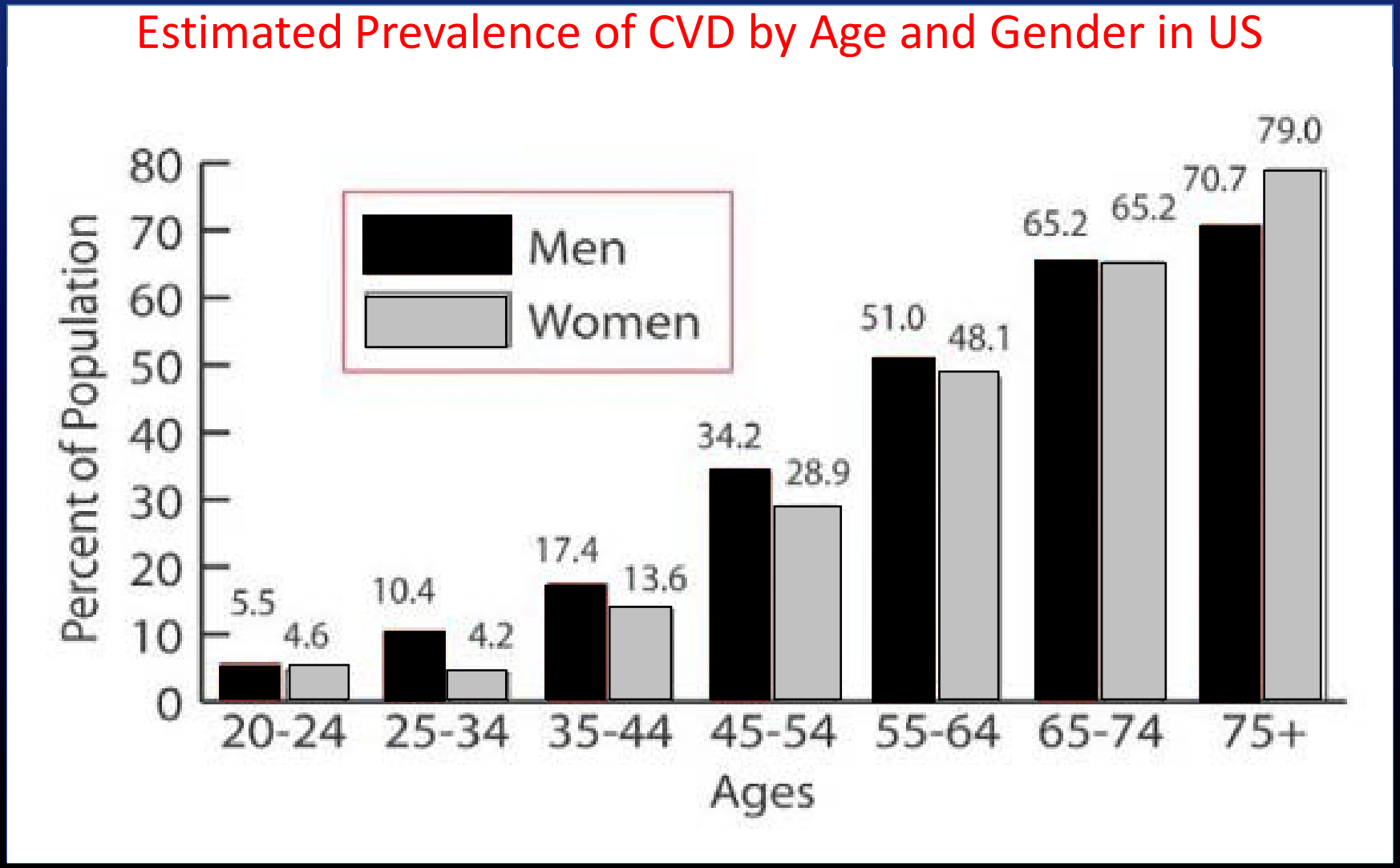


Pope et al. NEJM 2009

Estimated Direct and Indirect Costs of CV Disease & Stroke in the US



Susceptibility Increases with Age and Prevalent CVD



Source: AHA 2004 Heart and Stroke Statistical Update

What We Know with "Near Certainty"

- Short-term exposure to fine PM ($PM_{2.5}$)
  - Increases hospital admissions for CV disease
    - 0.5 to 3.4% per 10 $\mu g/m^3$ increase in $PM_{2.5}$
    - Ischemic heart disease and CHF increase risk
  - Increases CV mortality
    - 0.5 to 0.85% at mean 24-hr average $PM_{2.5} > 13 \mu g/m^3$
- PM_{10}
  - $PM_{2.5}$ contains $PM_{2.5}$ and findings generally follow $PM_{2.5}$
- Many studies implicate traffic related particles as a major contributor to morbidity and mortality

- For Ultrafine PM we know little with certainty.

What Do We Believe We Know?

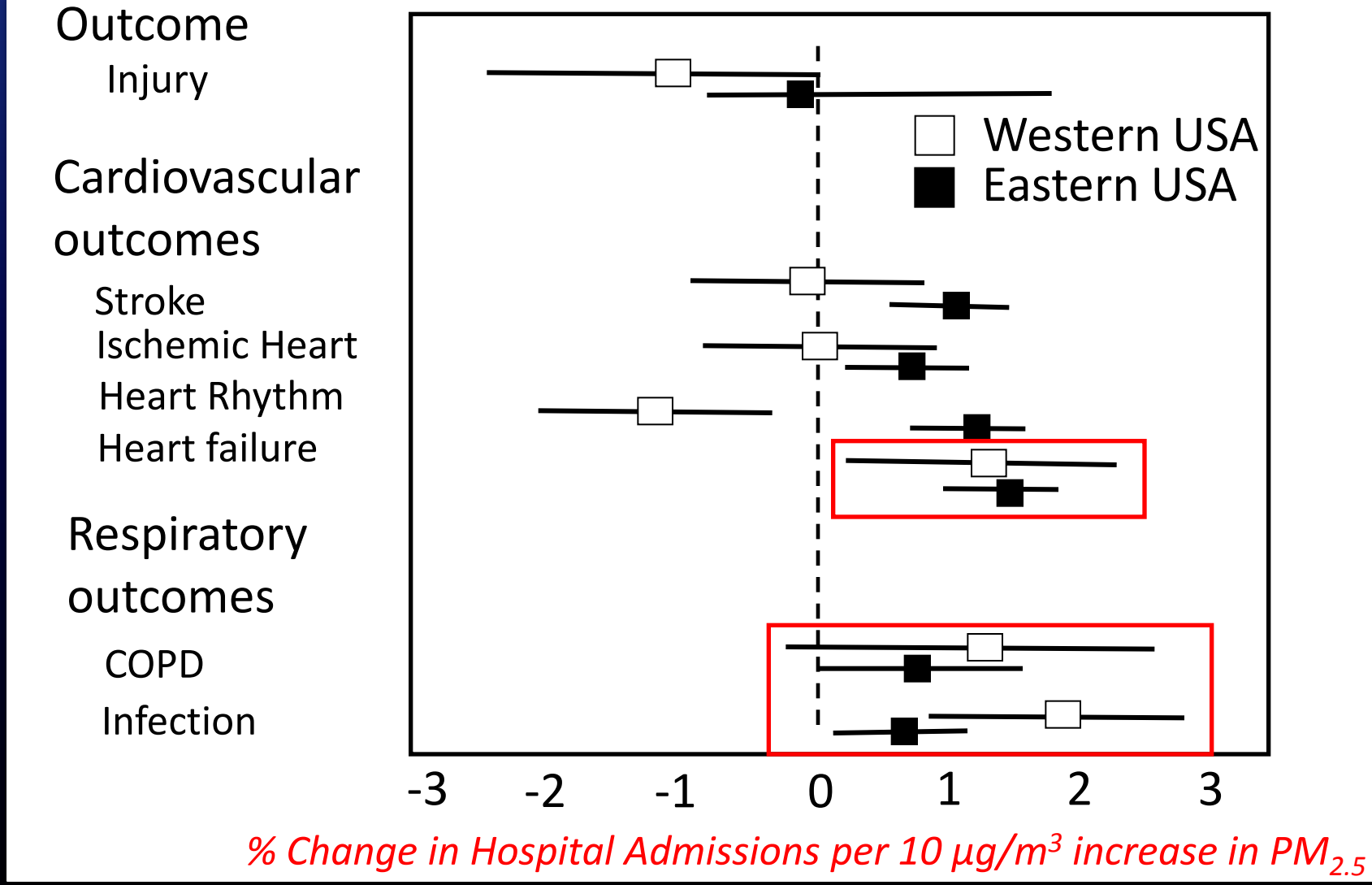
Health effects measured in epidemiological and human exposure studies associated with PM

- Pulmonary and systemic inflammation
  - Systemic and cardiovascular oxidative stress
- Blood pressure
- Heart Rhythm
  - Heart Rate Variability (HRV)
- Arrhythmia
- Ischemia
  - ST segment changes
- Vascular function
  - Most consistent finding after CAPs and diesel exhaust
- Hemostasis and thrombosis
- Cardiac contractility

What We Do Not Know

- Are the respiratory and cardiovascular health effects associated with PM in susceptible populations:
  - secondary to ultrafine, fine, coarse PM, gases or some combination
  - related to oxidative stress, alterations in hemostasis and thrombosis, neural activation, or other mechanisms
- Does Ultrafine PM have short-term or long-term neurological consequences?
- What sources and/or constituents are most important?
- Are the effects additive or synergistic with other pollutants?
- To what extent does genetic background or epigenetics contribute?

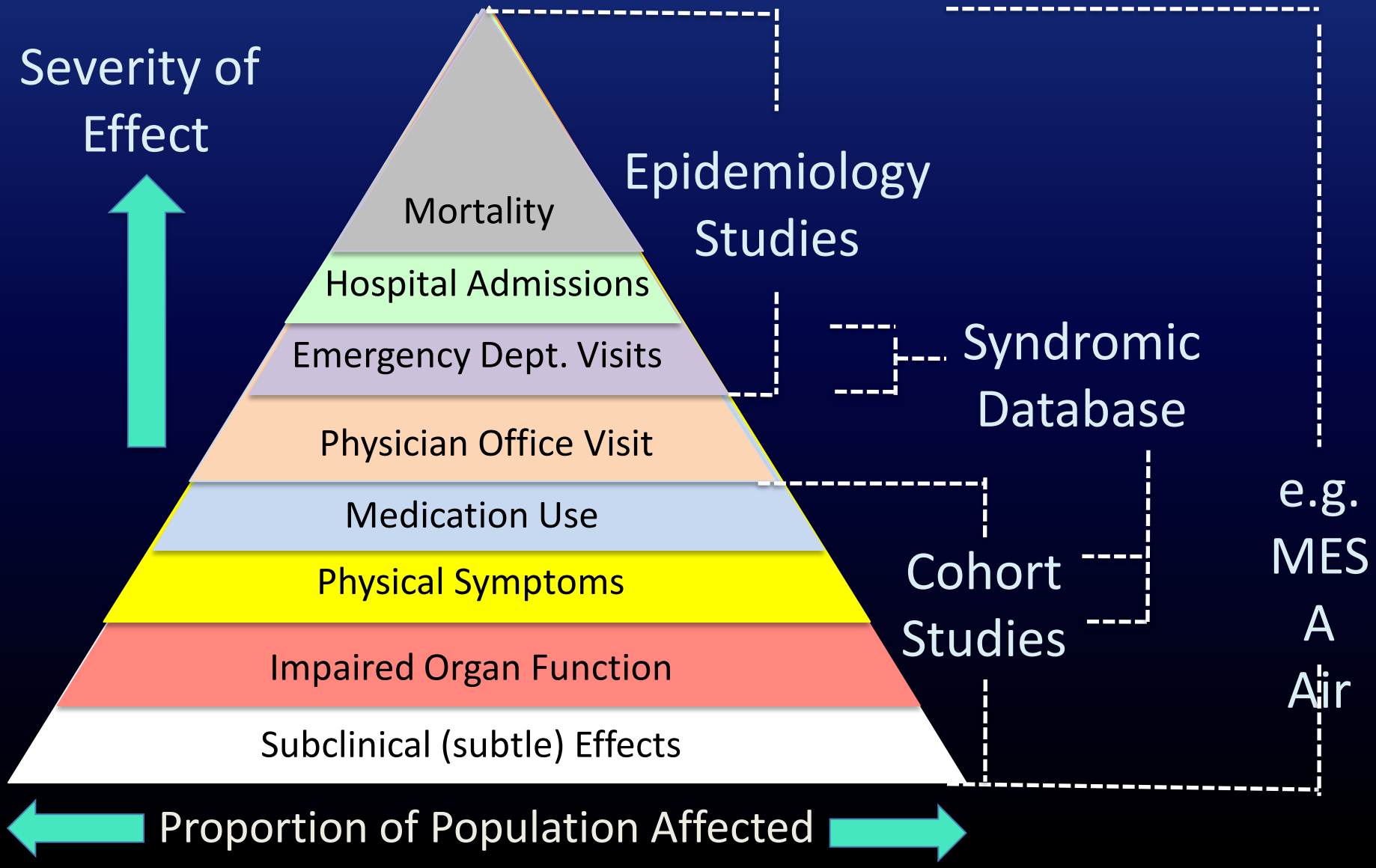
Regional $PM_{2.5}$-Associated Hospitalization



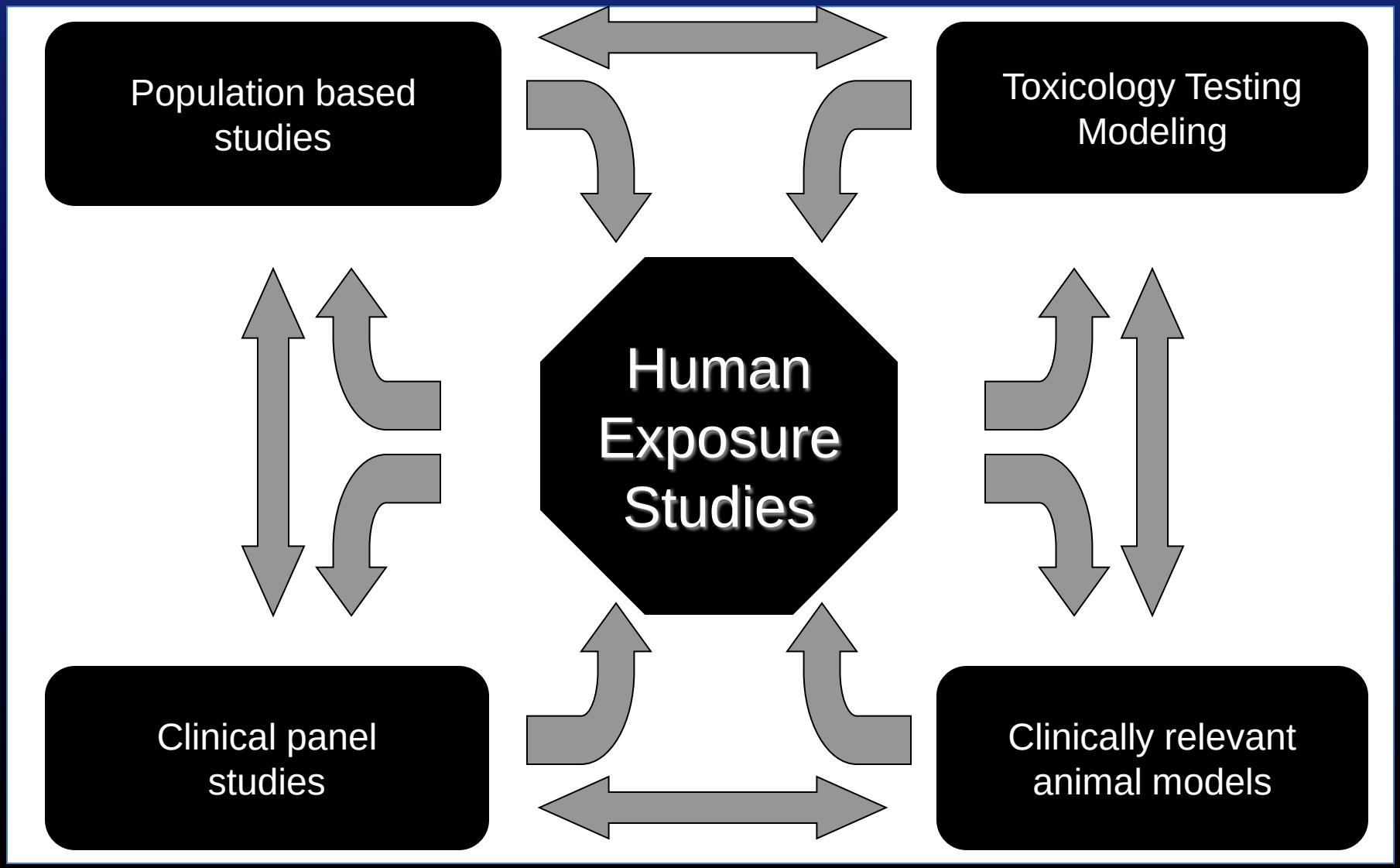
Dominici et al, JAMA, 2006

Air Pollution Health Effects Pyramid

Progression of Effect



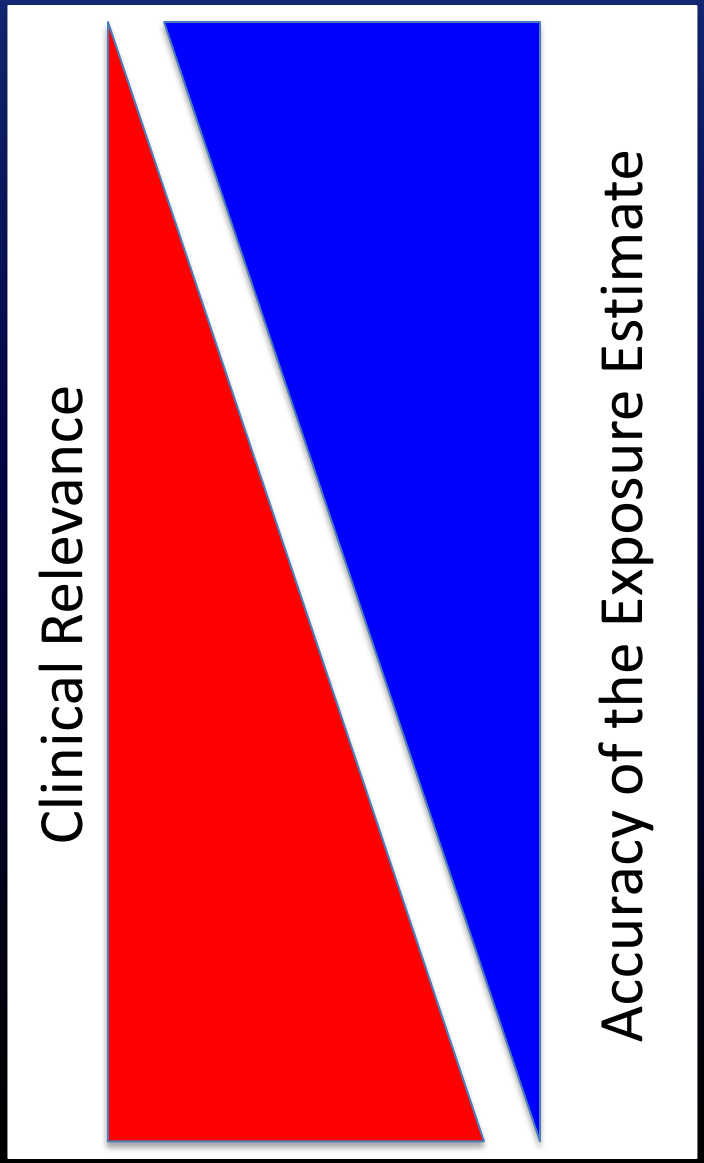
How Do We Learn About Health Effects



Scientific Methods Used to Study Health Effects

Strengths and Limitations of Experimental Models

- **Animal toxicology Studies**
  - Exposure precisely defined
  - Controlled conditions
- **Chamber Studies**
  - Small number of subject
  - Exposures are well defined
  - Case cross-over designs
  - Short-term effects
- **Cohort studies**
  - Small number of subjects
  - Exposures are less well defined
  - Repeated measure design
  - Short-term effects
- **Epidemiology studies**
  - Large number of subjects
  - Exposures are significant limitation
  - Cross sectional designs
  - Short-term and long-term effects

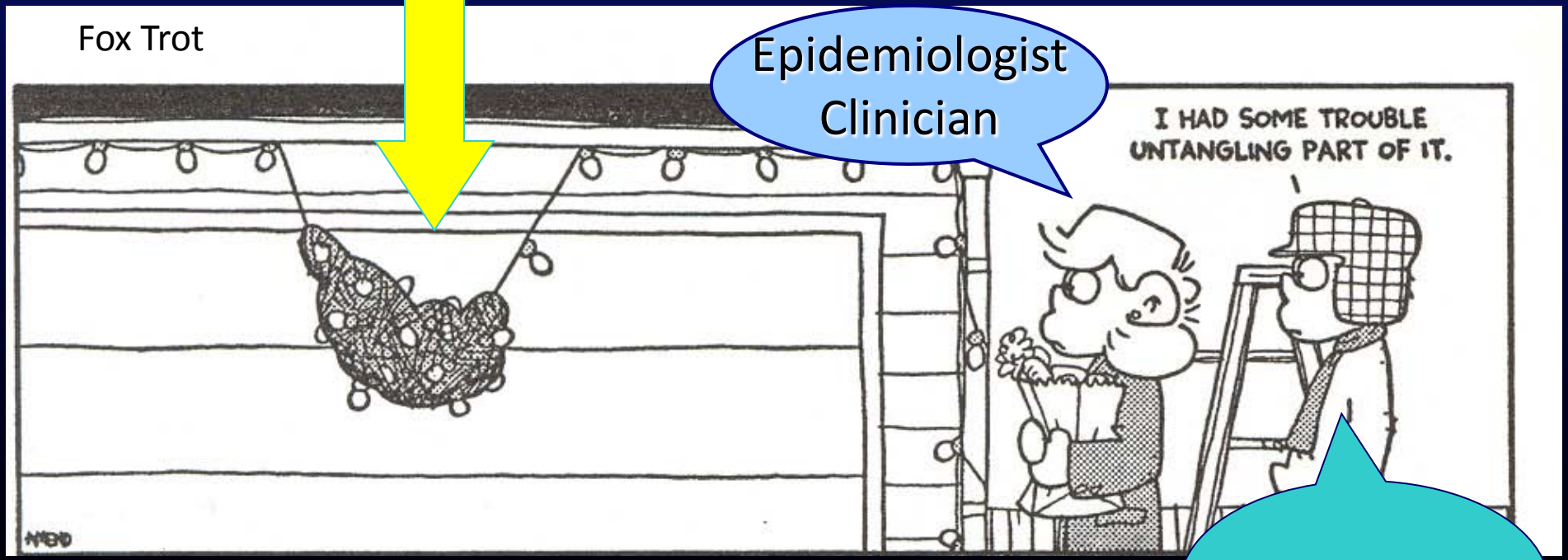


Mechanisms of Systemic Toxicity of PM

PM Exposure

Mechanisms

Morbidity
Mortality
Physiological and biochemical endpoints



PM: A New Challenge to Air Pollution Toxicologists

- For many years toxicologists focused on respiratory tract responses to air pollutants:
  - Ozone
  - NO_2
  - SO_2
- The association between PM and cardiovascular effects required a new approach to the study of air pollution:
  - Autonomic nervous system effects
  - Cardiac effects
  - Vascular effects (hemostasis and thrombosis, inflammation, endothelial function)
  - Systemic antioxidant defenses

Combustion-Related Ultrafine PM (Nanoparticles)

Specific challenges related to identifying and measuring health effects of ultrafine PM

Epidemiology Studies

- Few studies address short-term and long-term health effects of UFPM
- Few direct measures of UFPM
- Typically epidemiology studies measure $PM_{2.5}$ and then report:
  - Traffic-related indicators (NO_2, CO, black carbon, and organic carbon)
  - Proximity to roadways

Human Concentrated Air Particle Studies

- Ambient air (Constituents of UFPM will depend on the airshed)
- Diesel-exhaust
- Man-made PM (TiO_2, carbon particles)

Animal Studies

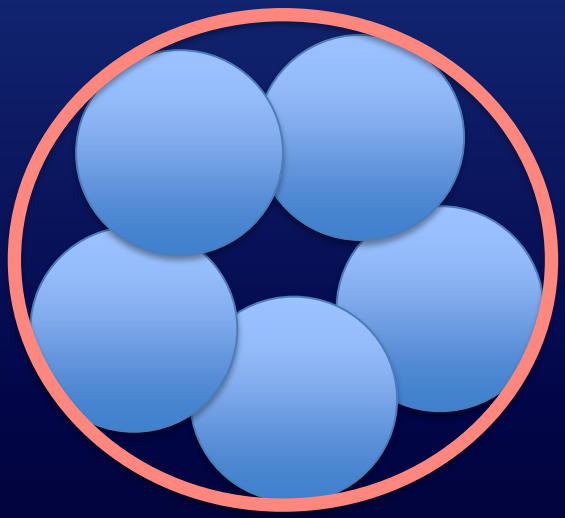
- CAPs studies,or diesel emissions
- Man-made PM

What Properties of PM are Responsible for these Effects?

- Ambient Particles include:
  - Inorganic components (sulfates nitrates, ammonium)
  - Trace metals
  - Elemental and organic carbon
  - Adsorbed volatile and semi-volatile components
  - Crustal materials
  - Biological components (e.g. bacteria, spores, pollen in coarse PM)

- In addition to particle chemistry, particle size is also an important component of toxicity:
  - Dosimetry in the lung
  - Translocation from the lung to other organs

Relative Size of Particulate Matter



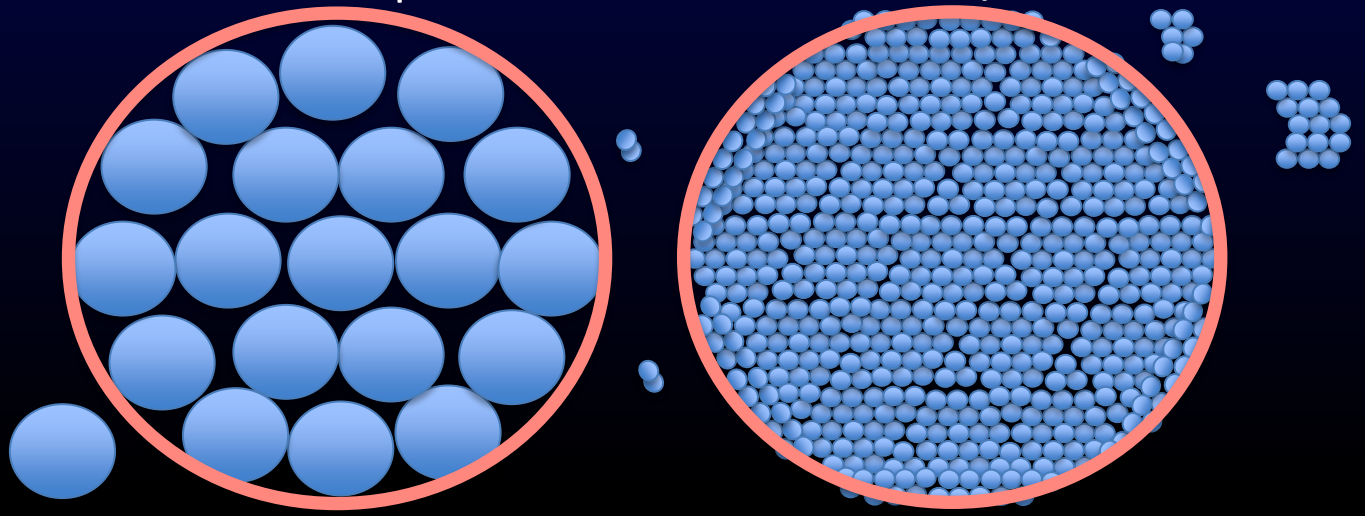
COARSE
2.5-10 µm

UF PM have -

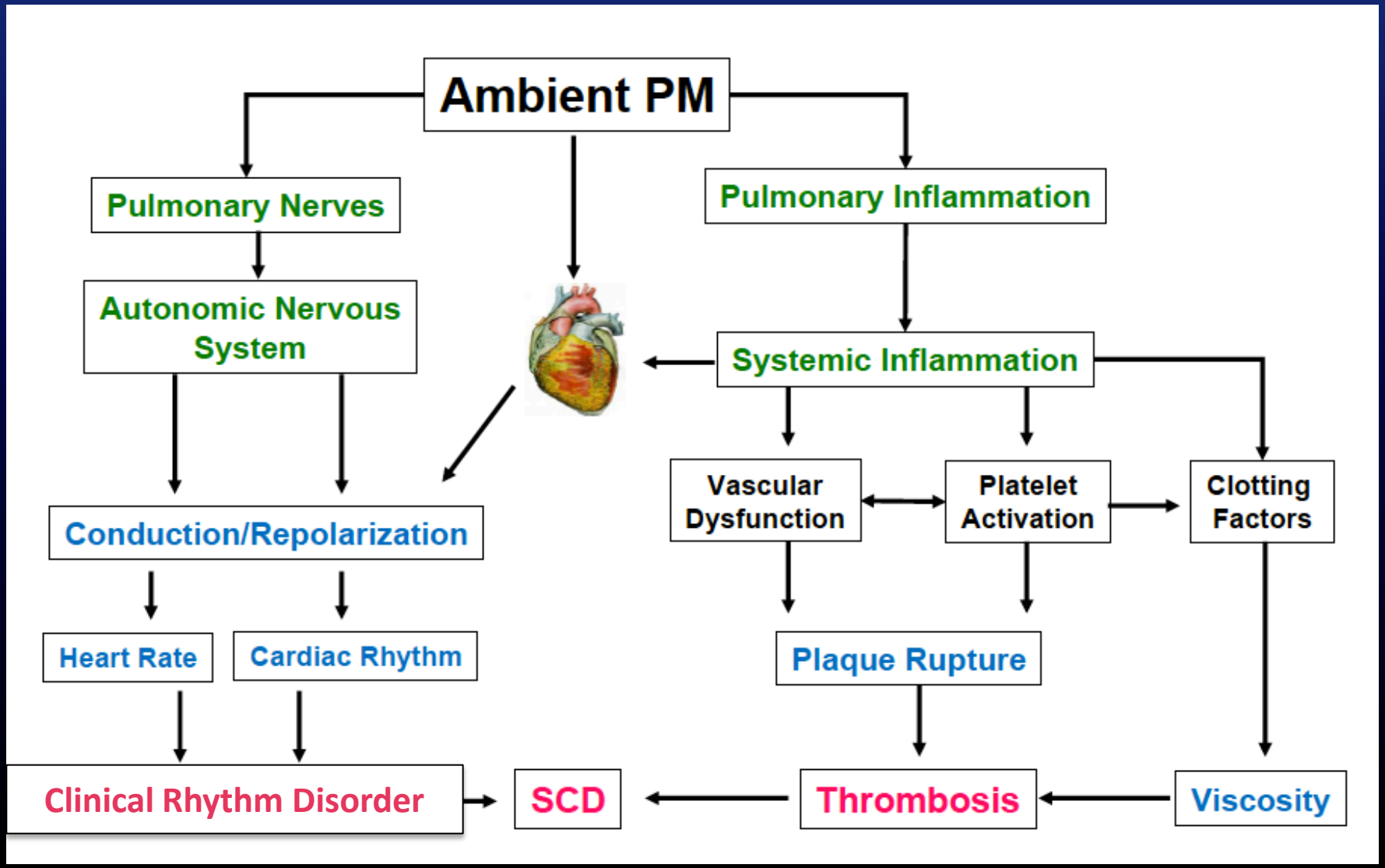
- greater surface area than larger PM particles
- greater thrombogenic potency and oxidative potential
- the capability to translocate to other organs
- greater efficiency of deposition within the lung with deeper penetration.

FINE
<2.5 µm

ULTRAFINE
<0.1 µm

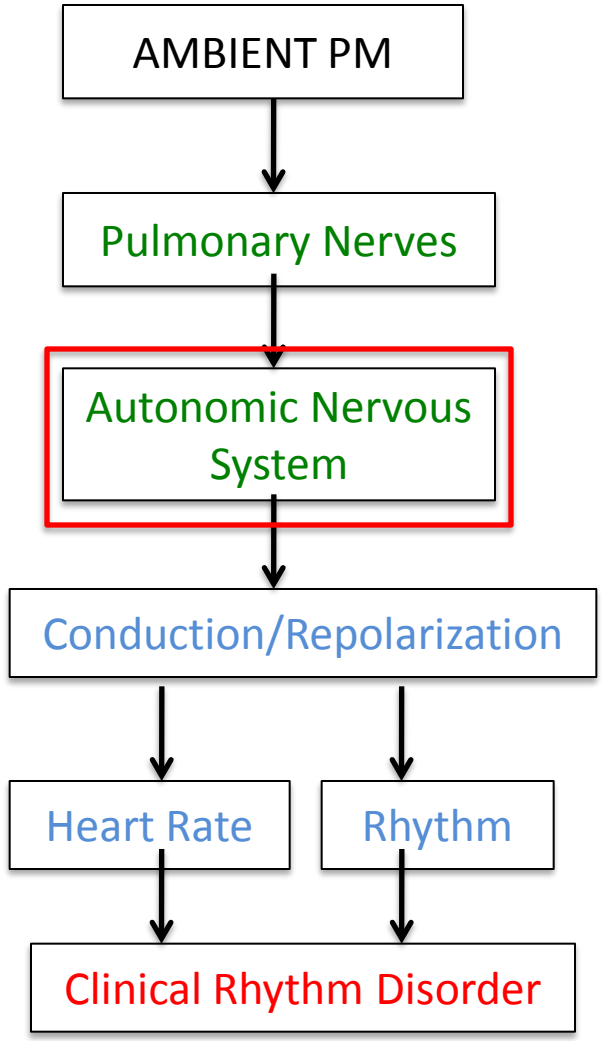


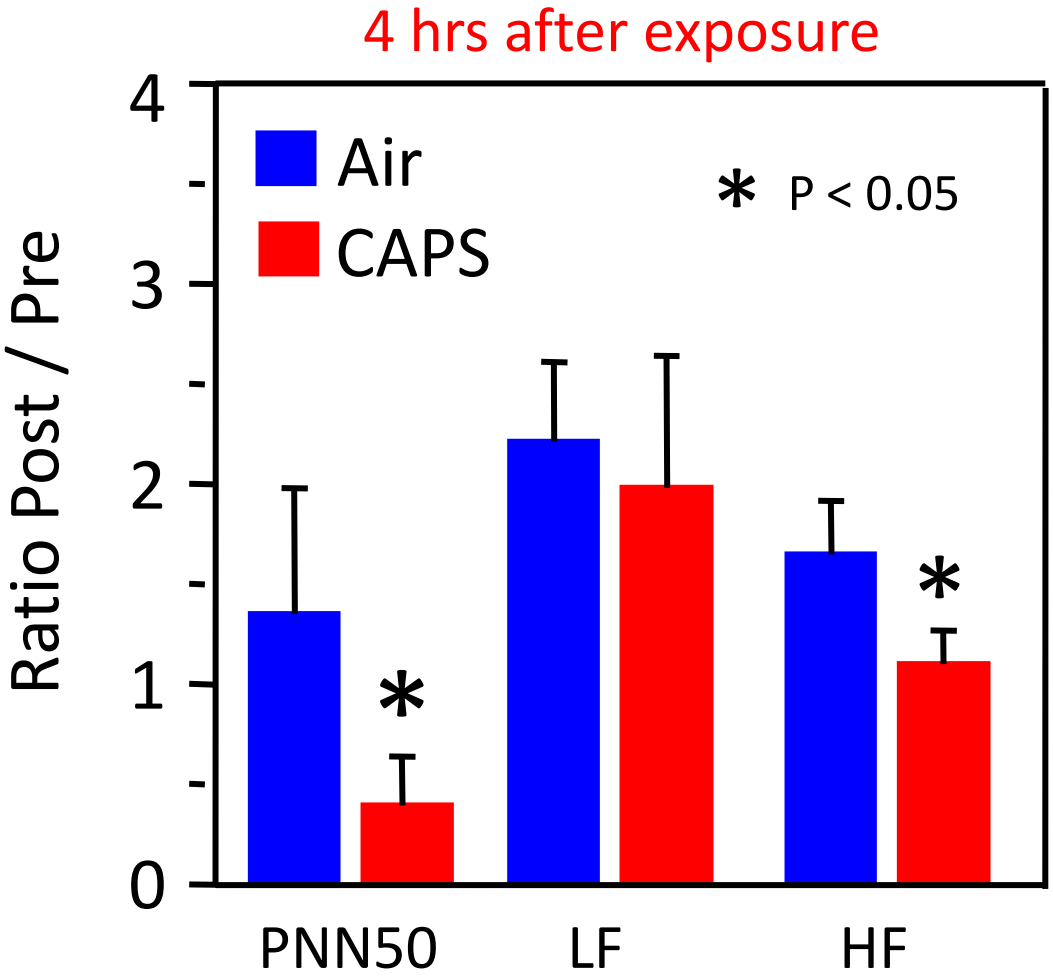
Mechanistic Pathways of Combustion-Related UFPM-Induced Cardiorespiratory Effects



Fine PM CAPS Affects the Autonomic Nervous System

Healthy Aged-Adult Cohort Chapel Hill, NC, USA Airshed

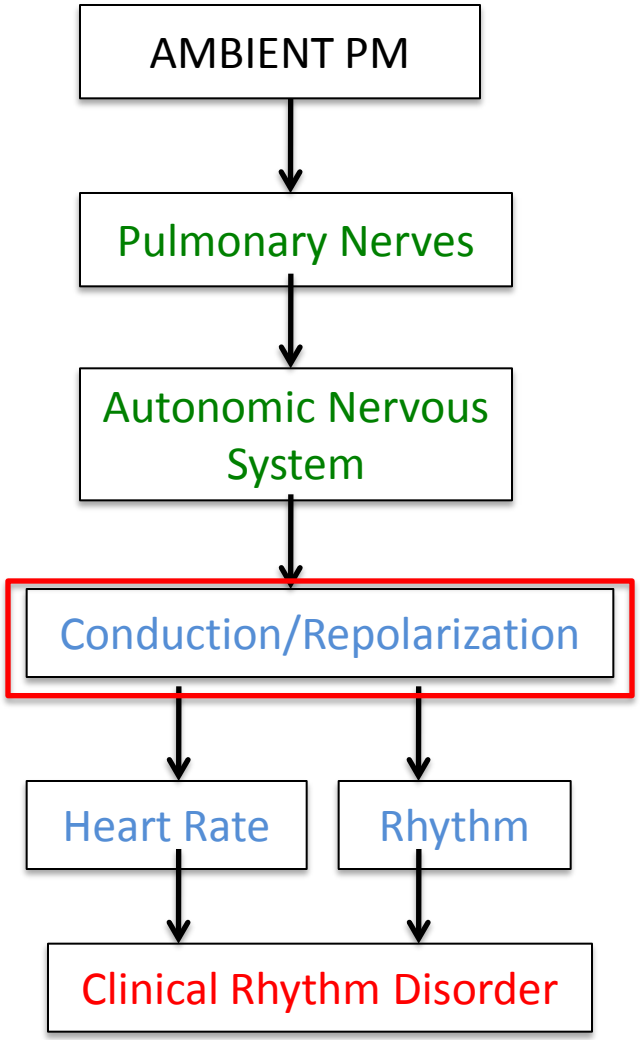




Devlin et al. Eur Resp J 2003

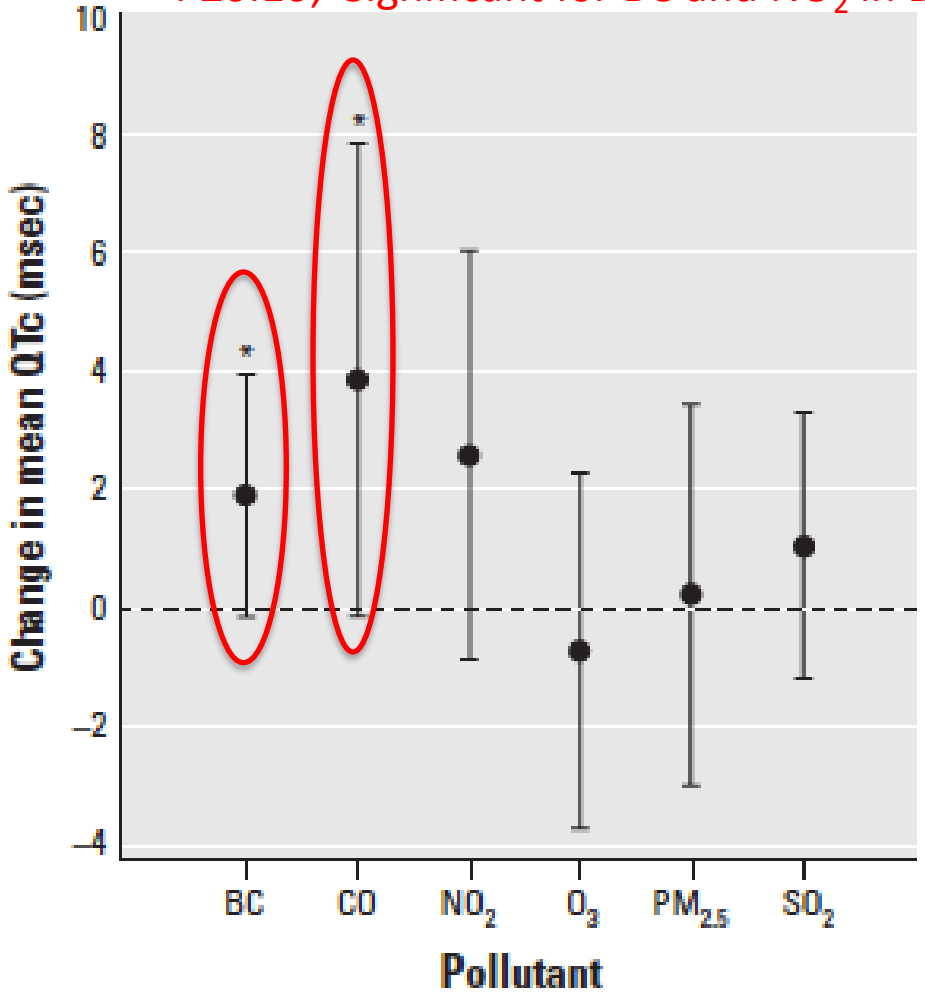
Traffic-Related Change in QTc per IQR

Veterans Affairs Normative Aging Study – Boston, MA Airshed



Cumulative exposure to pollutant during previous 10 hr

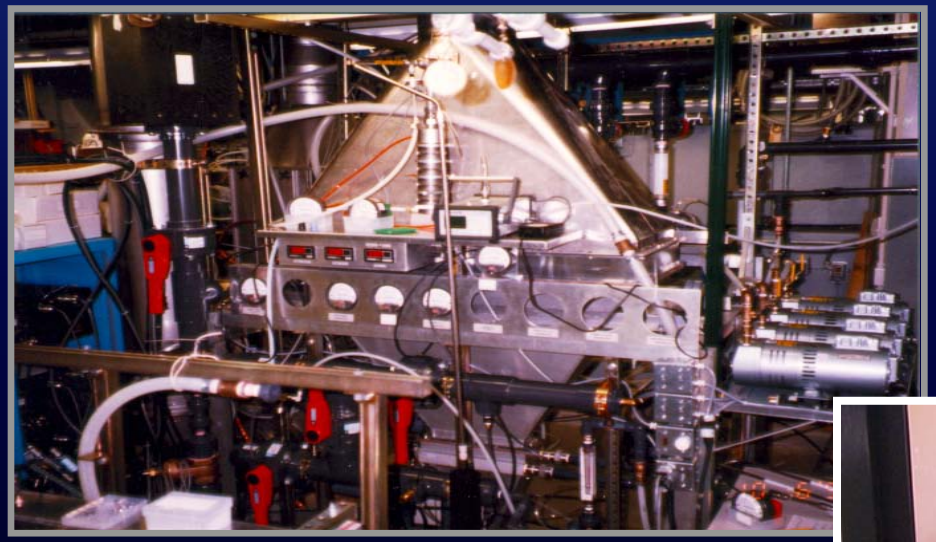
* P≤0.10; Significant for BC and NO_2 in DM



Baja et al. EHP 2010

Concentrated Air Particle Studies

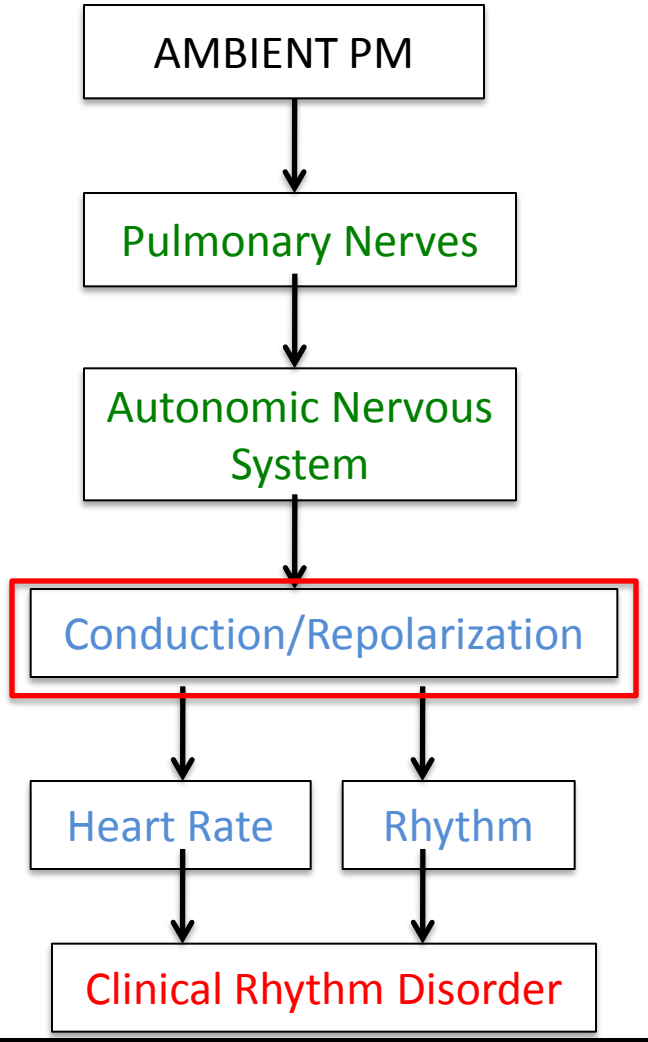
National Health Effects and Environmental Research Laboratory (NHEERL) Chapel Hill, NC

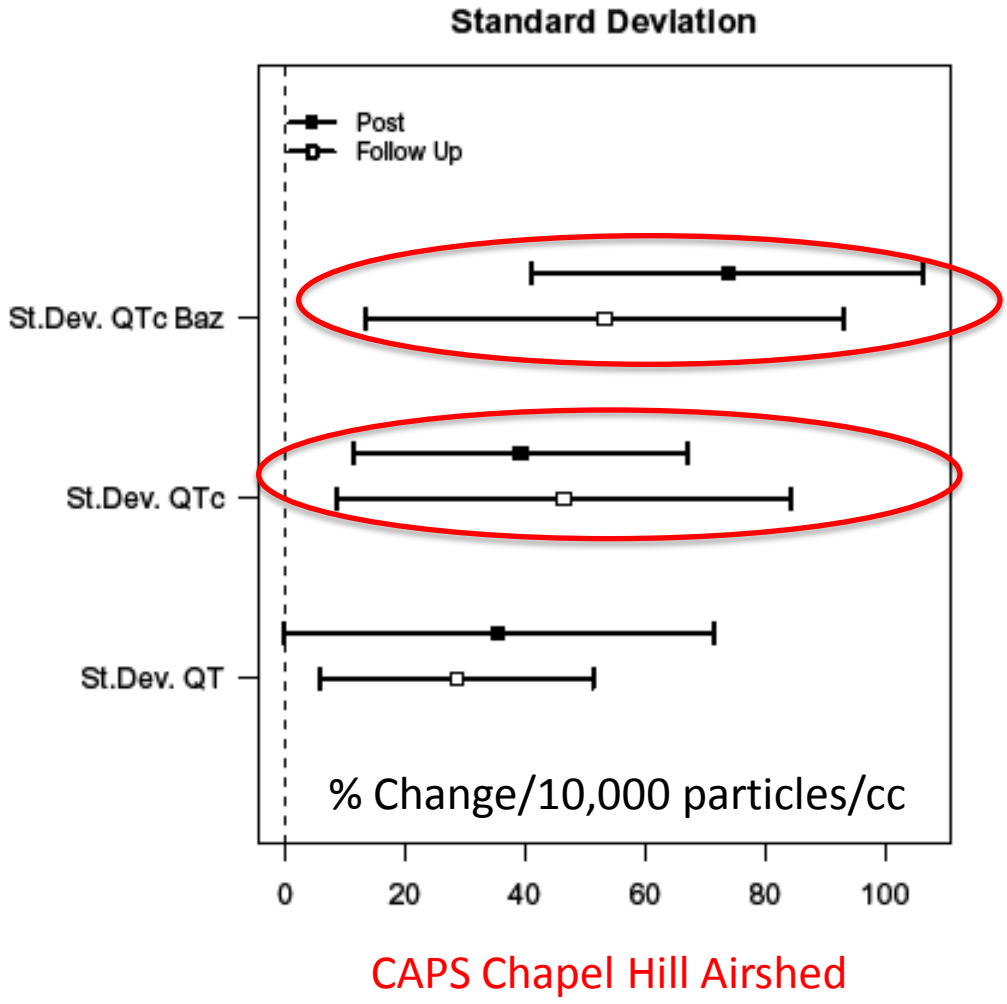


Particle concentrator

Exposure chamber

Ultrafine PM Modifies Cardiac Electrophysiology and Cardiac Repolarization

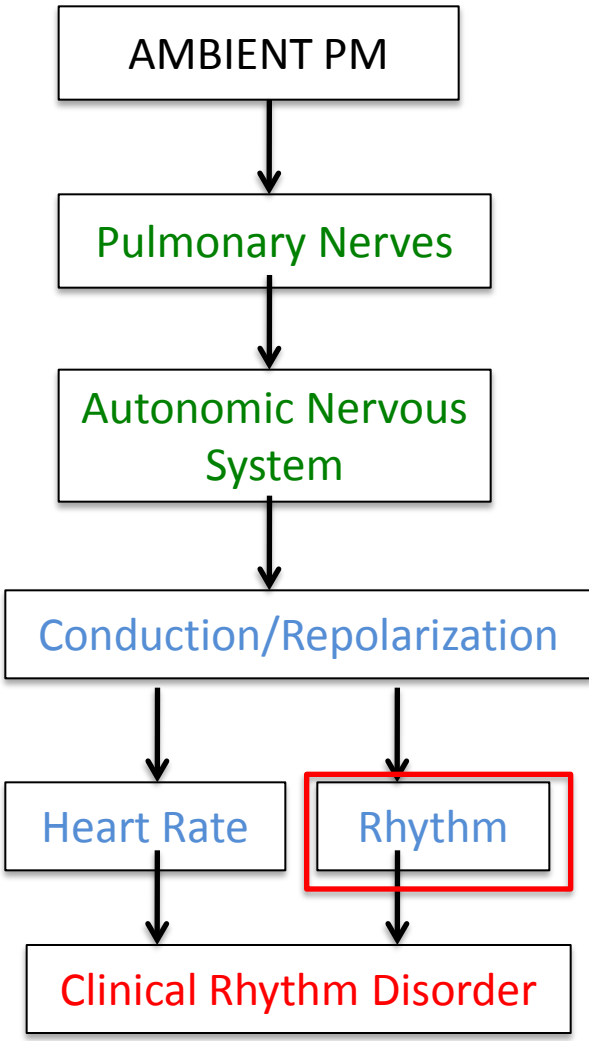




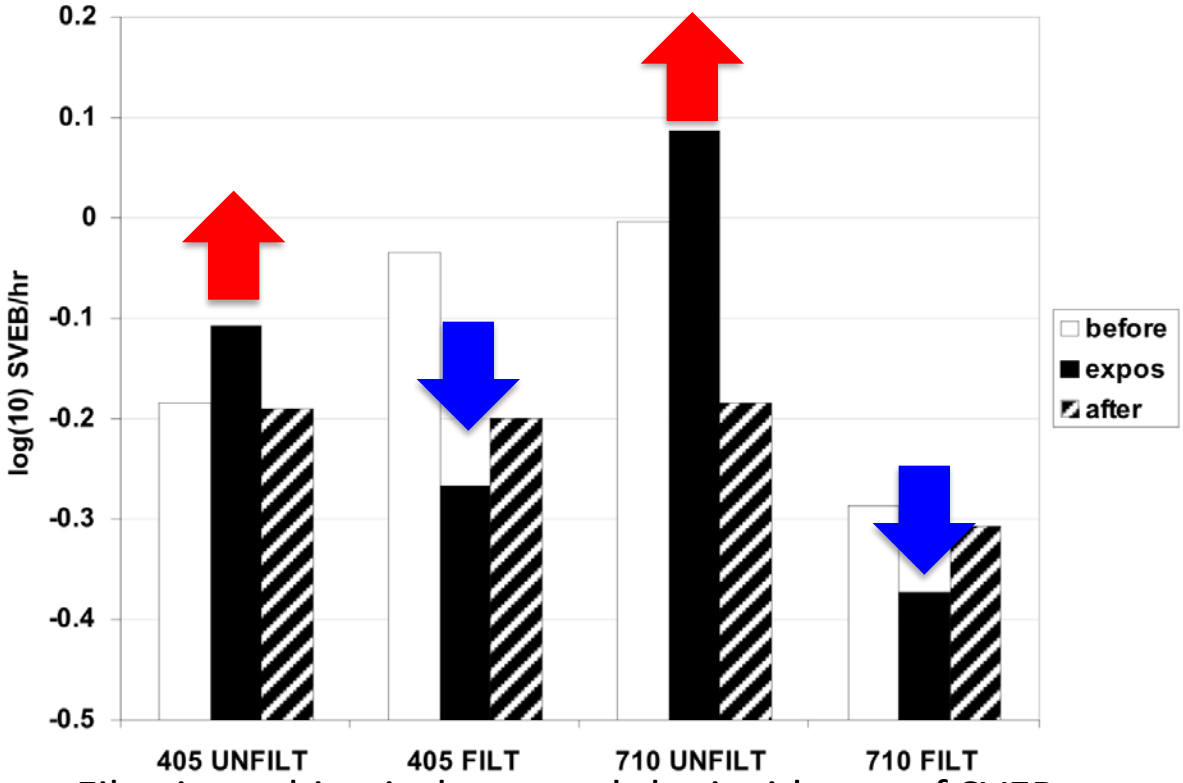
Samet et al., 2008

Exposure to Traffic-Related UFPM and PAH Increases the Frequency of Premature Heart Beats

California Freeway Study: Highway Air vs Filtered Highway Air



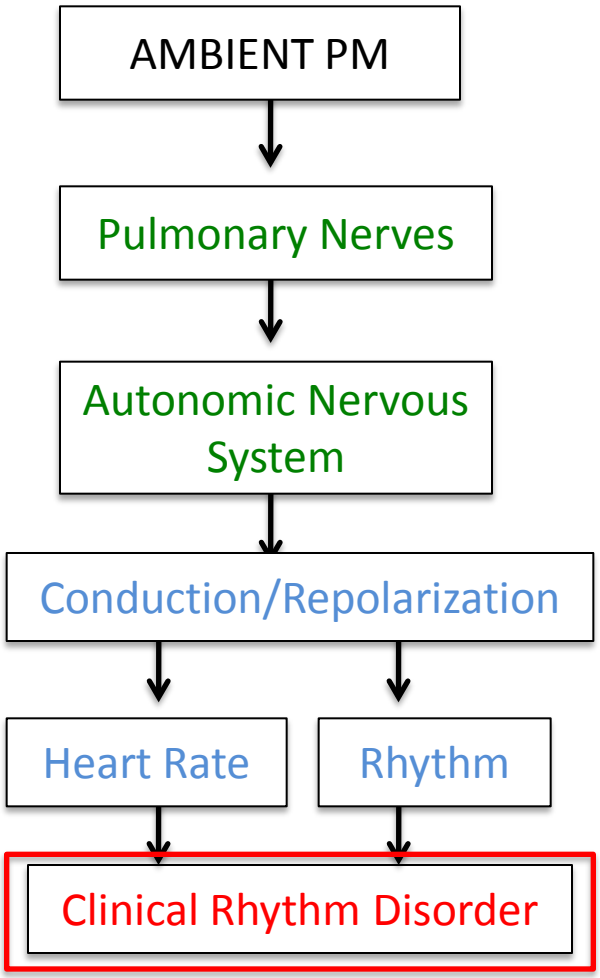
Mean incidence of supraventricular ectopic beats (SVEBs/hr) before, during and after exposure



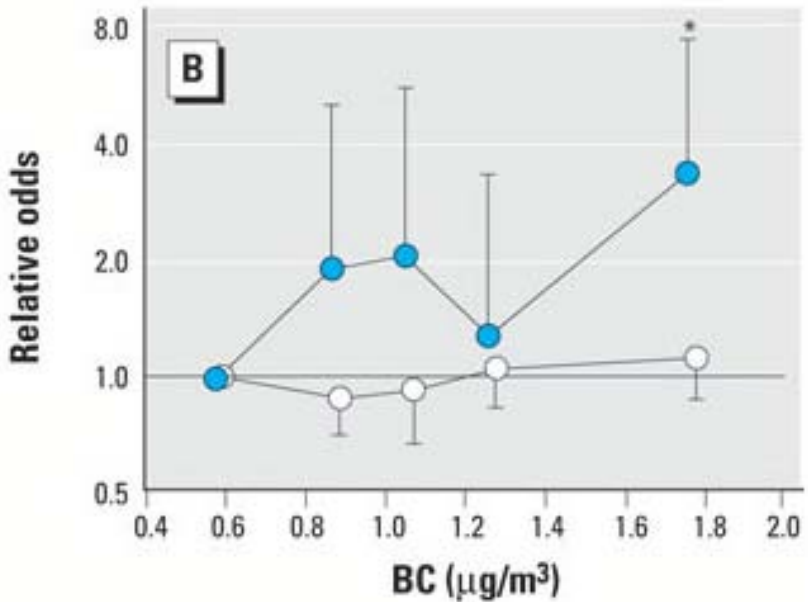
- Filtering cabin air decreased the incidence of SVEBs.
- No associations between UFPM and ventricular arrhythmia

Traffic-Related PM Increases the Frequency of Serious Ventricular Arrhythmia

ICD Cohort: Boston, MA Airshed



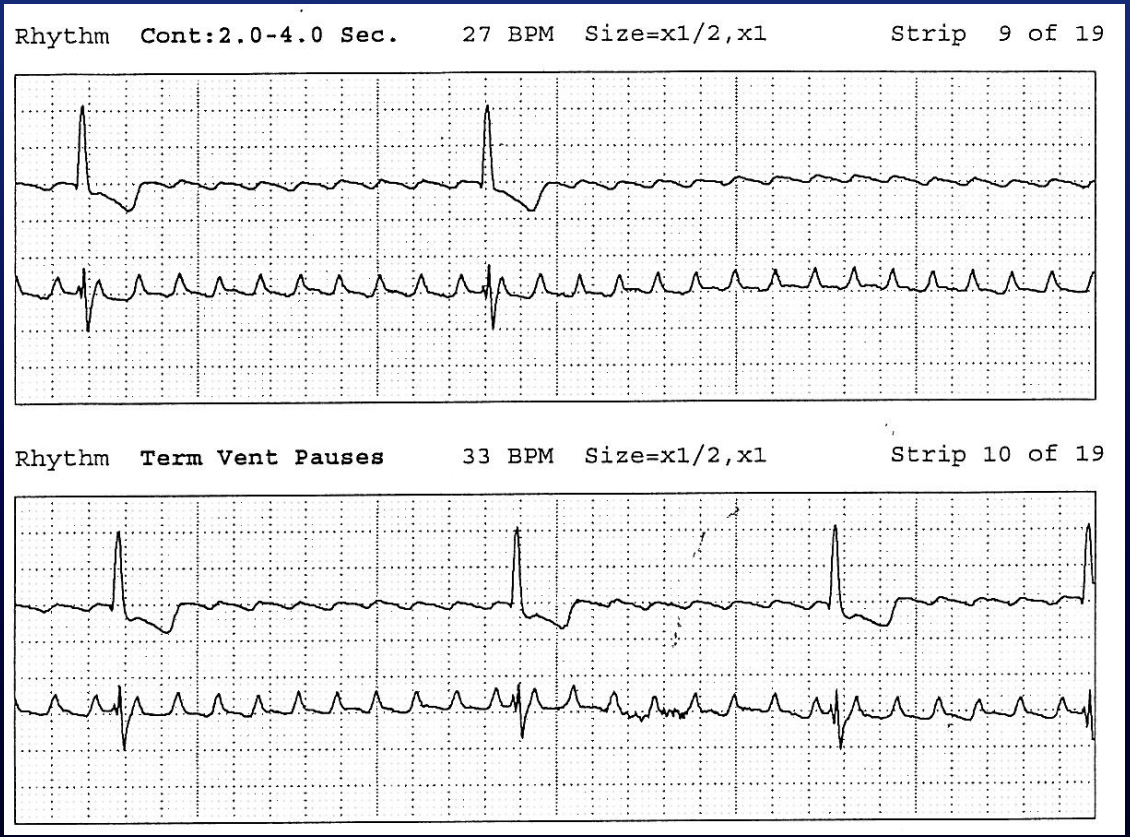
Relative Odds of a Ventricular Arrhythmia



- Ventricular arrhythmia detection more likely during a time of electrical instability.
- Association with black carbon (BC) suggest traffic exposure

Dockery et al. EHP 2005

Atrial Flutter with High-Grade AV Block



Risk factors for atrial fibrillation and atrial flutter

- Age greater than 60 years
- Ischemic heart disease
- Valvular disease
- Large left atrium
- Premature supraventricular beats

If traffic-related combustion product exposure increases premature supraventricular beats, then to what extent does air pollution contribute to atrial fibrillation and atrial flutter?

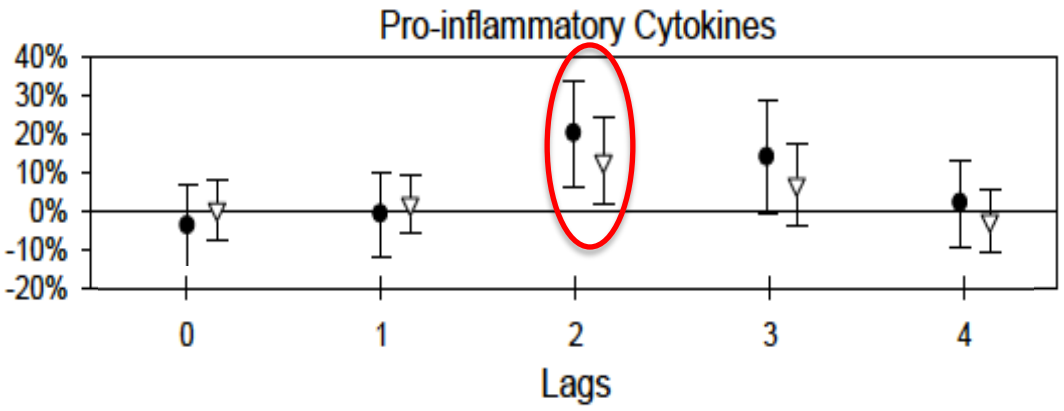
Consequences of atrial fibrillation and atrial flutter

- Palpitations and shortness of breath
- Fatigue and exercise intolerance
- Stroke and myocardial infarction
- Heart failure

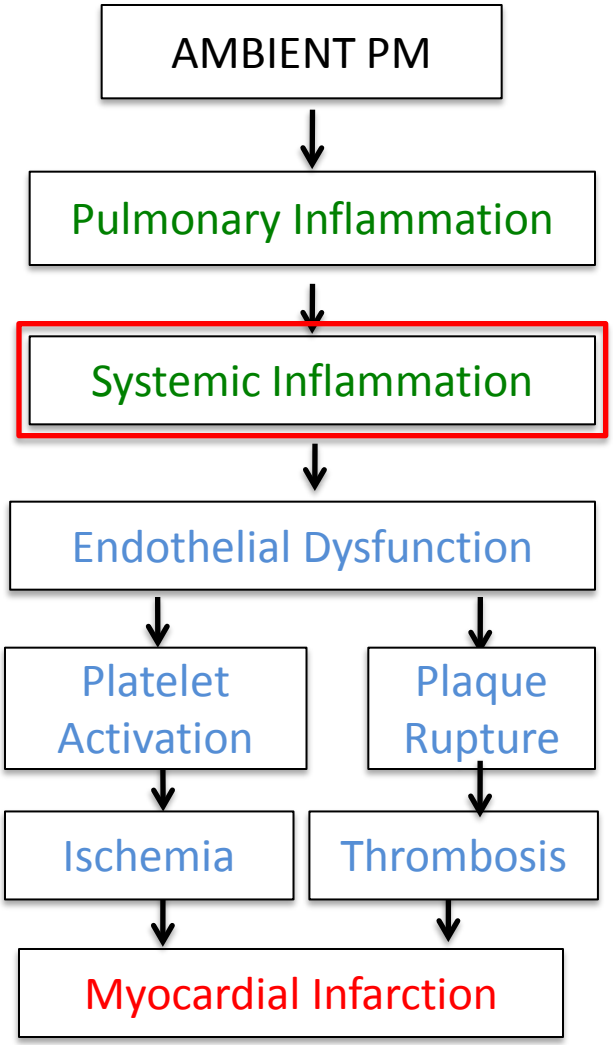
Fine PM Modulates Systemic Inflammation

Diabetic Cohort Repeated Measures: Chapel Hill, NC, USA Airshed

IL-6 (solid circle) and TNF-alpha (open triangle)



- % Change in mean IL-6 (solid circle) and TNF-a (open triangles) per 10µg/m^3 increase in $PM_{2.5}$
- IL-6 and TNF-a increase with a lag of 2 days

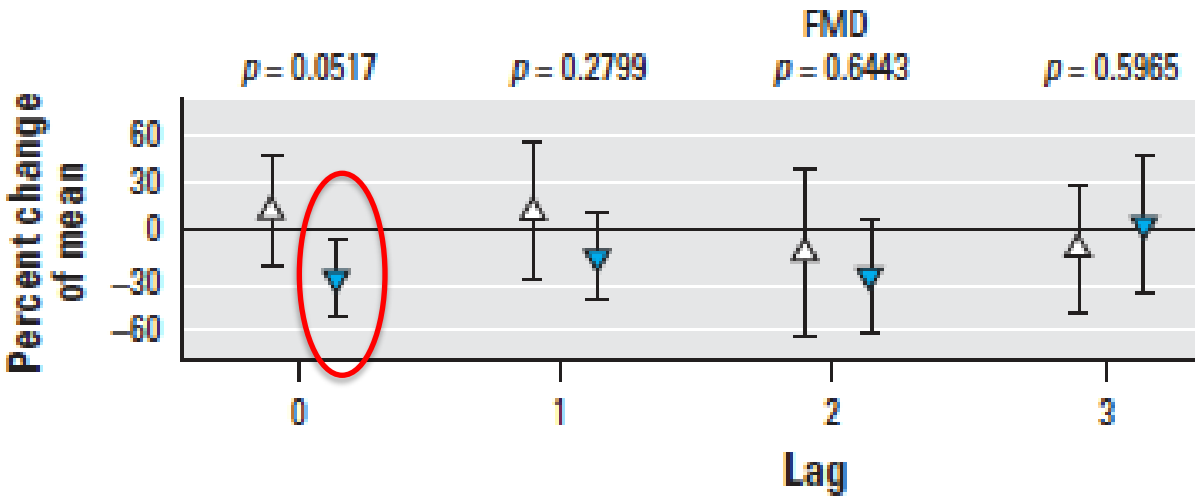


Schneider et al. P&FT, 2010

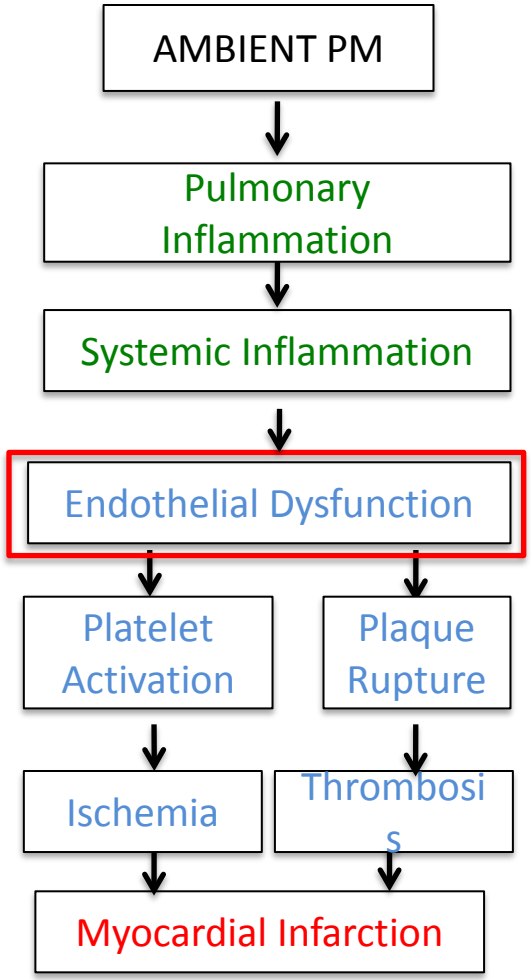
Fine PM Modulates Endothelial Function

Diabetic Cohort Repeated Measures: Chapel Hill, NC, USA Airshed

Effect modification of FMD by GSTM1 genotype



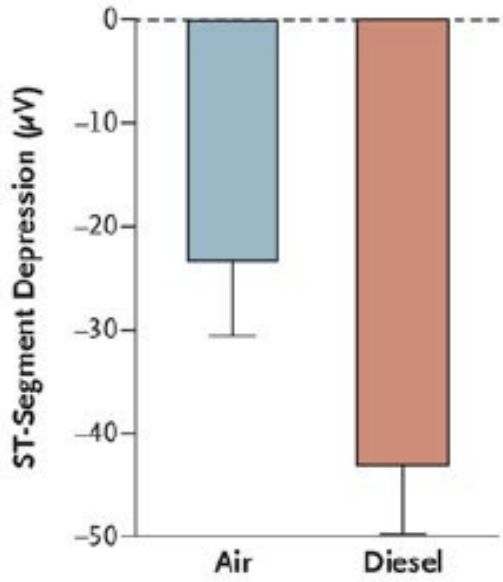
- Diabetic patients with GSTM1 null shows an immediate decrease FMD to hyperemic stress



Schneider et al. EHP 2008

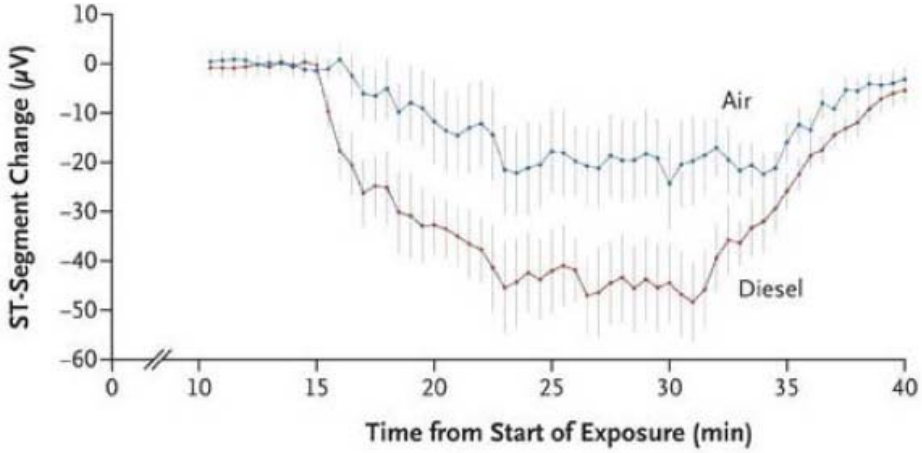
Ultrafine PM Increases Ischemia

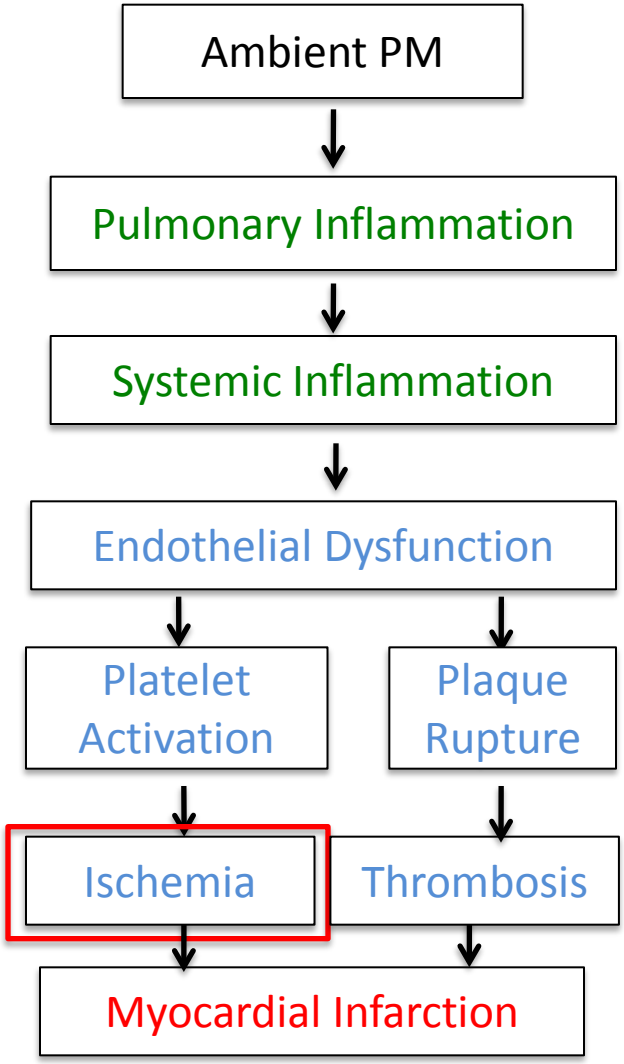
Diesel emissions at 300 µg/m^3



N=20, History of MI
Increase of ST depression suggests increased magnitude of ischemia

Pekkanen et al. 2002
Showed Increased ST depression with UFPM in a cohort of CAD patients.

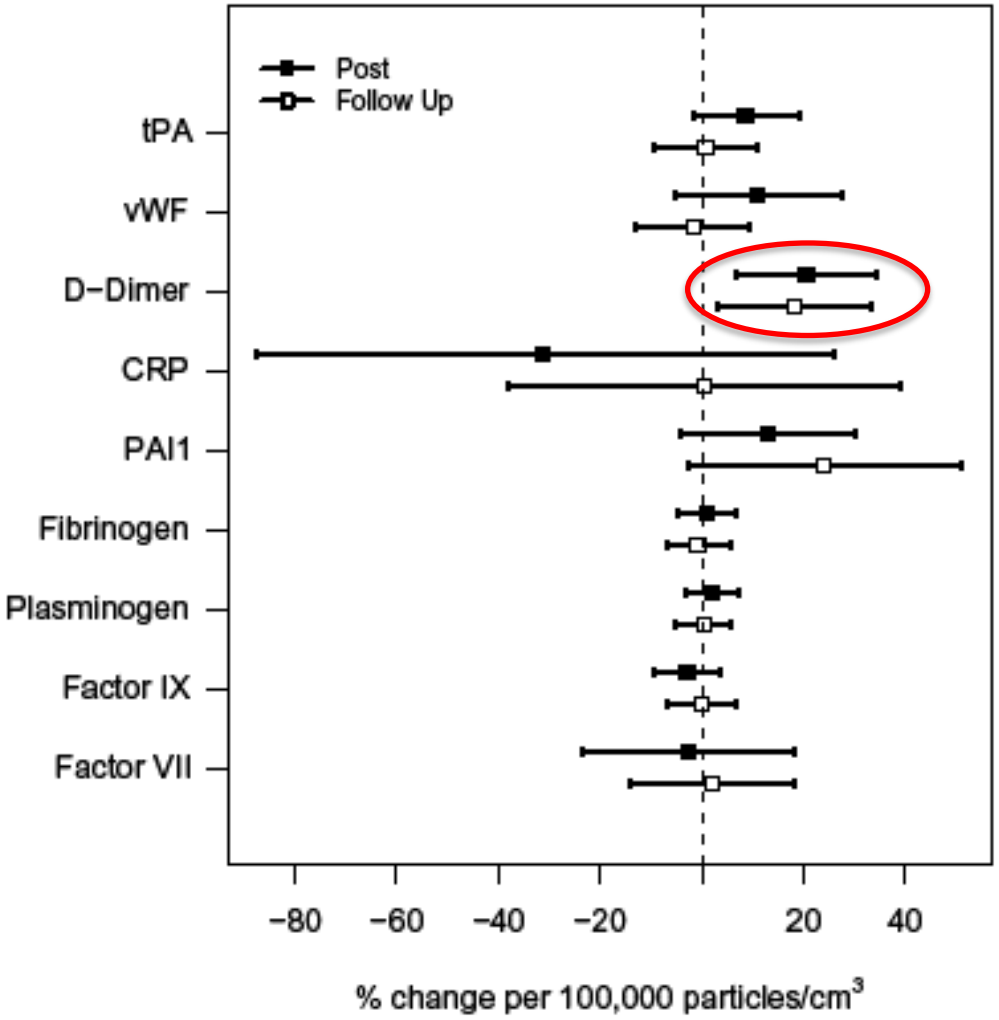


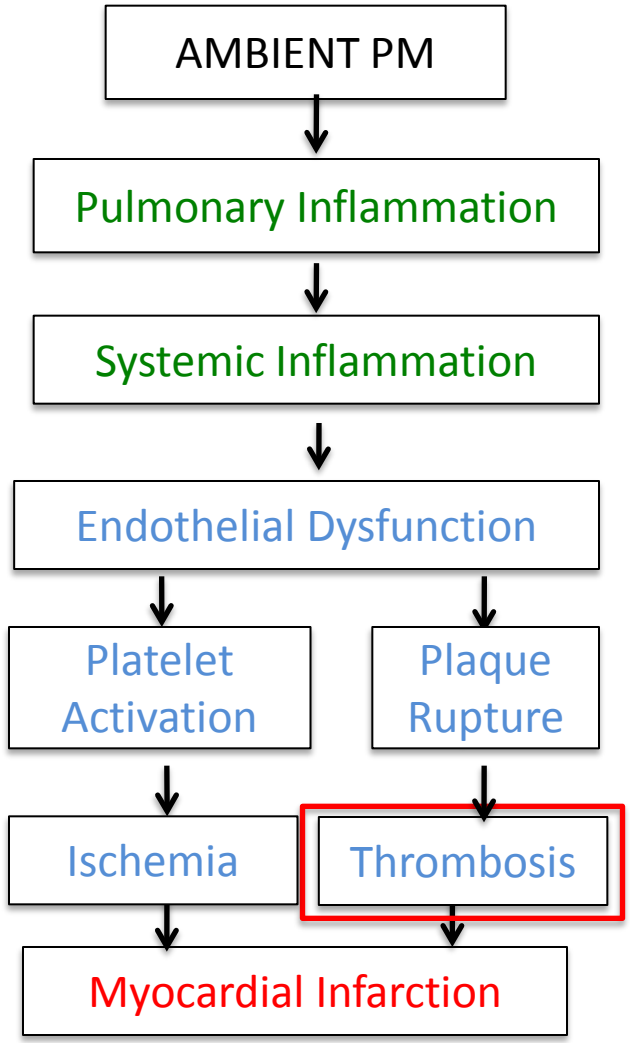


Mills et al., 2008

Ultrafine PM Increases d-Dimers

Chapel Hill Airshed



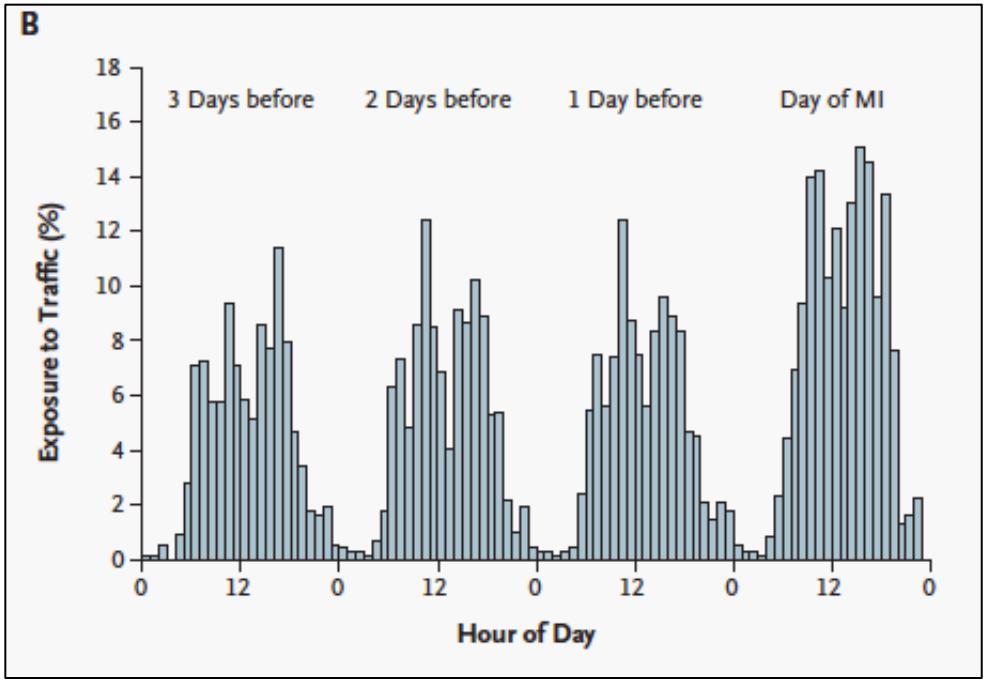


Samet et al., 2008

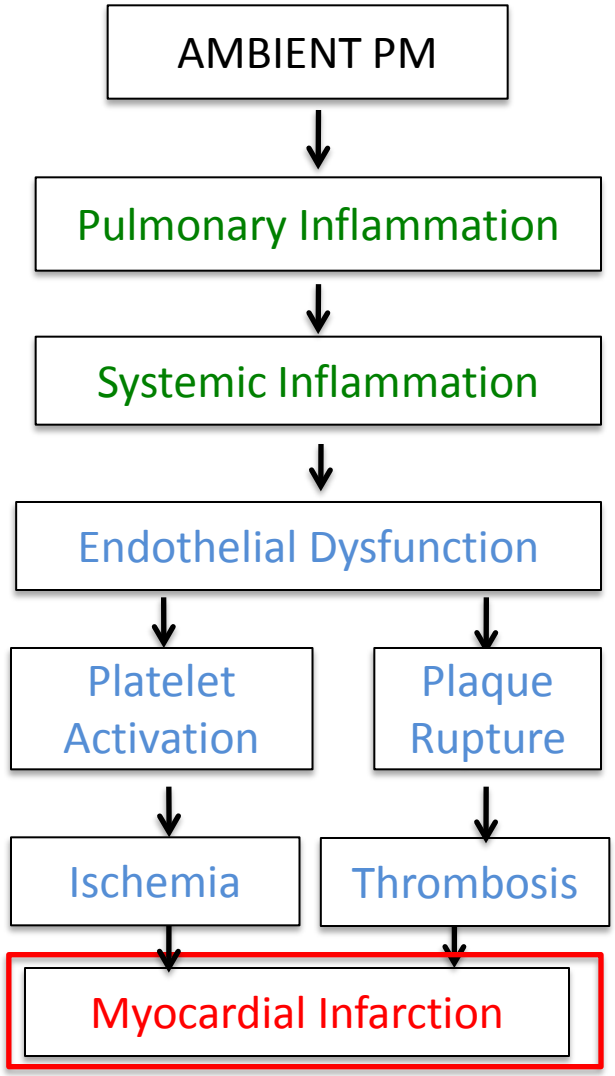
Time Spent in Traffic is Associated with MI

Region of Augsburg, Germany

Onset of nonfatal myocardial infarctions in relation to traffic exposure



Time spent in traffic was associated with the onset of myocardial infarction



Peters et al. NEJM 2004

What Components of Traffic Exposure Produce Health Effects?

NC Highway Patrol Study

Raleigh, NC, USA Air Shed

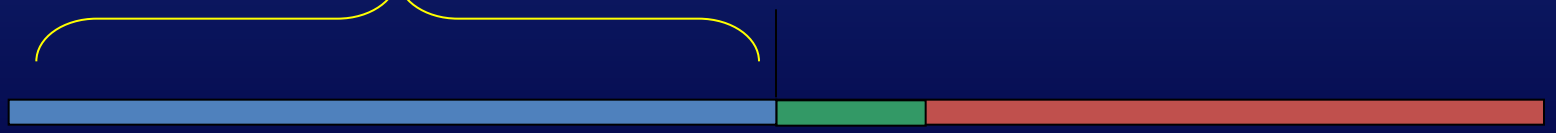
- Cars were fitted with air pollution monitors on the back of the passenger seat
- Measurements were made during regular patrol

Riediker et al. AJRCCM 2004

Daily Schedule

Raleigh, NC, USA Air Shed

Occupational $PM_{2.5}$ -Exposure



3 PM WORK Midnight SLEEP 9 AM

Continuous ambulatory EKG

Resting HRV
Lung Function

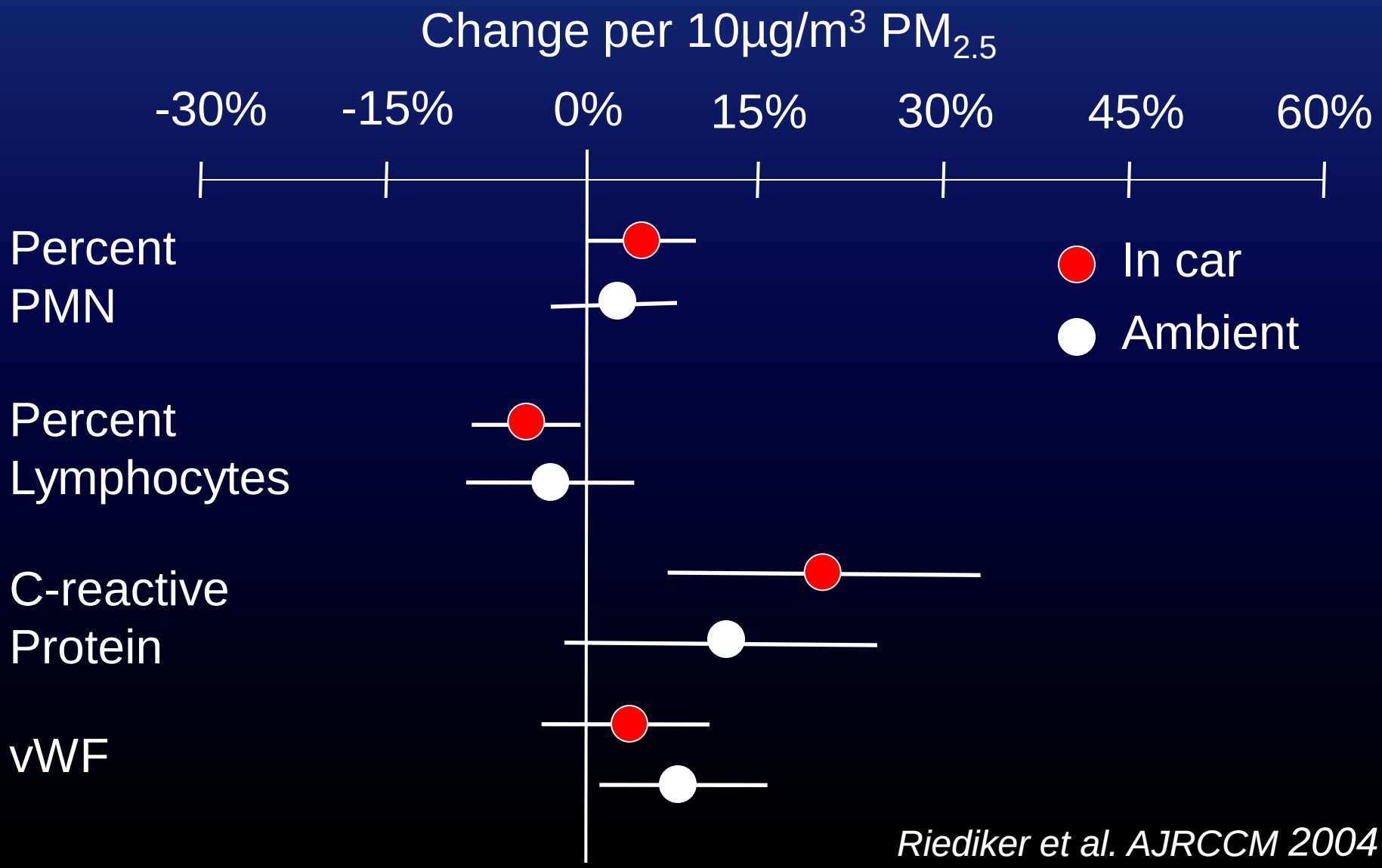
Lung Function
Resting HRV

Resting HRV

Riediker et al. AJRCCM 2004

PM Induced Changes in Blood Parameters

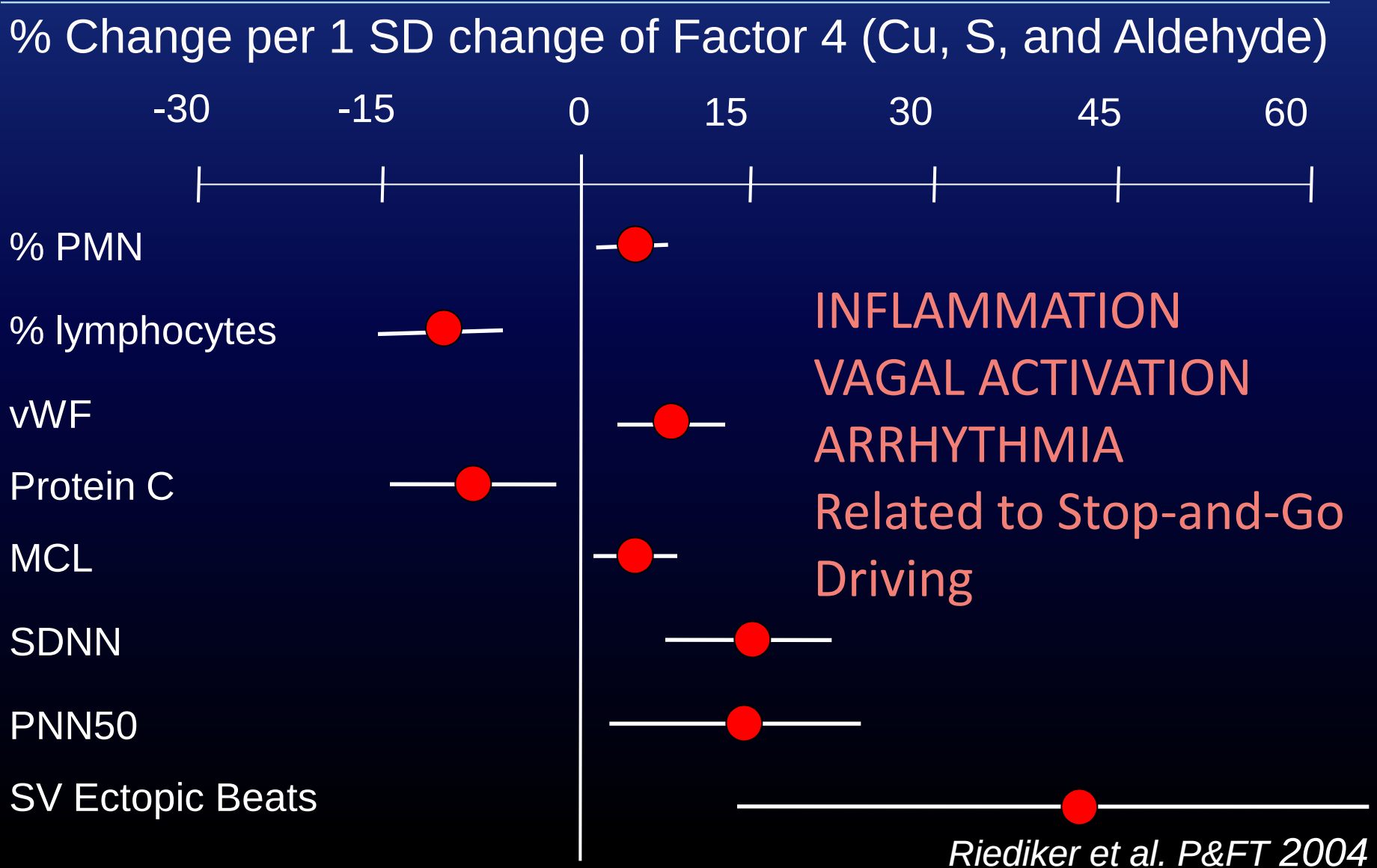
Raleigh, NC, USA Air Shed



Riediker et al. AJRCCM 2004

NC Highway Patrol Study

Raleigh, NC, USA Air Shed



Riediker et al. P&FT 2004

Differential Effects of Size-Fractionated CAPs

Particle Characteristics of CAPs exposure studies at NHEERL

Subjects | PM Mass | PM Number | PM Size

	Subject #	M/F	Age (yrs)	PM mass concentration (ug/m^3)	High PM mass concentration (ug/m^3)	PM number concentration ($10e^3/cc$)	High PM number concentration ($10e^3/cc$)	PM size (NMAD or MMAD, um)
Fine	38*	36/2	18–40	120.4 ± 14.1	206.7 ± 19.2	—	—	0.65 ± 0.03
Coarse	14	8/6	18–35	89.0 ± 49.5	119.0 ± 42.2	—	—	3.59 ± 0.58
Ultrafine	20	11/9	18–35	47.0 ± 20.2	55.3 ± 18.4	151.8 ± 165.3	156.5 ± 32.4	0.049 ± 0.009

*(30 PM, 8 Air Controls).

Opportunity to compare the effects of Ultrafine, Fine and Coarse PM from the same airshed in a young healthy cohort.

Samet Inhal Tox 2007

Differential Effects of Size-Fractionated CAPs

Young Healthy Volunteers at the US EPA Human Studies Facility

	Pulmonary Effects			Heart	Blood
	Pulmonary function	BAL fluid cells	BAL fluid markers	Cardiac endpoints	Plasma factors
Fine	No Effect	↑ Total ↑ PMN ↑ Monocytes	↓ IL-8	No Effect (Trend to ↓ HRV)	↑ FIBRINOGEN
Coarse	No Effect	↑ PMN	↓ Protein	↓ SDNN 20 hr Post	Trend to ↑ Clotting
Ultrafine	No Effect	No Effect	No Effect	↓ SDNN 24 hr Post (AMBULATORY)	↑ D-DIMER

- No PM of any size fraction affected pulmonary function.
- Fine and coarse PM increased cell counts in BAL.
- Ultrafine PM had no effect on BAL, but increased D-dimer an indicator of fibrinolysis.

Samet Inhal Tox 2007

Ultrafine PM Decreases Coronary Blood Flow

Near- and Far-Road PM (Ultrafine vs Fine and Coarse PM)

Physiological Cardiac Endpoints at End of Control Period Before Ischemia/Reperfusion

	Coronary flow rate (mL/min)	LVDP (cm H_2O)	$+dP/dt_{max}$ (mm Hg/sec)	$-dP/dt_{min}$ (mm Hg/sec)	Heart rate (bpm)
NR					
Coarse	2.9 ± 0.6	131 ± 12	4,387 ± 306	–4,267 ± 571	380 ± 41
Fine	2.0 ± 0.7*	119 ± 15	4,093 ± 748	–3,846 ± 1,374	333 ± 42
Ultrafine	1.7 ± 0.7*	144 ± 11	4,663 ± 422	–4,327 ± 305	378 ± 22
FR					
Coarse	3.2 ± 1.5	141 ± 10	4,933 ± 394	–5,017 ± 481	416 ± 10
Fine	3.0 ± 1.4	151 ± 25	4,517 ± 955	–3,223 ± 339	358 ± 29
Ultrafine	2.5 ± 0.7	150 ± 9	4,870 ± 125	–4,129 ± 419	389 ± 18
Saline	3.9 ± 1.4	113 ± 4	3,877 ± 295	–3,045 ± 381	412 ± 17

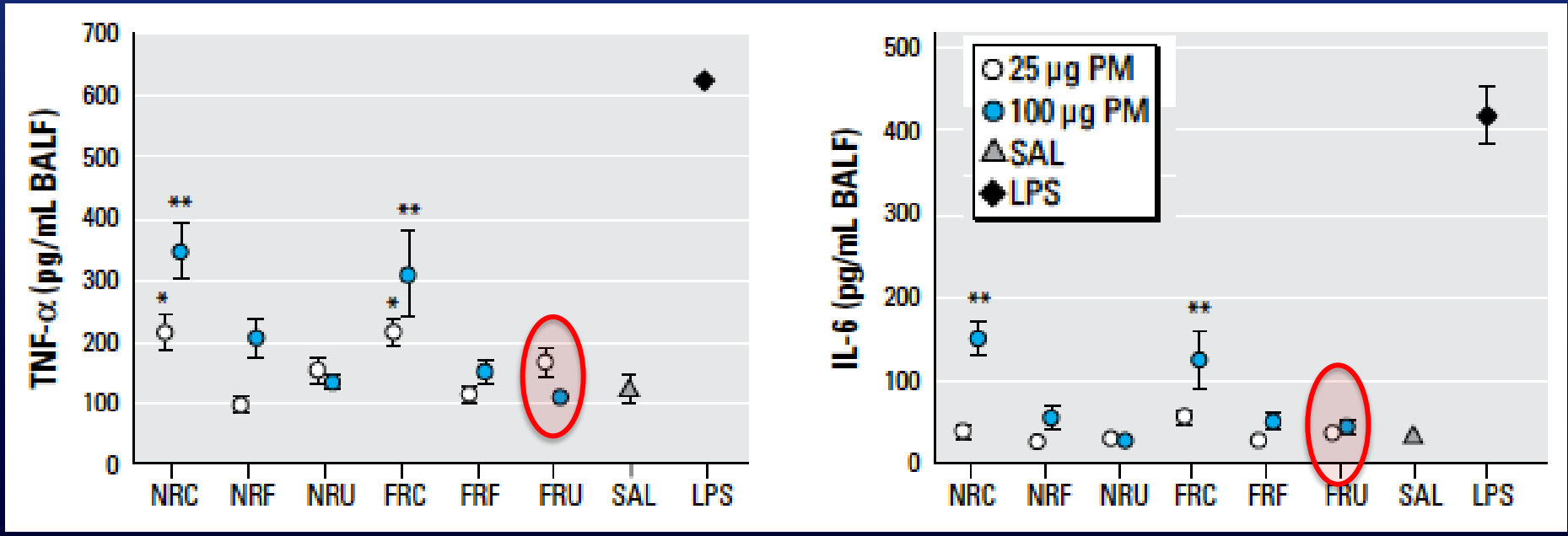
bpm, beats per minute. PM-exposed animals aspirated 100 µg PM.
*$p < 0.05$ compared with the saline group.

- Coarse PM did not affect coronary flow, or mechanical function of the heart.
- Ultrafine and fine PM decreased coronary artery blood flow without a change in HR or mechanical function.

Cho et al. EHP 2009

Pulmonary Inflammation

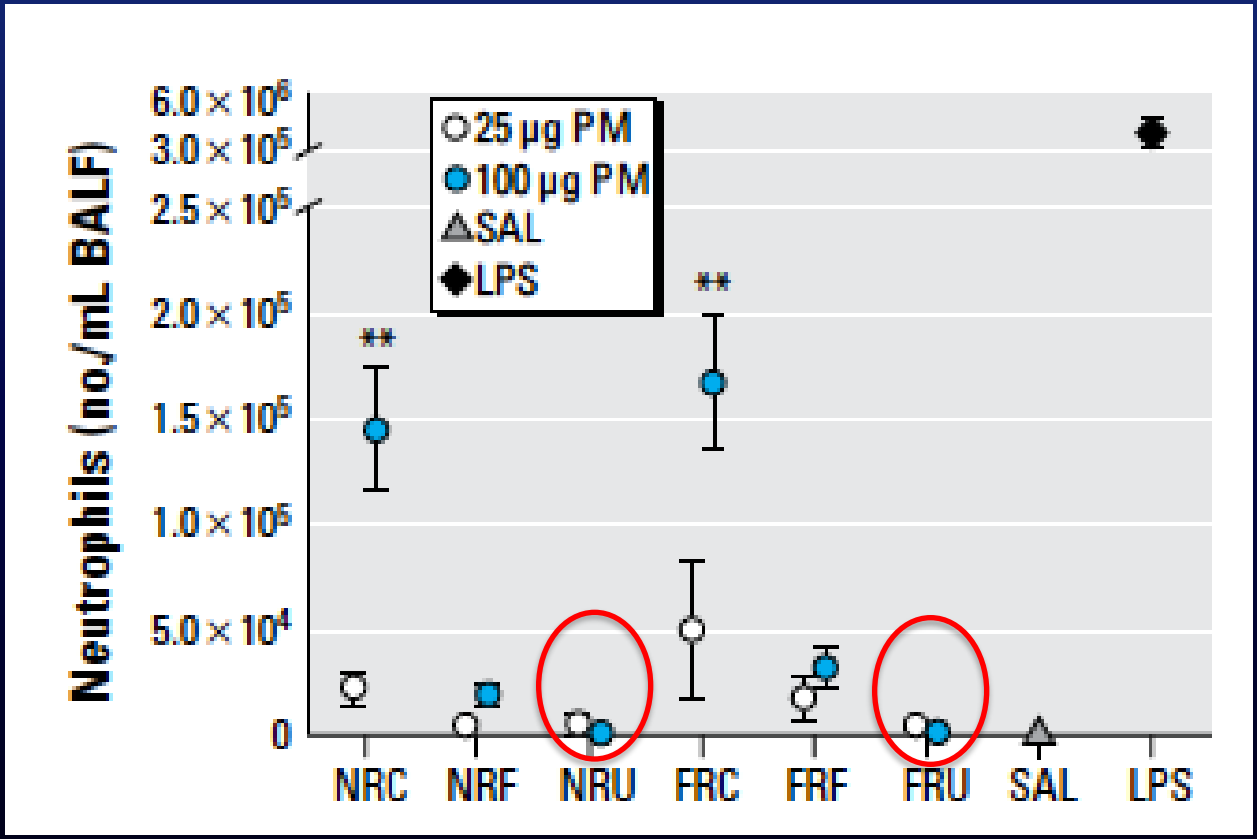
Near- and Far-Road PM (Ultrafine vs Fine and Coarse PM)



- TNF-a and IL-6 increase in BALF 4 hours after exposure to near road and far road coarse PM.
- Ultrafine did not affect inflammation in the lung.

Cho et al. EHP 2009

Pulmonary Inflammation in Near- and Far-Road Exposures



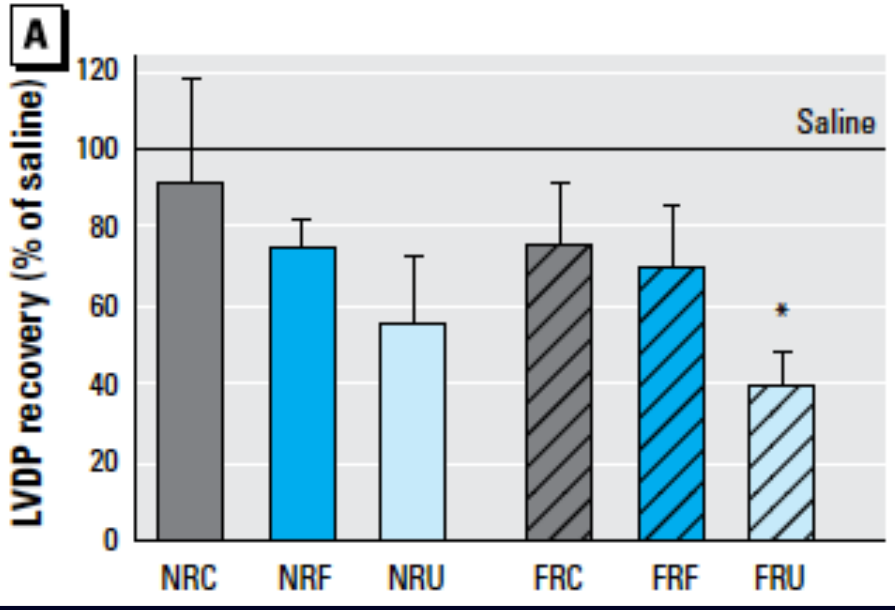
- Neutrophils in BALF 18-hr post-exposure do not increase after UF exposure

Cho et al. EHP 2009

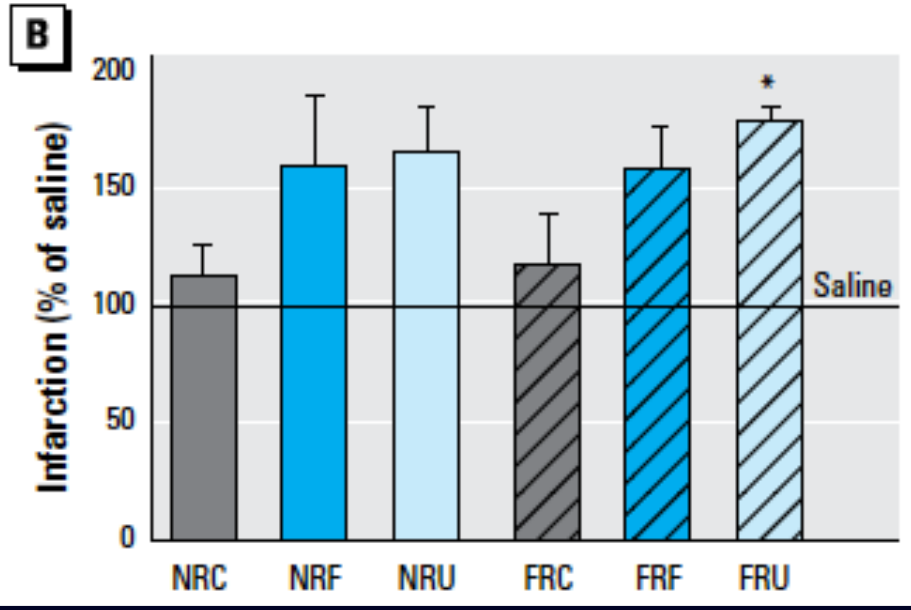
Ischemia-Reperfusion Injury in Murine Hearts

Near- and Far-Road PM Exposures (Ultrafine vs Fine and Coarse PM)

Mechanical Recovery



Size of Infarction

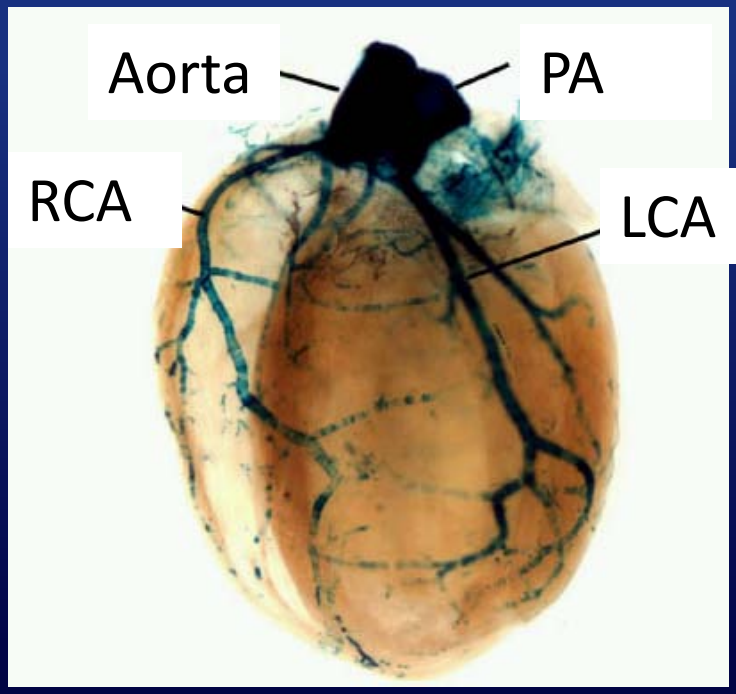


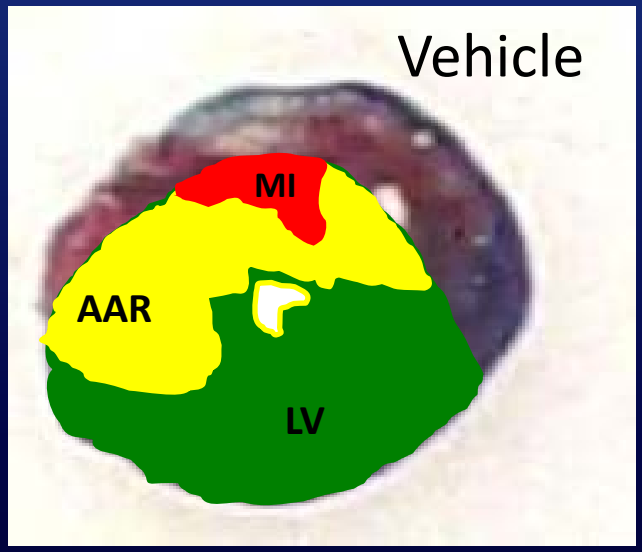
- Ultrafine PM near and far from roads decreased mechanical function and increased cellular injury after ischemia/reperfusion.
- Findings confirmed findings of Cozzi et al.

Cho et al. EHP 2009

Cardiac Injury after I/R

UFPM from Chapel Hill Airshed





20 min ischemia, 2 hr reperfusion

Re-ligate; infuse Evan's blue to stain all of heart except area at risk

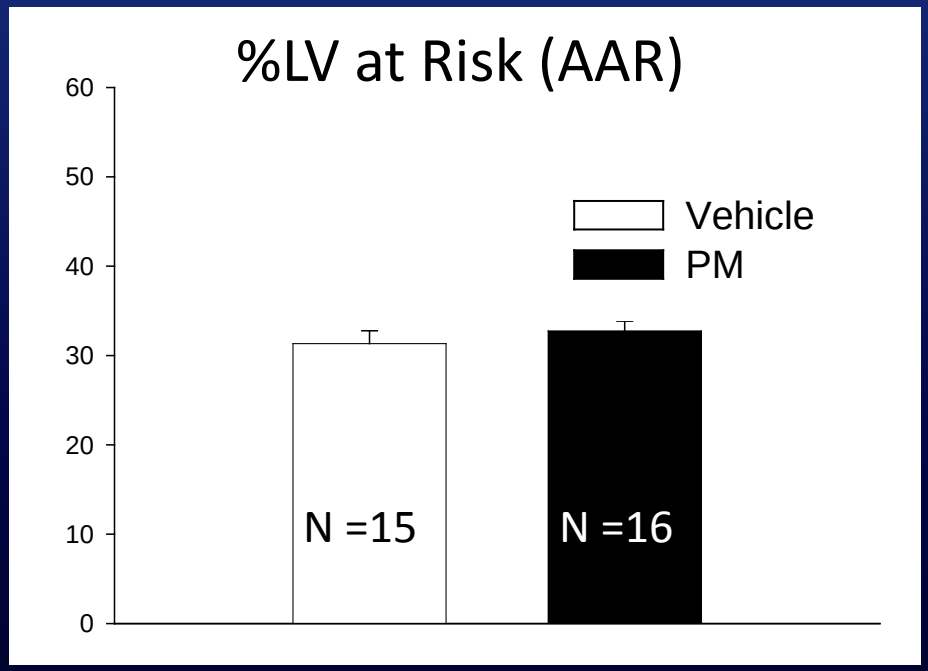
Section heart; incubate in TTC to demarcate the viable (pink) from the infarct (pale)

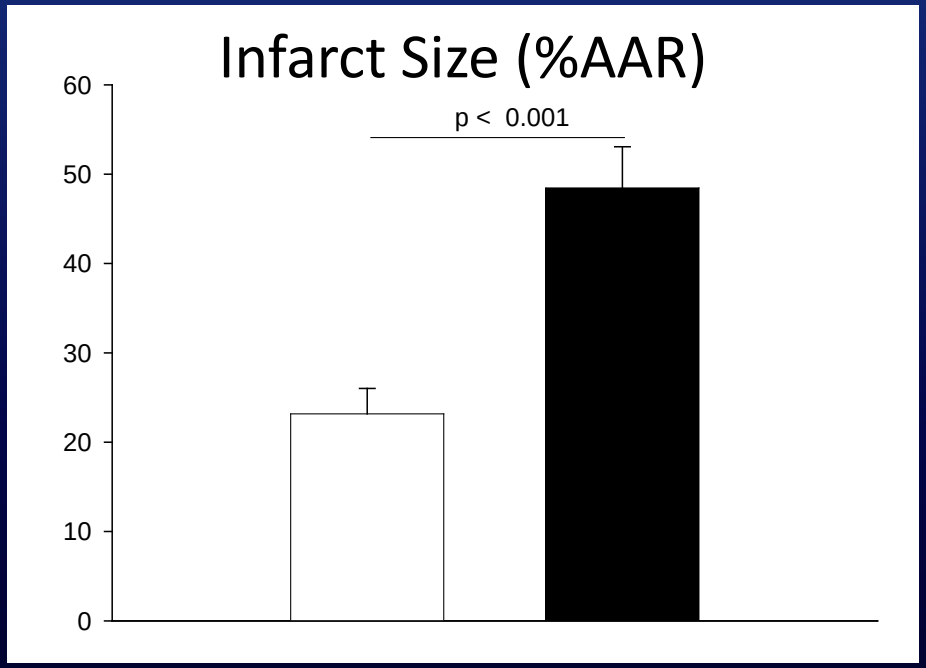
Analyze infarct with ImageJ

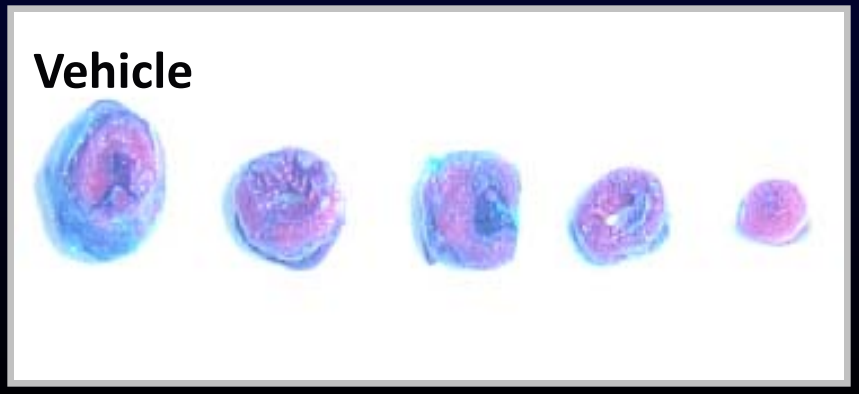
Paraffin-imbed infarct, H&E stain slides

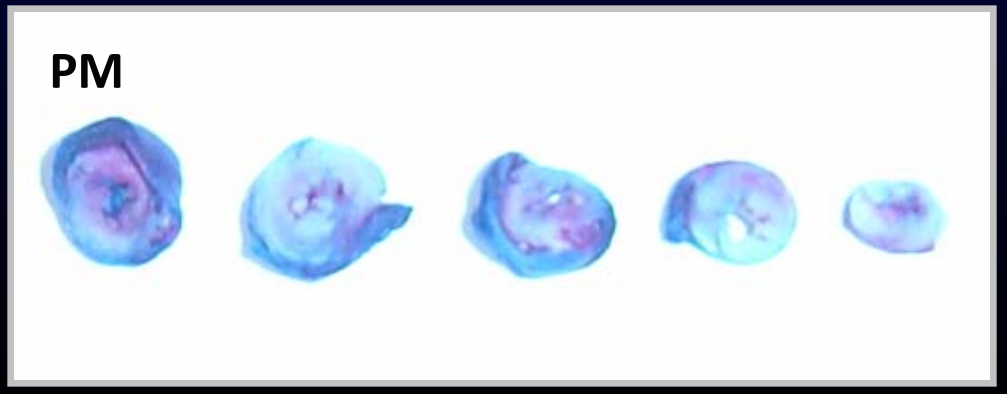
Infarct Size after Ischemia-Reperfusion

UFPM from Chapel Hill Airshed





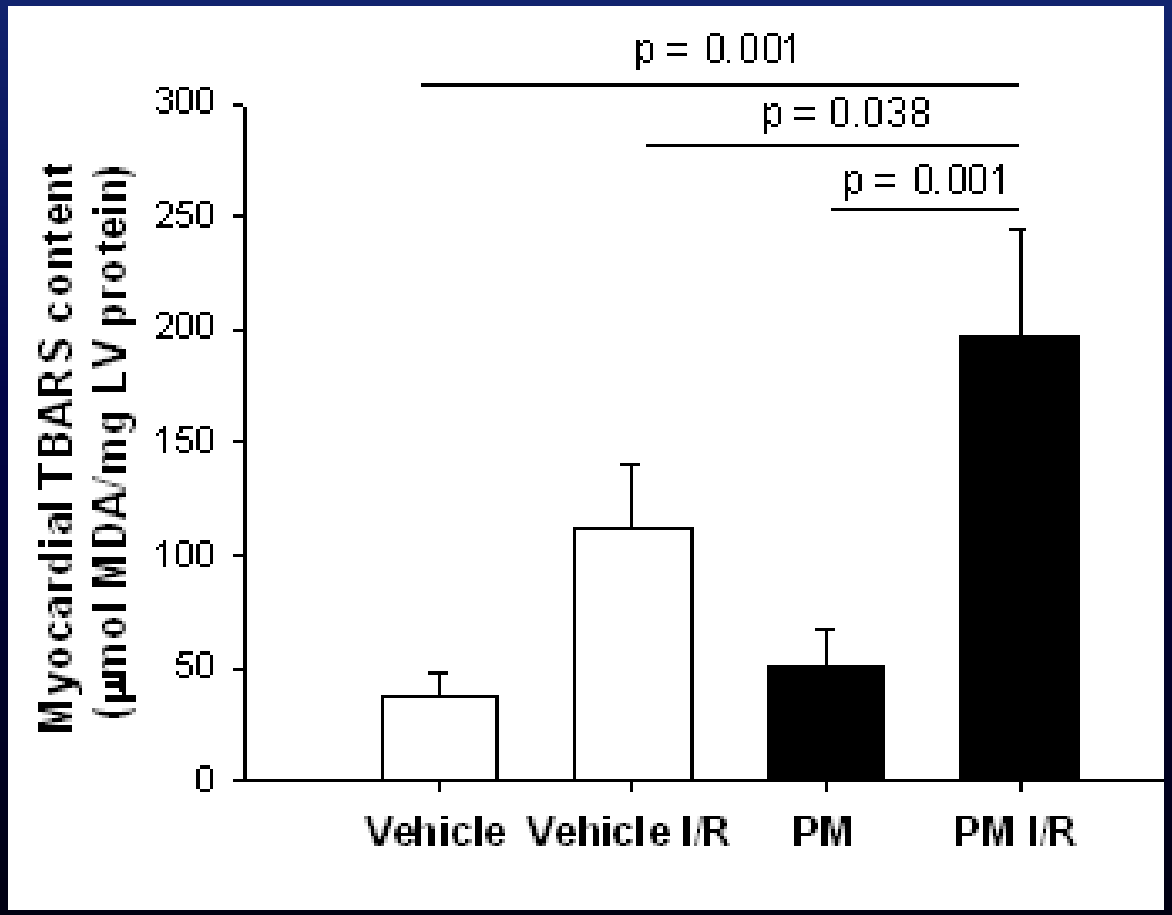




Cozzi et al. *Am J Physiol Heart Circ Physiol*. 2006

Myocardial Oxidative Stress

UFPM from Chapel Hill Airshed



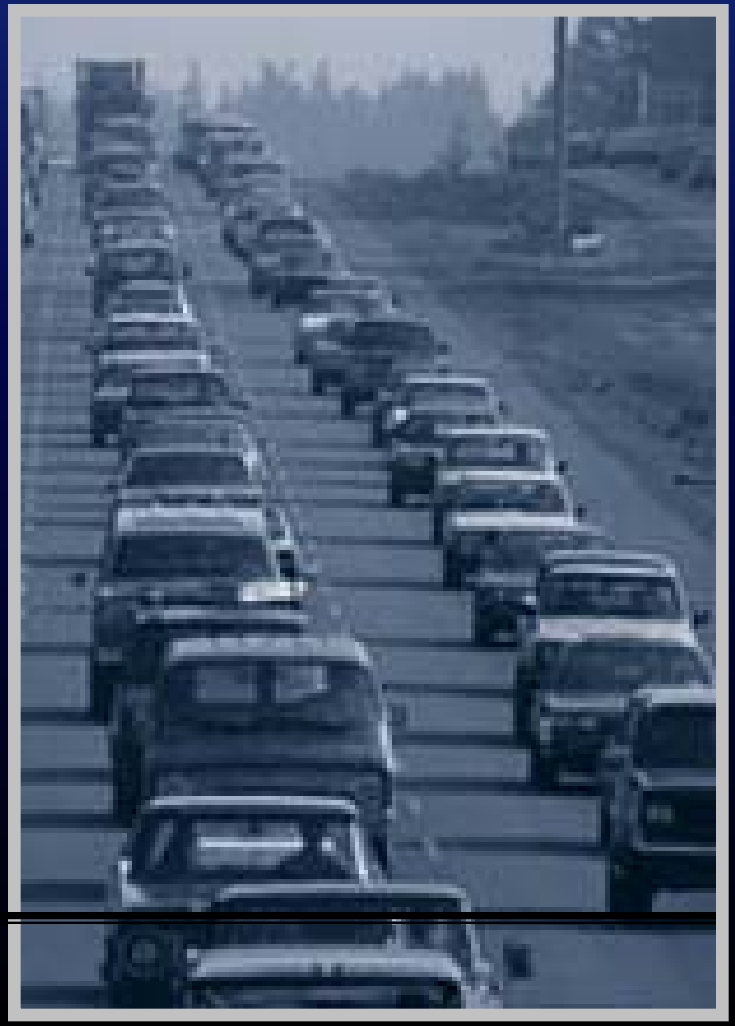
- LV 24 hrs after exposure either before or after induction of I/R
- Oxidative stress - TBARS
- TBARS within the myocardium are increased in both the PM-exposed non-I/R and I/R mouse groups compared to Vehicle controls
- UFPM exposure increases myocardium neutrophil density.

n = 5 in each group, repeated in triplicate

Cozzi et al. *Am J Physiol Heart Circ Physiol*. 2006

California Freeway Study

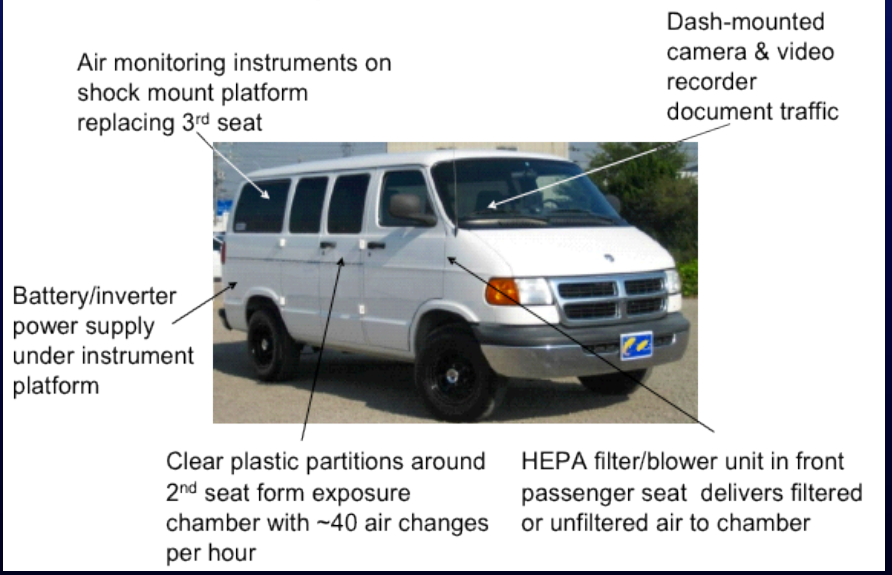
Traffic-Related Ultrafine PM has Biochemical and Electrophysiological Effects



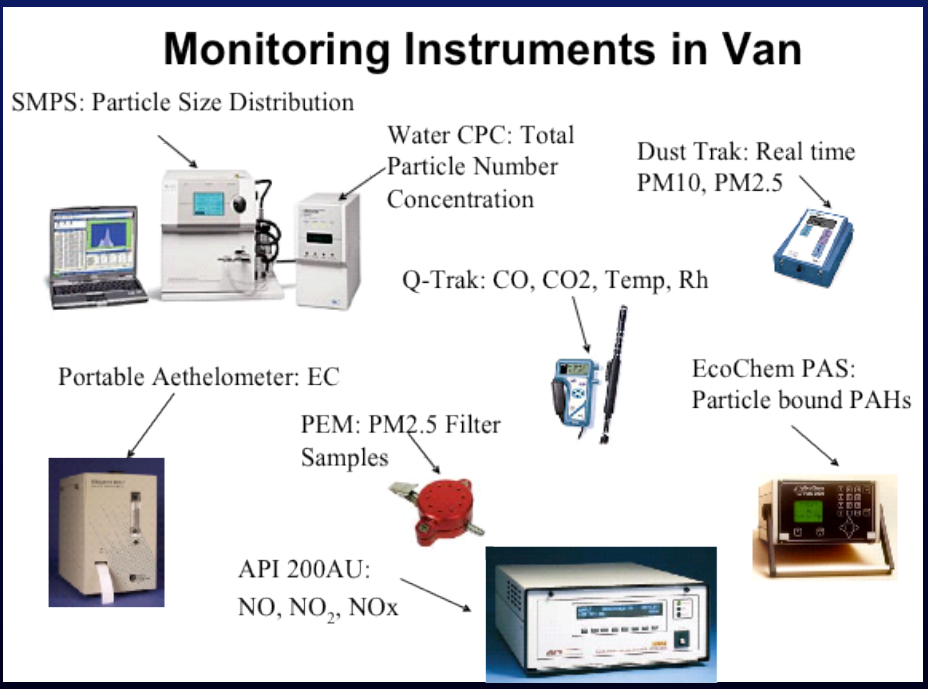
California Freeway Study

Traffic-Related Ultrafine PM has Biochemical and Electrophysiological Effects

A conventional 9-passenger van was converted to a mobile exposure chamber as shown.

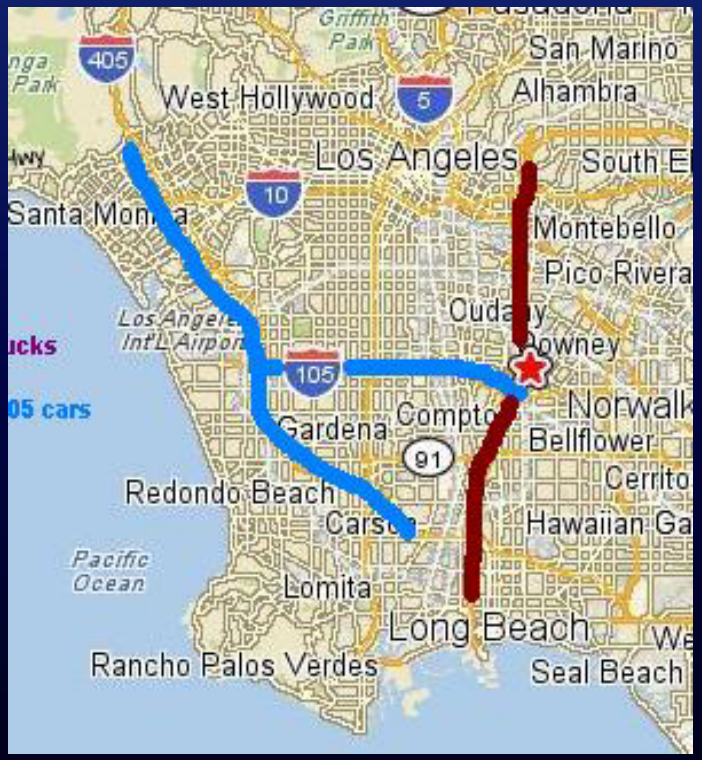


Monitoring Instruments in Van



California Freeway Study

Traffic-Related Ultrafine PM has Biochemical and Electrophysiological Effects



Subjects are exposed, 1 or 2 at a time, for 2-h periods, at 1 week intervals, random order/double-blind, to:

- I-710 freeway (mostly diesel trucks) unfiltered
- I-710 filtered
- I-405/105 freeway (mostly gasoline cars) unfiltered
- I-405/105 filtered

Responses are measured in terms of:

- 24-h Holter ECG (HRV, arrhythmia incidence)
- 24-h ambulatory blood pressure record
- Spirometry & vital signs (pre-, 0, 2, 22 h post-exposure)
- Venous blood assays for markers of inflammation (pre, 2, 22 h)
- Serial symptom recording via standardized questionnaire
- Time-activity diary recording

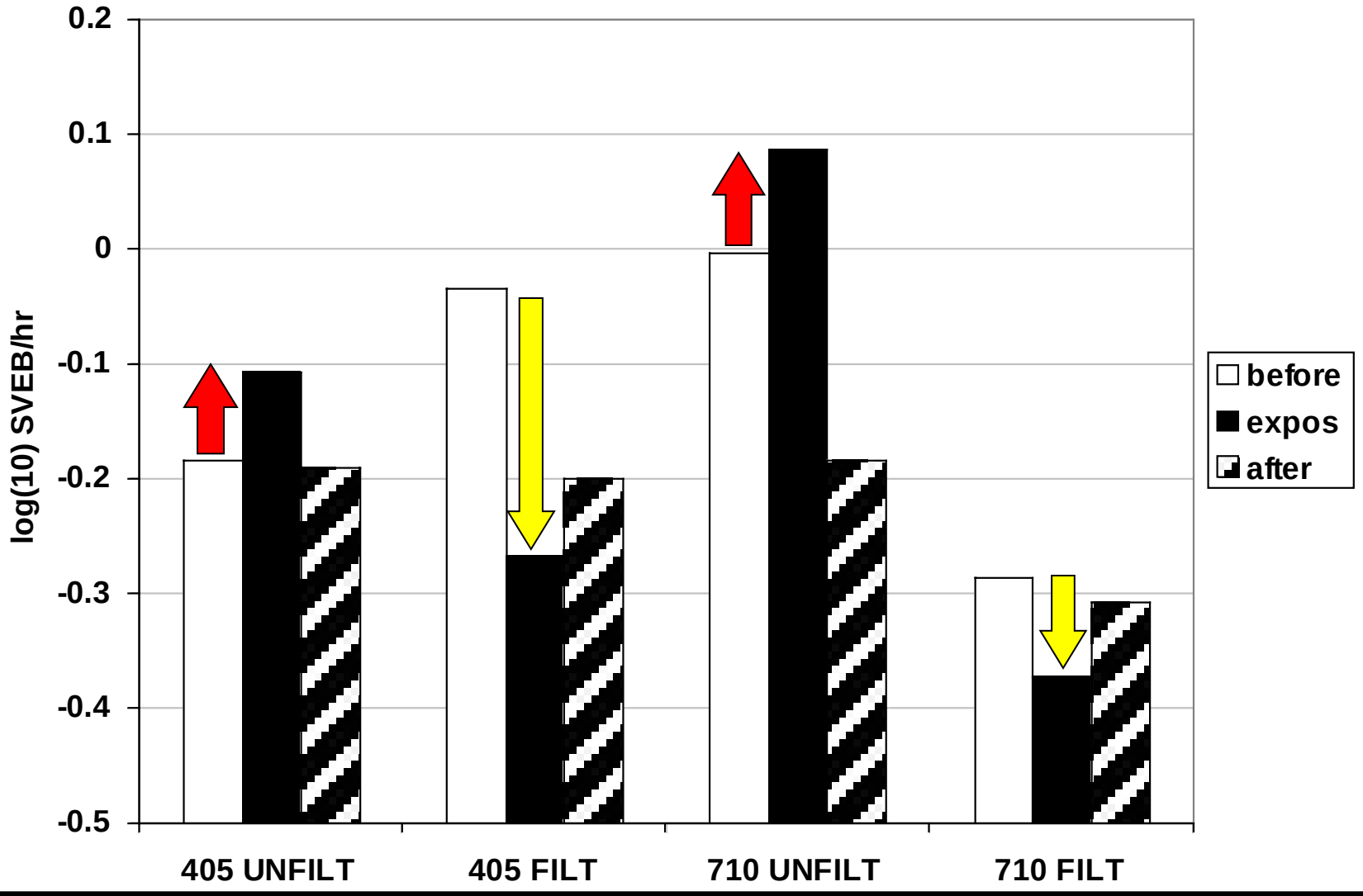
California Freeway Study

Environmental Measurements, by Freeway and Filter Condition

Variable	Units	I-405 unfilt.	I-405 filt.	I-710 unfilt.	I-710 filt.
Total Particle Number	count/cm^3	78,519	2,090	113,711	4,275
UFPs	count/cm^3	45,172	1,224	79,183	2,372
$PM_{2.5}$	µg/m³	43.4	8.6	56.4	9.3
PM_{10}	µg/m³	49.5	12.9	63.7	13.6
BC	µg/m³	5.55	0.88	9.80	0.95
PAH	ng/m^3	119	5	241	7
NOx	ppb	256	234	439	441
CO	ppm	2.72	2.67	3.48	2.73
Temperature	deg F	69.40	69.45	72.38	71.15
Rel. Humidity	%	32.73	34.88	30.61	29.47
Prior 24 hr Amb. PM-10	µg/m³	30.0	26.2	30.1	29.6
Prior 24 hr Amb. $PM_{2.5}$	µg/m³	24.0	21.7	21.5	23.6

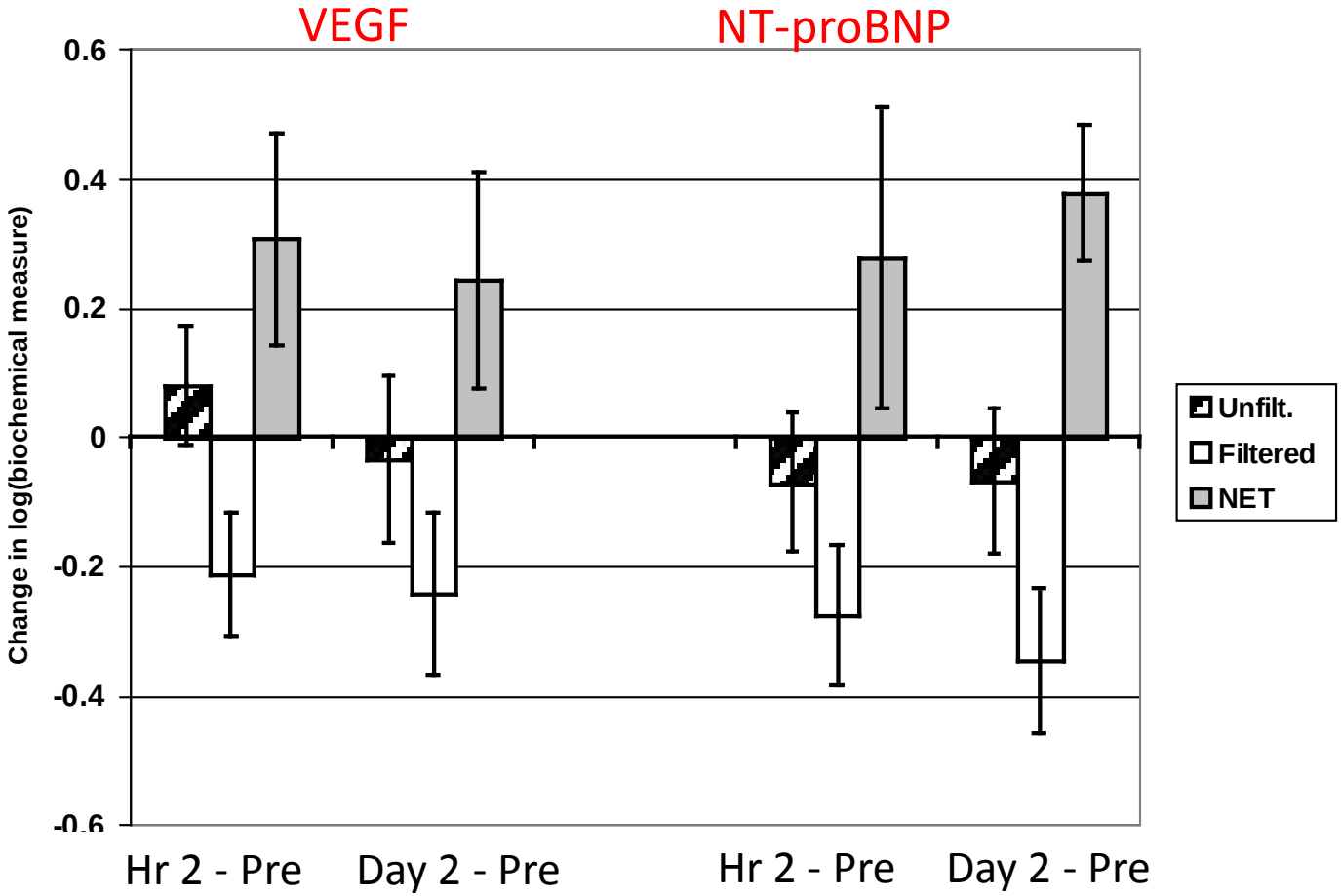
Supraventricular Ectopic Beats

Mean incidence of SVEBs



California Freeway Study

Net change in VEGF and NT-proBNP (filtered and unfiltered exposures



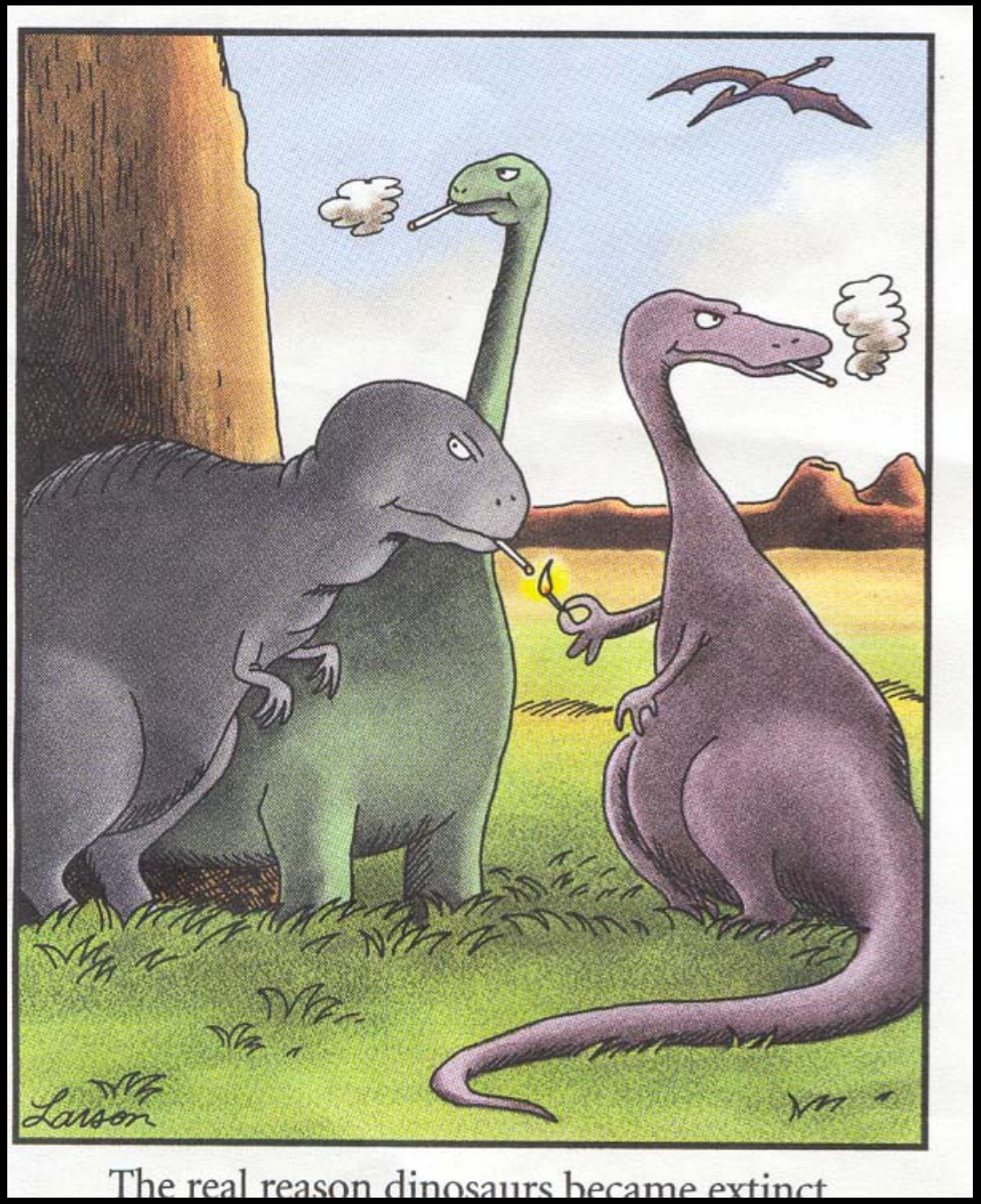
- VEGF and NT-proBNP show a relative decrease with filtering.
- Effects are related to UFPM and/or PAH
- Provides evidence that effects are not related to stress or gases

Are There Health Effects Associated with Ultrafine Particles?

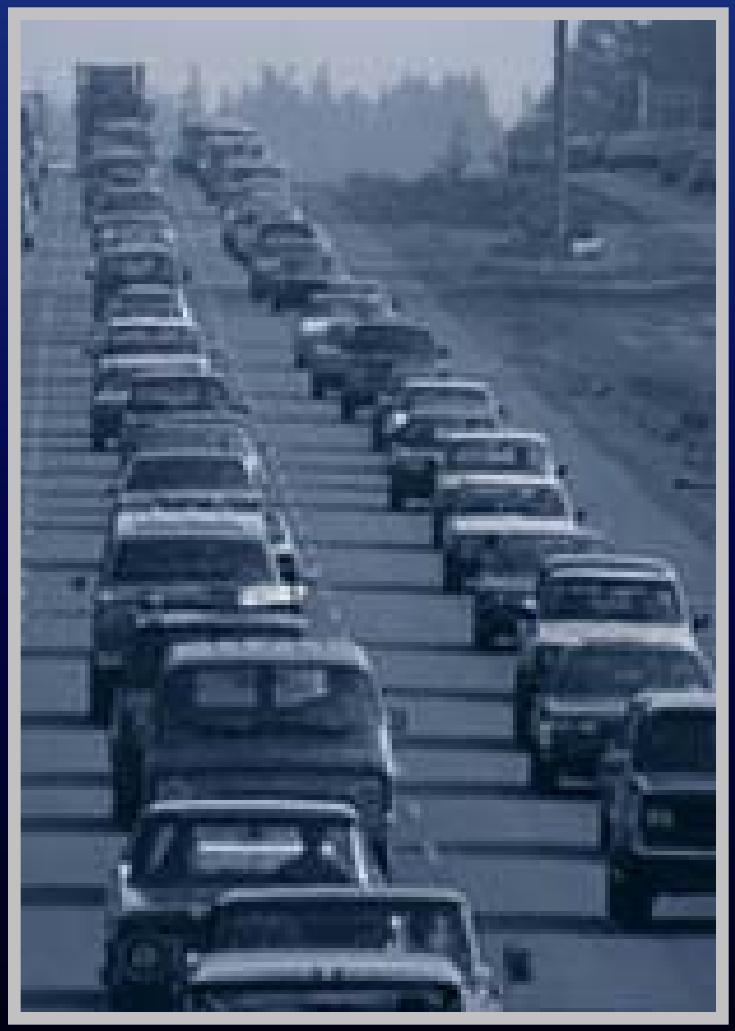
- Most studies have focused on fine PM effects (or PM_{10})
- Limited number of studies linking exposure of ultrafine PM to short-term or long-term health effects
- There is an increasing number of studies that have demonstrated health effects caused by ultrafine PM (usually enriched for organics)
- Human exposure studies and animal toxicology studies suggest that UF PM affects the cardiovascular system to a greater extent than the respiratory system.
- There is concern that these very small particles may exit the lung and directly impact other tissues within the body

”The real reason dinosaurs became extinct."

- Gary Larson



Time Course of Biochemical and Physiological Changes in Response to PM and UFPM



Air Pollution and Cardiac Risk (APACR)

Healthy Middle-Aged Cohort

Harrisburg, PA Airshed with Personal $PM_{2.5}$ Monitoring

- What is the relationship, and the time-course, between $PM_{2.5}$ and cardiac ventricular repolarization as measured by heart rate corrected QT interval?

Methods

Population: Air Pollution and Cardiac Risk (APACR) study

- Community-dwelling, N = 107
- Aged 45 or older, non-smokers
- No history of cardiac events in previous 6 months

Liao D et al. EHP 2010

Study Design and Analytic Methods

ECG Data: 24-hr Mortara H-12 digital recorders analyzed with SuperECG

- High-resolution (1,000 Hz sampling rate)
- Visually indentified and removed artifacts and arrhythmic beats
- Normal beat-to-beat QTs from each 30-min. segment were summarized as HR-corrected QT measures:

  QT Prolongation Index (QTI) *Rautaharju et al. J Electrocardiol 1991*

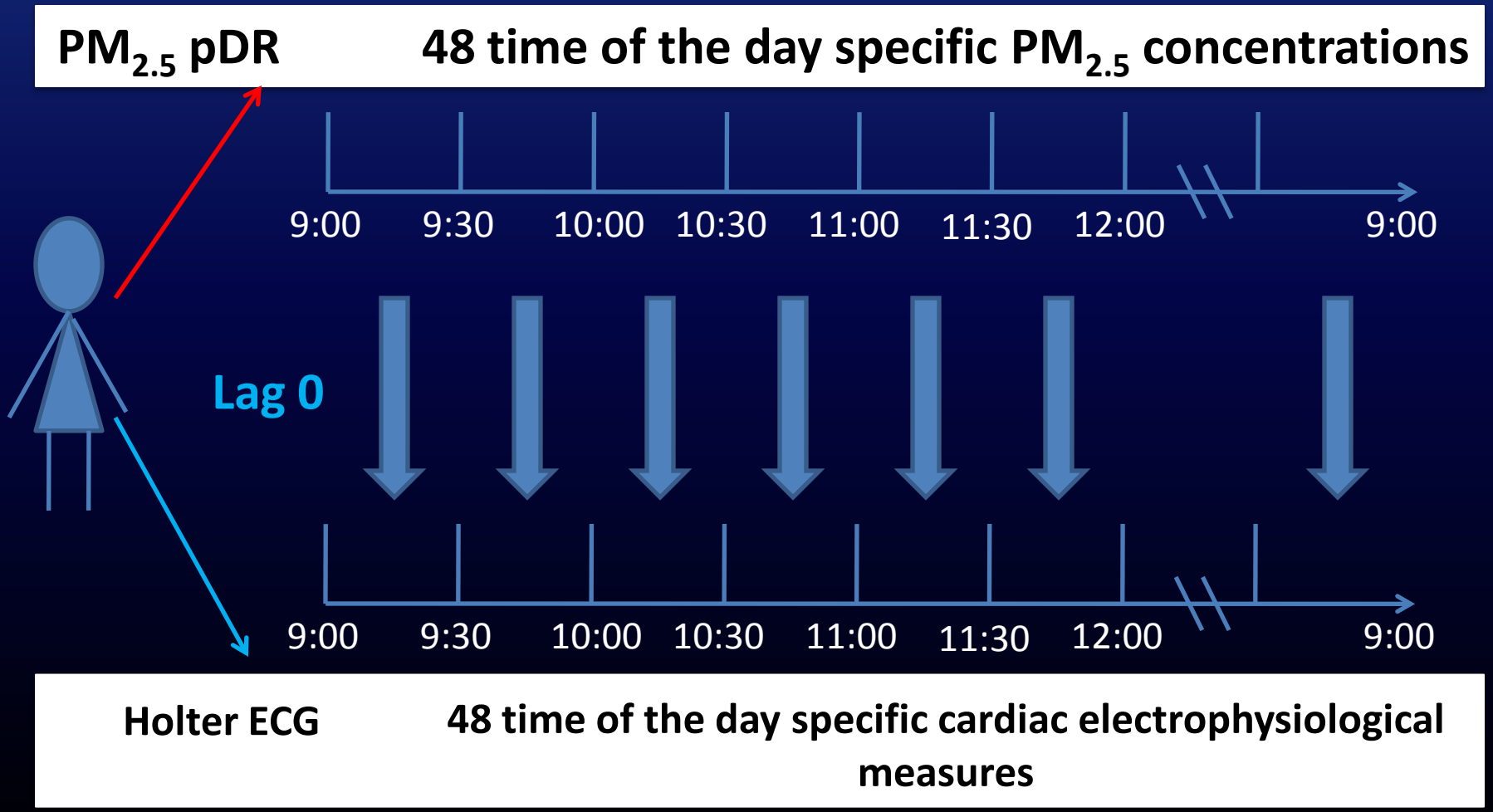
  Bazett's HR-corrected QT (QTcB)

$PM_{2.5}$ Data: pDR continuous personal exposure

- Active pump and cyclone size select inlet
- Individual level real-time $PM_{2.5}$ exposures, on 30-min basis.

Liao D et al. EHP 2010

Continuous ECG and PM Monitoring



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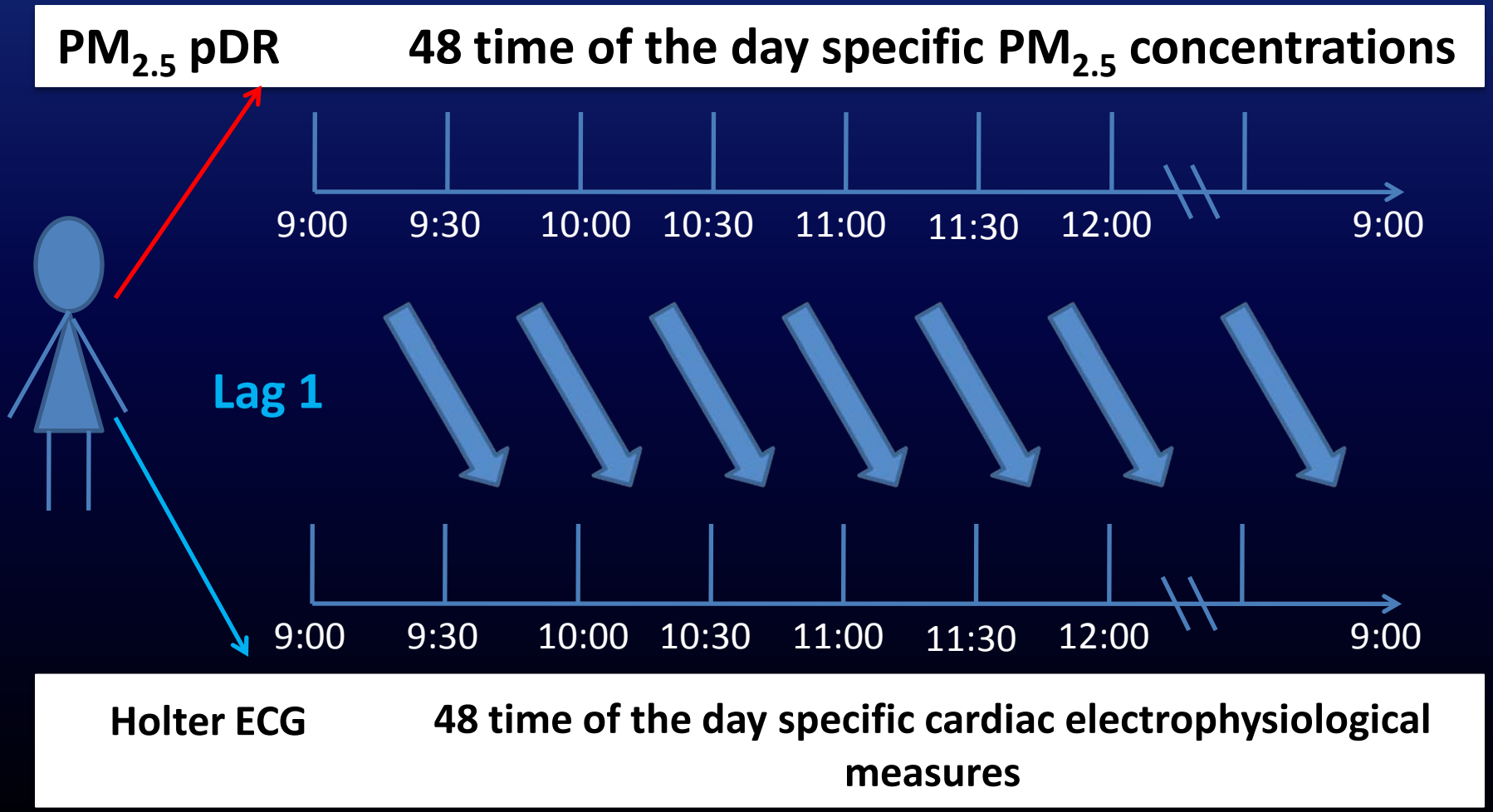
Lag 1 represents a 30 minute interval



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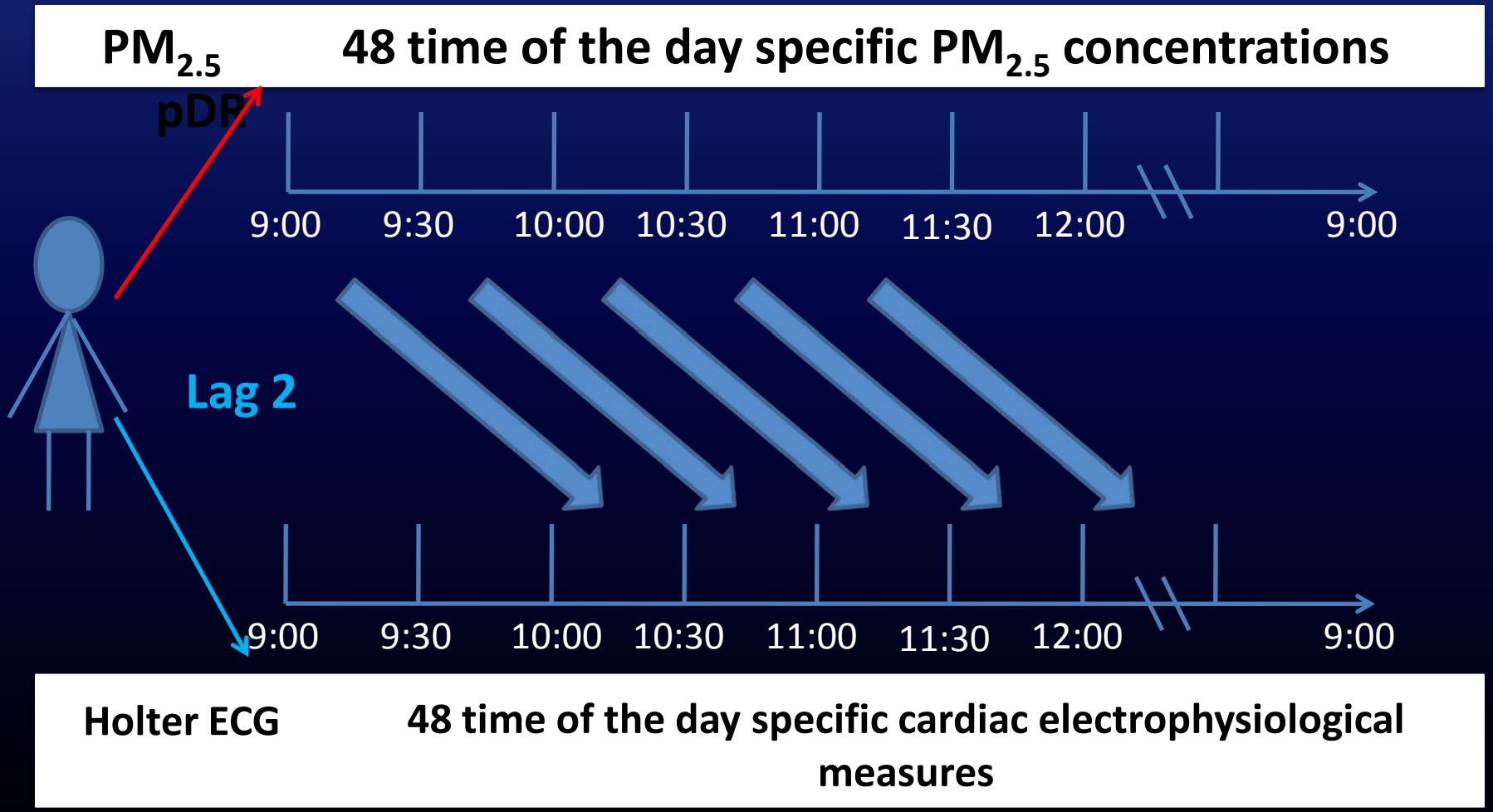
Lag 2 represents a 60 minute interval



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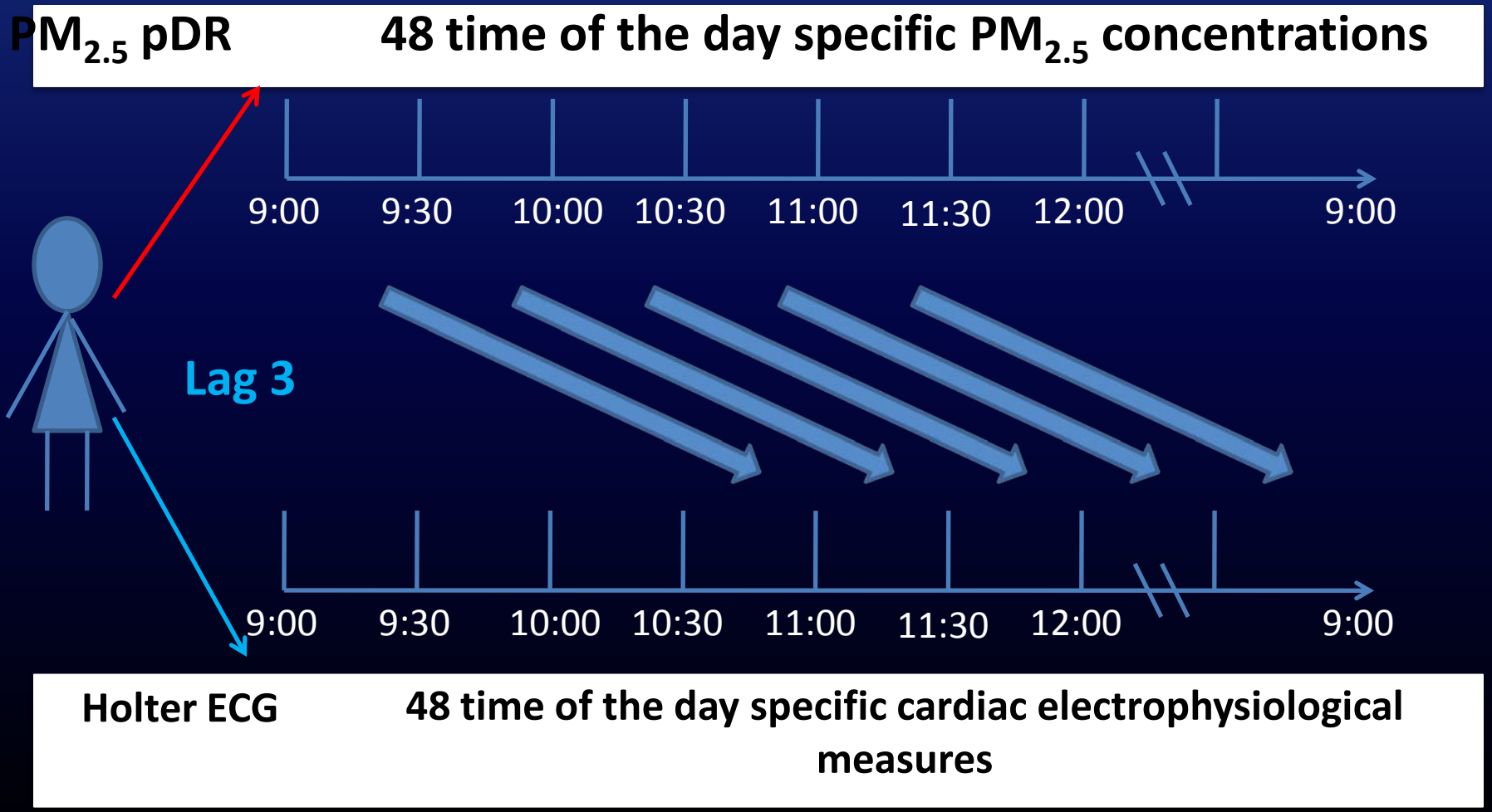
Lag 3 represents a 90 minute interval



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Air Pollution and Cardiac Risk (APACR)

Clinical Characteristics of Cohort

Proportion, Mean (SD) of major variables

Age (Years)	56 (7.6)	DBP (mm Hg)	75 (9)
Sex (% Male)	41	QTI (%)	111 (6.6)
Race (% White)	74	QT_cB (ms)	438 (23)
BMI (kg/m^2)	28 (5.9)	QT_cF (ms)	422 (22)
Hypertension (%)	35	$PM_{2.5}$ ($\mu g/m^3$)	14 (22)
Diabetes (%)	7.55	Temp. (^oC)	22 (3.5)
SBP (mm Hg)	122 (15)	RH (%)	40 (12.1)

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Regression coefficient (SE) of HR-corrected QTs per 10μg/m^3 increase in $PM_{2.5}$

	Lags	β (SE)
QTI (%)	Lag0, 0 hr	0.08 (0.04) p<0.05
	Lag1, 0.5 hr	0.05 (0.02) p<0.05
	Lag6, 3.0 hr	0.05 (0.03) p<0.05
	Lag7, 3.5 hr	0.08 (0.04) p<0.05
QTcB (ms)	Lag6, 3.0 hr	0.20 (0.09) p=0.05
	Lag7, 3.5 hr	0.20 (0.09) p=0.01
Adjusted for age, sex, race, Temp, & HR		

- $PM_{2.5}$ is associated significantly longer HR-corrected QT interval.
- Most of the adverse cardiac ventricular repolarization effects from direct $PM_{2.5}$ exposure occurred within 1 to 3 hours – immediate effects

Liao D et al. EHP 2010

Regression coefficient (SE) of HR-corrected QTs per 10μg/m^3 increase in $PM_{2.5}$ adjusted for HRV

	Lags	HRV	β (SE)
QTcB (ms)	Lag6	HF	0.15 (0.07) p<0.05
	Lag6	LF	0.15 (0.07) p<0.05
	Lag6	SDNN	0.15 (0.07) p<0.05
	Lag6	RMSSD	0.13 (0.07) p<0.05
QTcB (ms)	Lag7	HF	0.25 (0.09) p<0.01
	Lag7	LF	0.25 (0.09) p<0.01
	Lag7	SDNN	0.25 (0.09) p<0.01
	Lag7	RMSSD	0.24 (0.09) p<0.01
Adjusted for age, sex, race, Temp, relative humidity, diabetes, HTN, CVD and each of the HRV indices			

- Longer HR-corrected QT interval associated with $PM_{2.5}$ is independent of HRV changes.

Liao D et al. EHP 2010

T-Wave Alternans, Air Pollution and Traffic

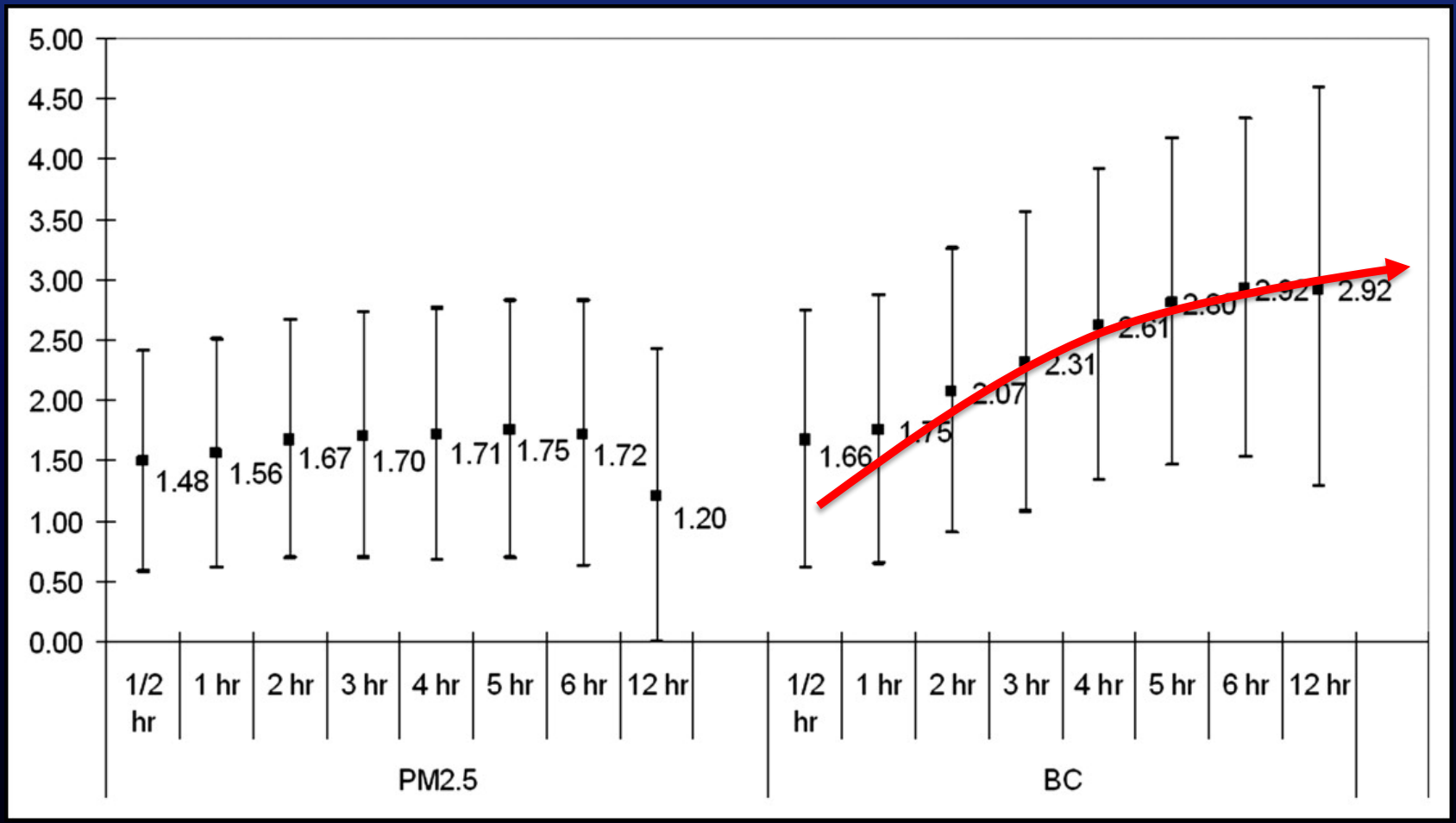
Cohort having ischemic heart disease – Boston, MA Airshed

- Subjects:
  - 48 patients (43 to 75 years old)
  - Studied 4 x over 1 yr after PCI for MI
- Exposure assessment:
  - Ambient and home indoor particulate pollution & BC
- TWA:
  - Ambulatory ECG (Marquette Seer Digital Recorder) 3-lead with modified V_5 and aVF position
  - Modified moving-average analysis (time-domain non-spectral technique)

Zanobetti et al. Am J Cardiol 2009

T-Wave Alternans, Air Pollution and Traffic

Cohort having ischemic heart disease – Boston, MA Airshed

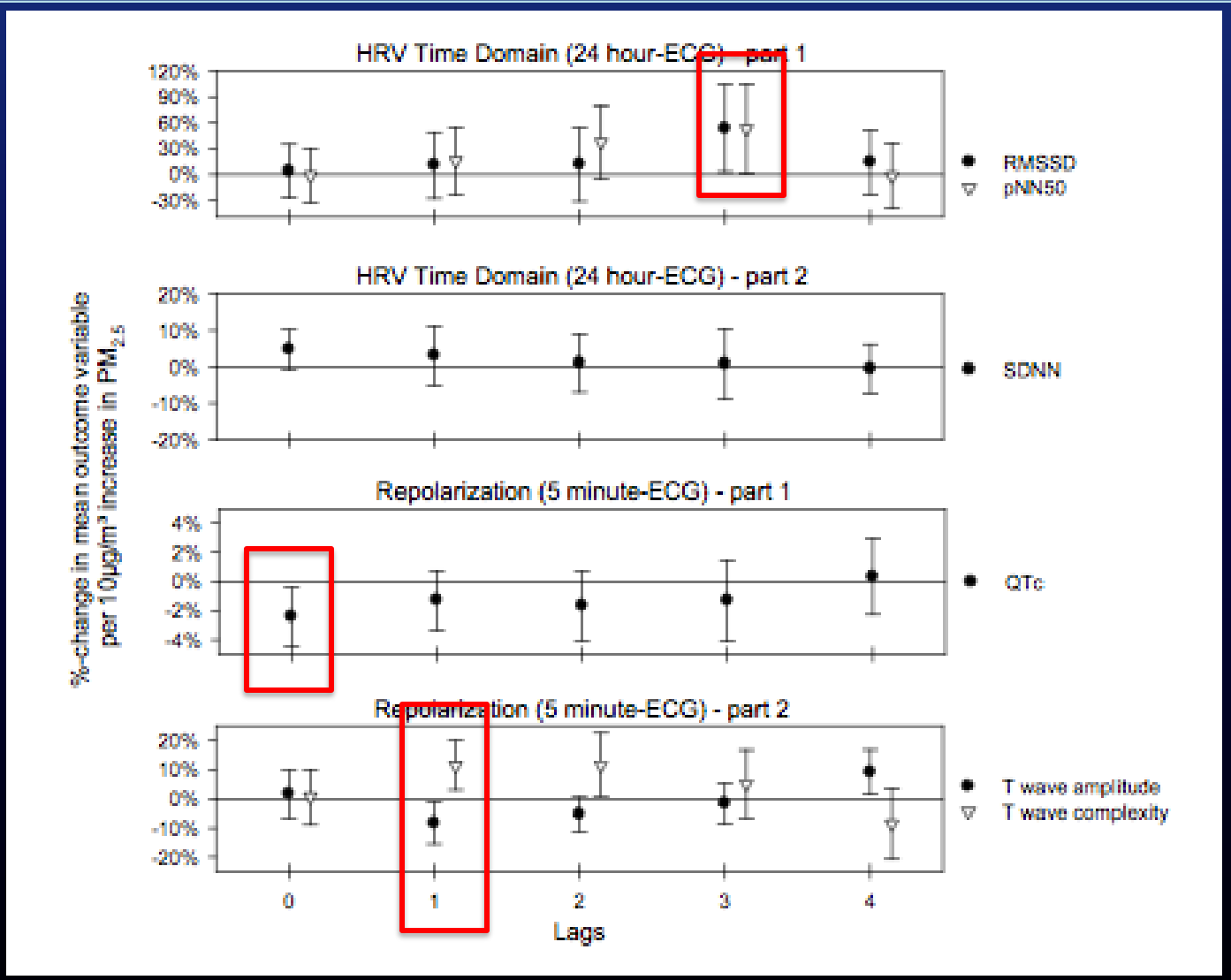


% change TWA-MAX for increasing times for ambient $PM_{2.5}$ and black carbon (BC)

Zanobetti et al. Am J Cardiol 2009

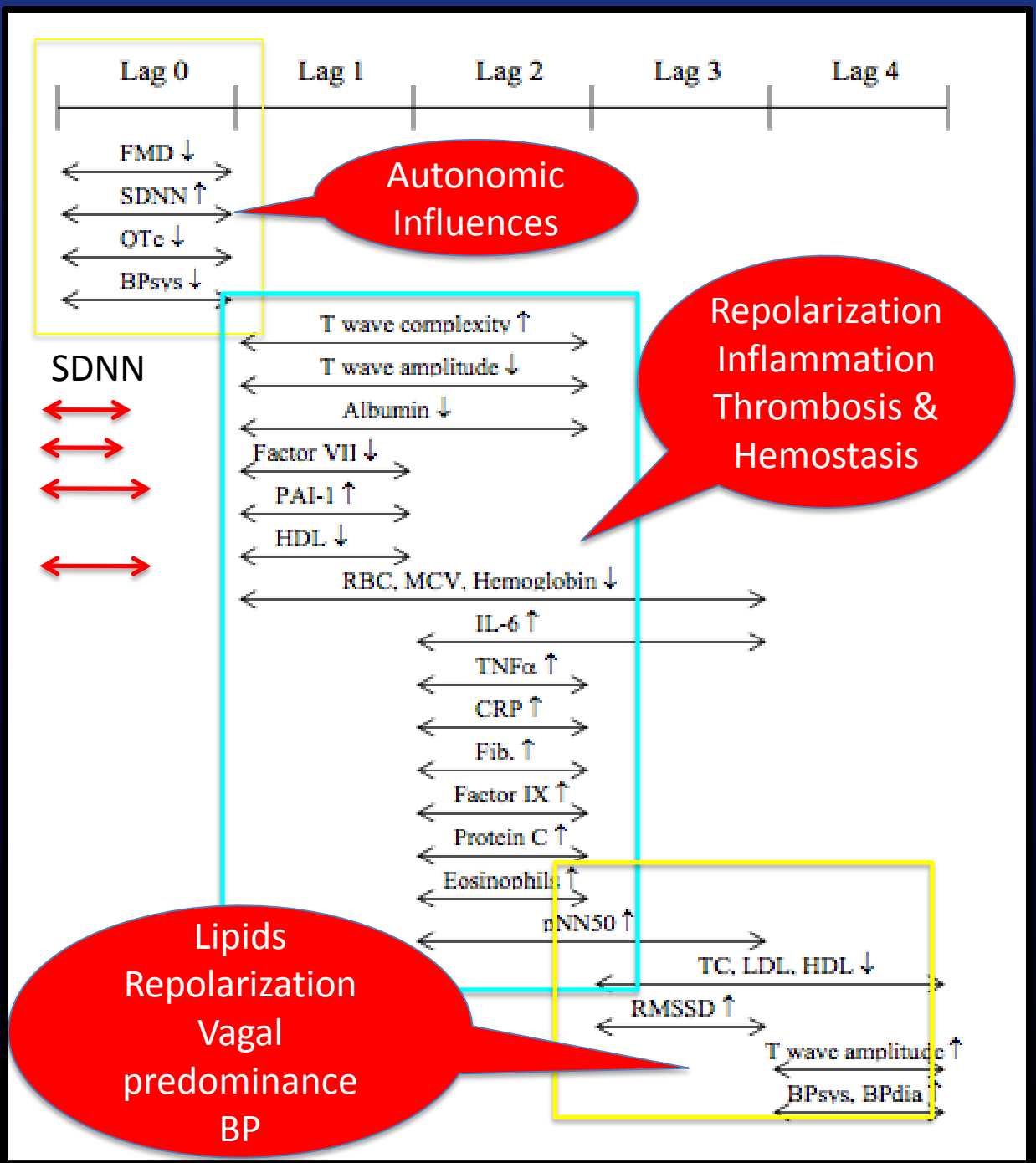
$PM_{2.5}$ and Electrocardiographic Parameters

Cohort having Diabetes – Chapel Hill, Raleigh, Durham, NC Airshed



Schneider et al. P&FT 2010

Time Course of Changes in ECG, Physiological, and Biochemical Endpoints



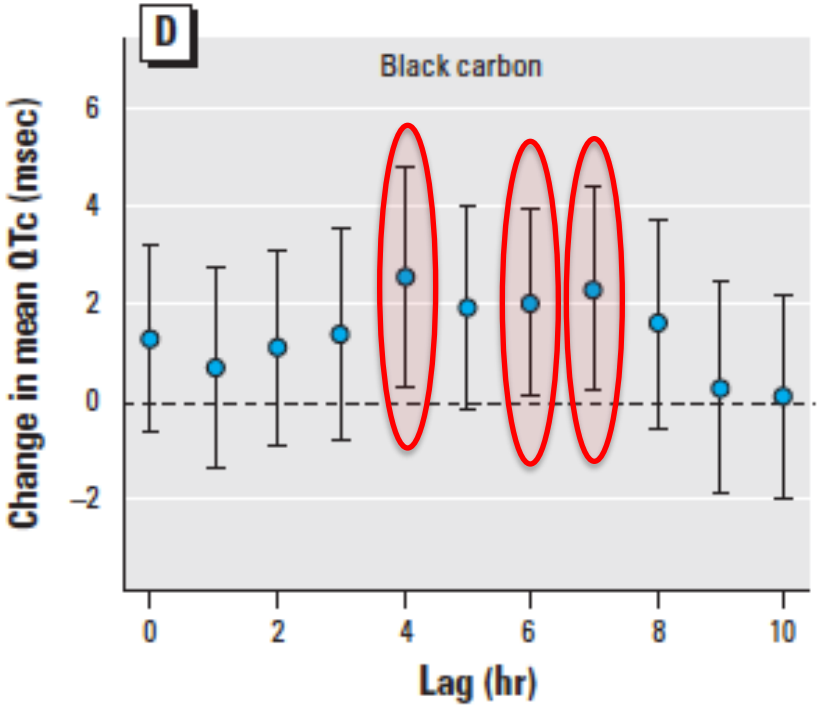
Araujo et al. showed dysfunctional HDL after exposure to ambient UF and F PM

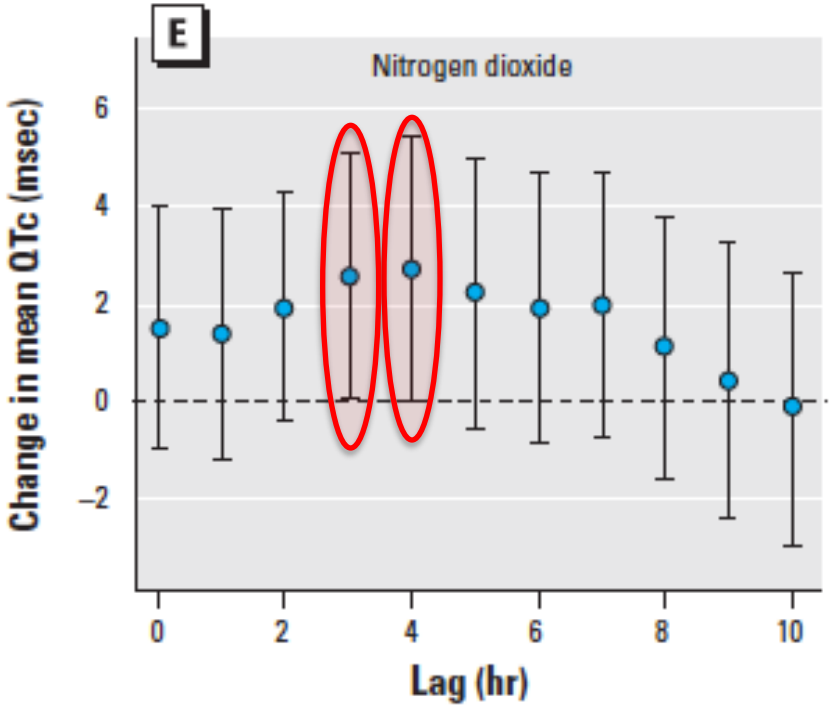
Schneider P&FT 2010

Unanswered Questions and Opportunities

Hong Kong, March 22, 2010

Change in Mean QTc per IQR Change Traffic-Related Pollutant



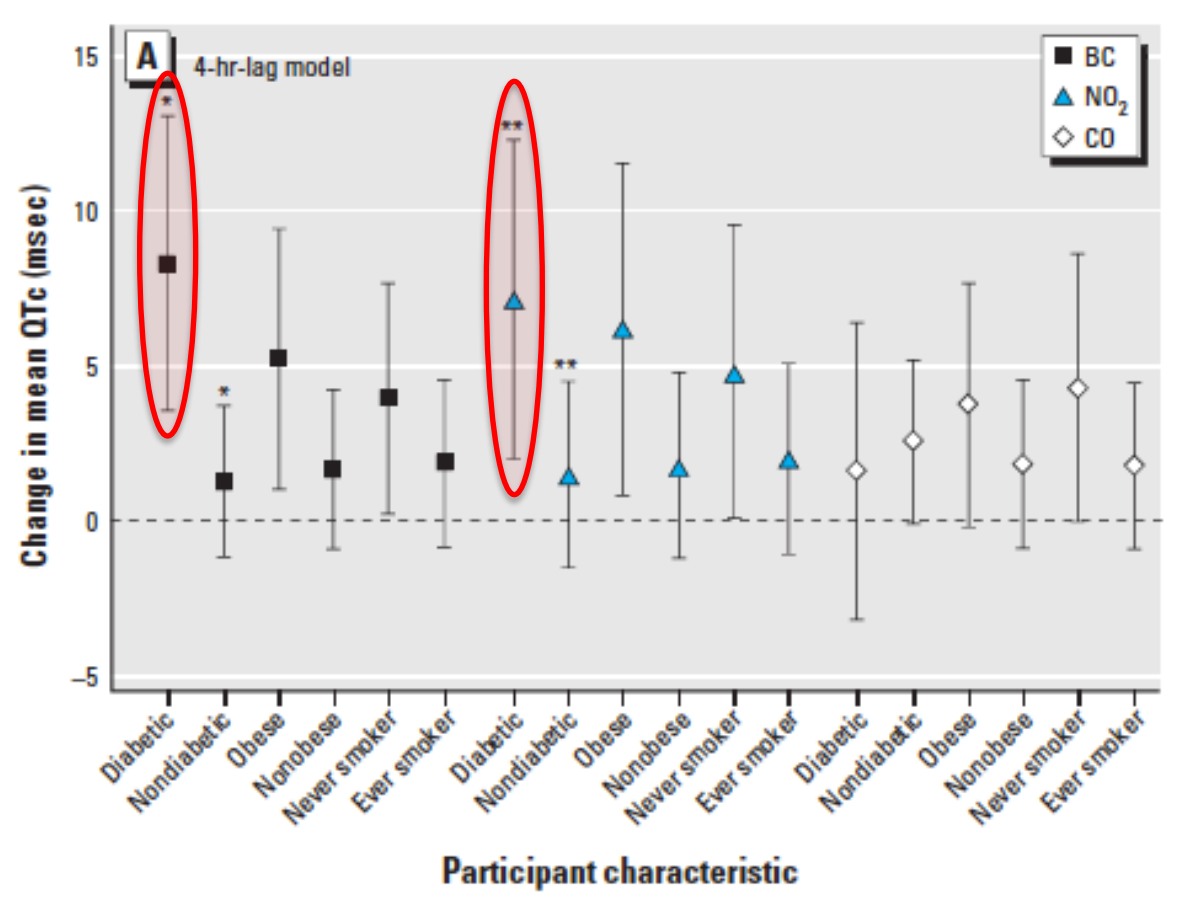


- Changes in cardiac repolarization as measured by QT interval corrected for heart rate [QTc] Single pollutant model of hourly exposure with random intercept using hourly lags.

Baja et al. EHP 2010

Adjusted change in mean QTc Change

Traffic-Related Pollutant Hourly Exposure with 4-Hr Lag

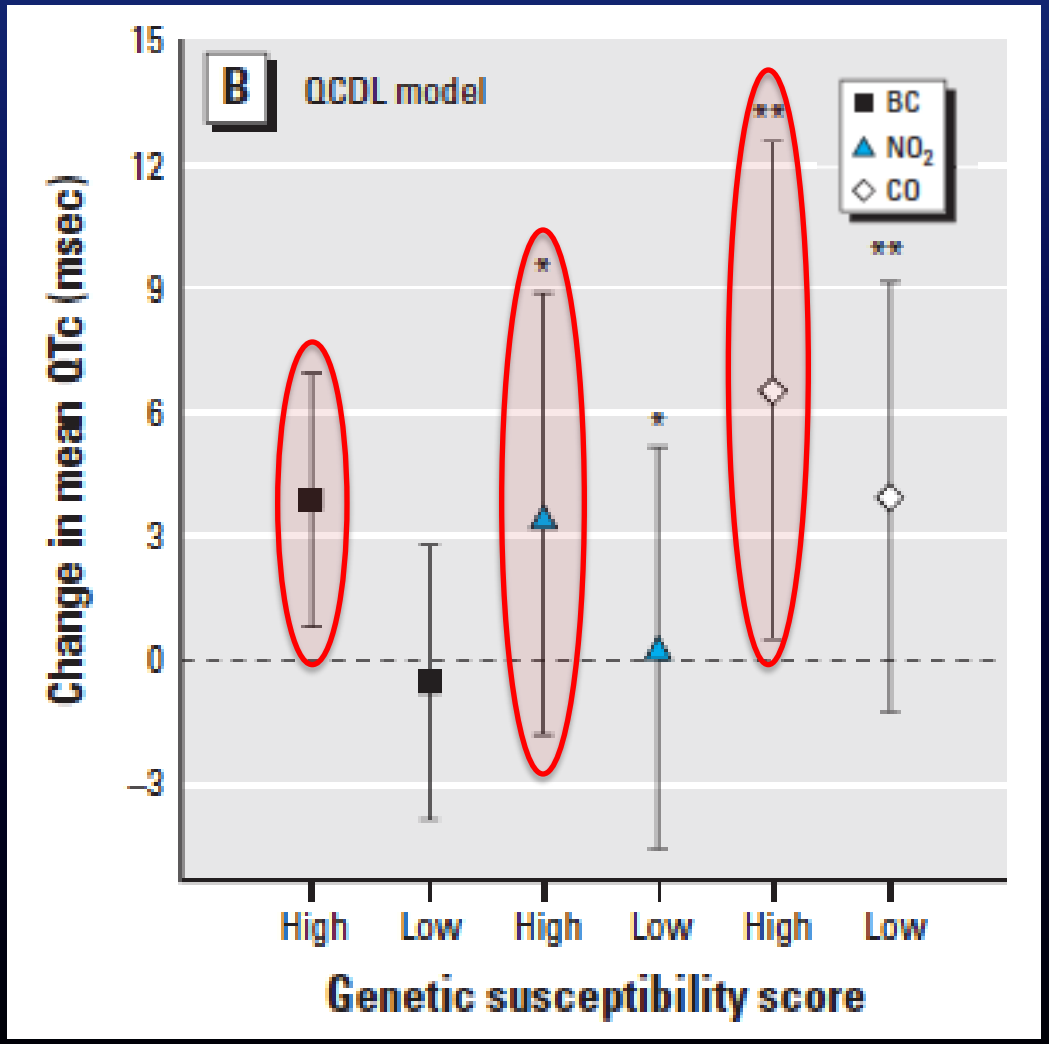


- Strong interaction was observed with in diabetes for BC, NO_2, but not CO.
- Effects with black carbon, NO_2 and CO implicate traffic-related PM and gas pollution

Baja et al. EHP 2010

Adjusted change in mean QTc Change per IQR

Traffic-Related Pollutant Hourly Exposure with 4-Hr Lag



- Genetic susceptibility to the effects of traffic-related pollutants is suggested by the differential response in individuals with GSS

Baja et al. EHP 2010

Adjusted effect estimates of change in mean QTc per IQR increase in traffic pollutant

Cumulative during the 10 hr before ECG measurement

		QCDL model		
Status/pollutant	Modifier	Change in mean QTc [msec (95% CI)]	*p*-Value	*p*-Value interaction
Diabetic status				
BC	DM	5.28 (0.67 to 9.90)	0.03	0.26
	Non-DM	1.43 (–0.79 to 3.65)	0.21	
NO_2	DM	7.10 (–0.12 to 14.32)	0.054	< 0.01
	Non-DM	1.22 (–2.67 to 5.12)	0.54	
CO	DM	3.78 (–3.59 to 11.14)	0.31	0.15
	Non-DM	3.91 (–0.62 to 8.44)	0.09	
Obesity status				
BC	Obese	3.97 (–0.07 to 8.01)	0.054	0.54
	Nonobese	1.23 (–1.14 to 3.60)	0.31	
NO_2	Obese	4.02 (–3.01 to 11.04)	0.26	< 0.01
	Nonobese	2.28 (–1.65 to 6.21)	0.25	
CO	Obese	3.38 (–4.27 to 11.02)	0.38	0.29
	Nonobese	3.90 (–0.57 to 8.37)	0.09	
Smoking Status				
BC	Never	4.32 (0.54 to 8.09)	0.03	0.74
	Ever	0.57 (–1.83 to 2.98)	0.64	
NO_2	Never	4.18 (–2.41 to 10.77)	0.21	< 0.01
	Ever	1.97 (–2.02 to 5.95)	0.33	
CO	Never	4.67 (–2.33 to 11.68)	0.19	0.14
	Ever	3.27 (–1.41 to 7.96)	0.17	

Baja et al. EHP 2010

Adjusted effect estimates for change in mean QTc with an IQRS change in cumulative traffic pollutant

By genetic

Table 4. Adjusted effect estimates for change in mean QTc with an IQR change in cumulative traffic pollutant exposure (during the 10 hr before ECG measurement) by genetic susceptibility to oxidative stress (high vs. low GSS).

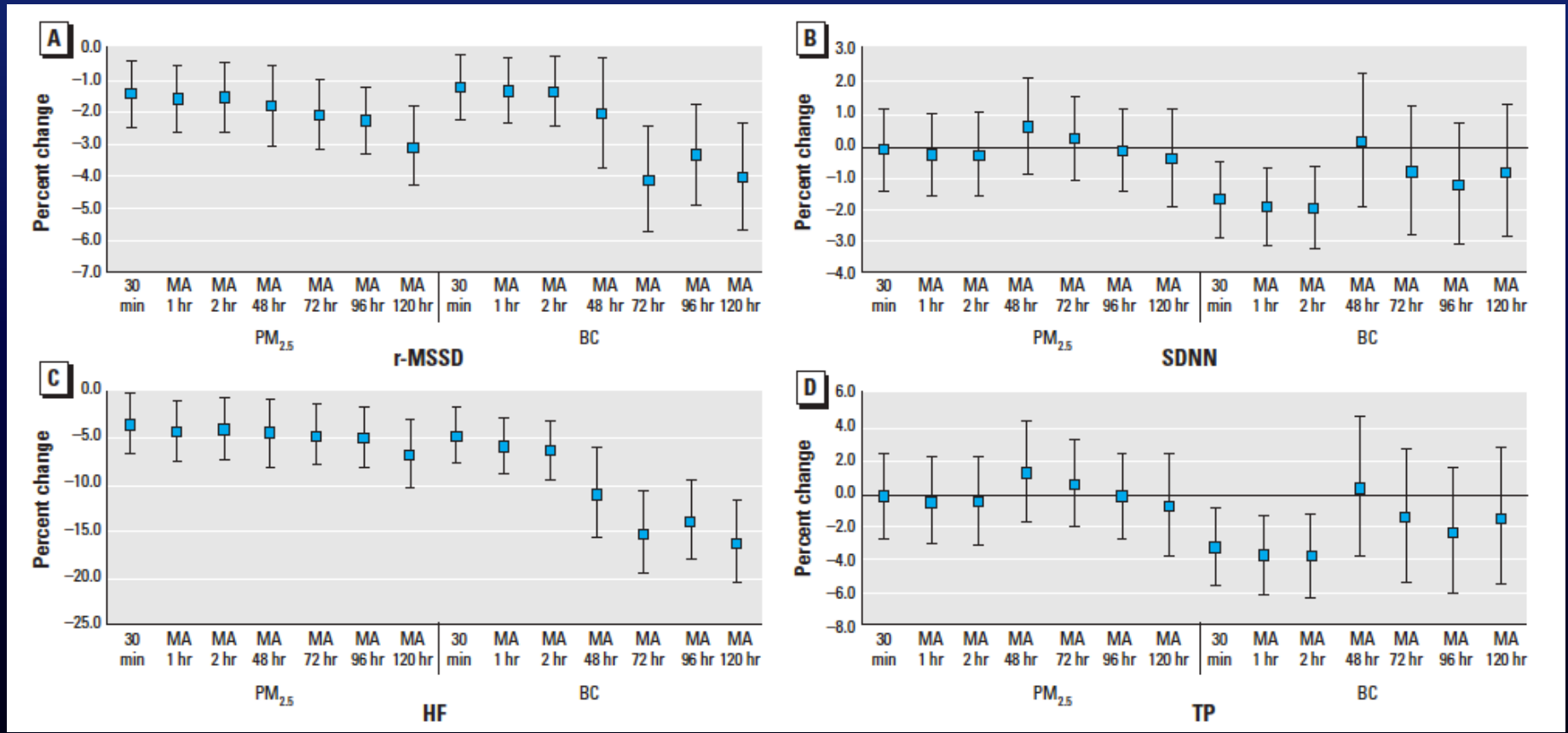
		QCDL model		
Pollutant	Modifier	Change in Mean QTc [msec (95% CI)]	*p*-Value	*p*-Value interaction
BC	High GSS	3.85 (0.78 to 6.93)	0.01	0.57
	Low GSS	–0.56 (–3.90 to 2.78)	0.74	
NO_2	High GSS	3.50 (–1.86 to 8.87)	0.20	< 0.01
	Low GSS	0.29 (–4.56 to 5.14)	0.90	
CO	High GSS	6.52 (0.49 to 12.55)	0.03	0.08
	Low GSS	3.94 (–1.28 to 9.16)	0.14	

GSS measures the genetic susceptibility of a participant to oxidative stress by adding all the unfavorable genotypes of the participant.

Baja et al. EHP 2010

Percent Change Heart Rate Variability

Associations with different averaging times of $PM_{2.5}$ and BC



Zanobetti et al. EHP 2010

Percent Change r-MSSD and HR

Control for traffic exposure on association with ambient PM

Exposure		Percent change (95% CI) r-MSSD	Percent change (95% CI) HF
Models including ambient $PM_{2.5}$			
Model 1	2-hr mean ambient $PM_{2.5}$	–2.0 (–3.3 to –0.6)	–5.2 (–9.2 to –1.1)
	In traffic, previous 2 hr	–15.2 (–24.8 to –4.4)	–39.2 (–58.0 to –12.0)
	In traffic, part of the previous 2 hr	–2.8 (–5.4 to –0.2)	–4.8 (–12.4 to 3.4)
Model 2	2-hr mean ambient $PM_{2.5}$	–2.2 (–3.6 to –0.9)	–5.9 (–9.8 to –1.8)
Model 3	2-hr mean ambient $PM_{2.5}$, not home	–7.9 (–10.3 to –5.3)	–14.8 (–21.6 to –7.4)
	2-hr mean ambient $PM_{2.5}$, home	0.4 (–1.3 to 2.1)	–1.6 (–6.6 to 3.6)
	2-hr mean ambient $PM_{2.5}$, home part of time	–4.0 (–7.0 to –0.9)	–9.3 (–17.8 to 0.0)
Models including indoor $PM_{2.5}$ at home			
Model 4	30-min mean indoor $PM_{2.5}$	0.2 (–0.8 to 1.3)	–0.8 (–4.0 to 2.5)
Model 5	2-hr mean indoor $PM_{2.5}$	0.0 (–1.1 to 1.2)	–1.3 (–4.9 to 2.5)
Models including ambient BC			
Model 1	2-hr mean ambient BC	–2.2 (–4.0 to –0.4)	–10.4 (–15.4 to –5.2)
	In traffic, previous 2 hr	–15.7 (–25.2 to –5.0)	–38.5 (–57.4 to –11.1)
	In traffic, part of the previous 2 hr	–2.9 (–5.5 to –0.3)	–4.9 (–12.5 to 3.3)
Model 2	2-hr mean ambient BC	–2.5 (–4.3 to –0.7)	–11.1 (–15.9 to –5.9)
Model 3	2-hr mean ambient BC, not home	–6.9 (–10.1 to –3.6)	–17.4 (–25.9 to –8.0)
	2-hr mean ambient BC, home	0.4 (–1.8 to 2.8)	–5.2 (–11.7 to 1.7)
	2-hr mean ambient BC, home part of time	–6.5 (–10.2 to –2.6)	–22.2 (–31.5 to –11.6)
Models including indoor BC at home			
Model 4	30-min mean indoor BC	2.1 (0.0 to 4.2)	2.1 (–4.3 to 8.8)
Model 5	2-hr mean indoor BC	2.0 (–0.2 to 4.4)	2.3 (–4.7 to 9.8)

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Percent Change r-MSSD and HF

72 hour mean in two-pollutant models

Variable (72-hr mean)	Percent change (95% CI)	
	$PM_{2.5}$	BC
r-MSSD		
NO_2	1.16 (–0.97 to 3.34)	2.27 (0.00 to 4.59)
$PM_{2.5}$ or BC	–2.32 (–3.41 to –1.21)	–5.53 (–7.71 to –3.29)
O_3	–1.13 (–2.92 to 0.69)	–2.50 (–4.11 to –0.86)
$PM_{2.5}$ or BC	–1.71 (–2.71 to –0.70)	–4.06 (–5.81 to –2.28)
HF		
NO_2	–7.63 (–13.44 to –1.44)	1.06 (–5.61 to 8.21)
$PM_{2.5}$ or BC	–2.38 (–6.49 to 1.91)	–15.36 (–20.99 to –9.32)
O_3	6.89 (0.99 to 13.15)	1.81 (–3.33 to 7.23)
$PM_{2.5}$ or BC	–7.09 (–10.65 to –3.39)	–14.72 (–19.22 to –9.97)

Pollutant effects are scaled to IQR.

Zanobetti et al. EHP 2010

Table 2. Mixed linear effects models estimating the change in BP (mmHg) associated with a 1-SD increase[a] in BC (1,067 visits) and $PM_{2.5}$ (949 visits) levels.[b]

	Change in BP (95% CI)	
Air pollutant	SBP	DBP
BC	1.46 (0.10 to 2.82)*	0.87 (0.15 to 1.59)*
$PM_{2.5}$	0.45 (–0.71 to 1.61)	0.01 (–0.60 to 0.61)

[a]Corresponding to a 0.43-μg/m^3 increase in 7-day average BC concentrations and a 4.98-μg/m^3 increase in 7-day average $PM_{2.5}$ concentrations. [b]All regression models are adjusted for age, cigarette smoking, pack-years of smoking, season of clinical visit, weekday of clinical visit, body mass index, diabetes status, statin use, fasting glucose level, 7-day moving average of temperature (linear and quadratic), 7-day moving average of relative humidity (linear and quadratic), hour of clinical visit, year of clinical visit, years of education, race/ethnicity, antihypertensive medication use, and daily alcohol intake. *$p < 0.05$.

Mordukhovich et al. EHP 2009

Table 3. Modification of the association between a 1-SD increase in BC and BP (mmHg) by SNPs related to antioxidative defense.[a]

Genetic variant	Change in BP (95% CI) SBP	DBP
Catalase C/T (rs480575)		
CC (*n* = 488)	1.27 (–0.77 to 3.30)	0.62 (–0.48 to 1.74)
CT (*n* = 358)	1.36 (–1.16 to 3.89)	0.57 (–0.74 to 1.88)
TT (*n* = 103)	–0.53 (–5.27 to 4.21)	0.59 (–2.12 to 3.29)
p-Value for interaction	0.50	0.77
Catalase C1167T (rs769217)		
CC (*n* = 539)	1.40 (–0.52 to 3.32)	0.66 (–0.37 to 1.70)
CT (*n* = 336)	1.49 (–1.05 to 4.04)	0.59 (–0.77 to 1.94)
TT (*n* = 62)	2.51 (–3.90 to 8.92)	0.42 (–3.19 to 4.03)
p-Value for interaction	0.37	0.95
Catalase C(–262)T (rs1001179)		
CC (*n* = 594)	1.17 (–0.66 to 3.01)	0.40 (–0.61 to 1.41)
CT (*n* = 289)	0.99 (–1.75 to 3.73)	0.97 (–0.39 to 2.33)
TT (*n* = 50)	1.44 (–8.10 to 10.98)	3.56 (–0.63 to 7.75)
p-Value for interaction	0.65	0.42
Catalase A/G (rs2284367)		
AA (*n* = 534)	1.35 (–0.58 to 3.28)	0.68 (–0.36 to 1.72)
AG (*n* = 305)	1.76 (–0.93 to 4.46)	0.67 (–0.72 to 2.06)
GG (*n* = 73)	7.20 (1.46 to 12.93)	2.24 (–1.34 to 5.83)
p-Value for interaction	0.61	0.80
Catalase A/G (rs2300181)		
AA (*n* = 498)	2.05 (0.06 to 4.04)	0.64 (–0.40 to 1.68)
AG (*n* = 358)	0.56 (–1.91 to 3.02)	0.38 (–0.87 to 1.64)
GG (*n* = 74)	2.33 (–3.77 to 8.42)	3.59 (–0.15 to 7.32)
p-Value for interaction	0.28	0.31
GSTP1 C2293T (rs1799811)		
AA (*n* = 769)	1.29 (–0.31 to 2.90)	0.47 (–0.38 to 1.32)
AG (*n* = 116)	–0.24 (–5.15 to 4.68)	1.08 (–1.37 to 3.52)
GG (*n* = 5)[b]	—	—
p-Value for interaction	0.33	0.66
GSTP1 A313G (rs1695)		
AA (*n* = 440)	3.20 (0.91 to 5.49)	0.83 (–0.36 to 2.01)
AG (*n* = 363)	–0.53 (–2.77 to 1.70)	0.10 (–1.14 to 1.33)
GG (*n* = 86)	–0.29 (–6.44 to 5.85)	2.48 (–0.26 to 5.21)
p-Value for interaction	0.38	0.46
NQO1 C609T (rs1800566)		
CC (*n* = 680)	1.85 (0.08 to 3.62)	1.10 (0.15 to 2.04)
CT (*n* = 298)	1.43 (–1.13 to 4.00)	0.50 (–0.86 to 1.86)
TT (*n* = 35)	–6.28 (–21.07 to 8.52)	–1.23 (–8.46 to 6.01)
p-Value for interaction	0.28	0.16

[a]All counts reported correspond to number of study center visits. Interaction test results represent interactions between BC and variant allele number only. All regression models are adjusted for age, cigarette smoking, pack-years of smoking, season of clinical visit, weekday of clinical visit, body mass index, diabetes status, statin use, fasting glucose level, 7-day moving average of temperature (linear and quadratic), 7-day moving average of relative humidity (linear and quadratic), hour of clinical visit, year of clinical visit, years of education, race/ethnicity, antihypertensive medication use, and daily alcohol intake. [b]Insufficient sample size to obtain sample estimates.

Zanobetti et al. EHP 2010

Table 4. Effect modification of the association between a 1-SD increase in BC concentrations and BP (mmHg) by gene variants related to oxidative stress.[a]

Genetic variant	Change in BP (95% CI)	
	SBP	DBP
GSTM1		
Present ($n = 494$)	0.79 (–1.20 to 2.77)	0.98 (–0.11 to 2.07)
Null ($n = 527$)	1.84 (–0.12 to 3.81)	0.76 (–0.23 to 1.74)
p-Value for interaction	0.31	0.84
GSTT1		
Present ($n = 736$)	1.26 (–0.38 to 2.91)	0.86 (–0.02 to 1.74)
Null ($n = 206$)	0.56 (–2.59 to 3.71)	–0.09 (–1.44 to 1.62)
p-Value for interaction	0.91	0.80
HMOX-1 microsatellite $(GT)_n$ repeat length		
< 25 repeats ($n = 122$)	–0.33 (–4.80 to 4.14)	1.16 (–1.01 to 3.32)
≥ 25 repeats ($n = 898$)	1.81 (0.34 to 3.29)	0.81 (0.02 to 1.61)
p-Value for interaction	0.64	0.78

[a]All counts reported correspond to number of study center visits. Interaction test results represent interactions between BC and variant allele number only. All regression models are adjusted for age, cigarette smoking, pack-years of smoking, season of clinical visit, weekday of clinical visit, body mass index, diabetes status, statin use, fasting glucose level, 7-day moving average of temperature (linear and quadratic), 7-day moving average of relative humidity (linear and quadratic), hour of clinical visit, year of clinical visit, years of education, race/ethnicity, antihypertensive medication use, and daily alcohol intake.

Zanobetti et al. EHP 2010

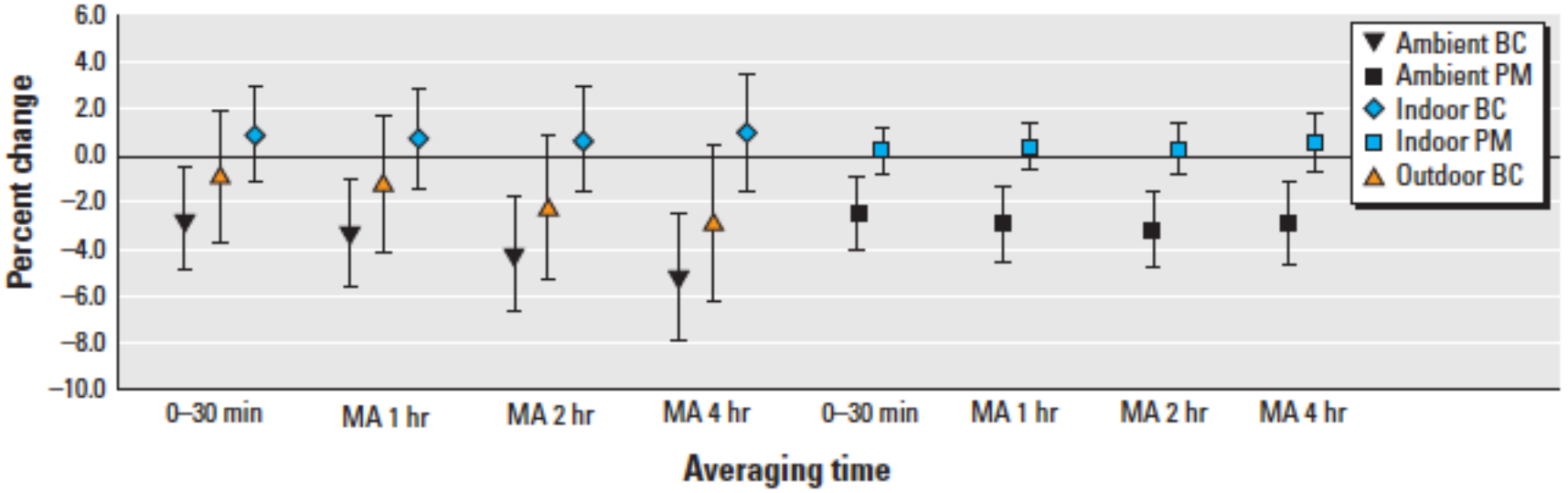

Figure 2. Percent change (95% CI) in r-MSSD (msec) associated with different averaging times of indoor $PM_{2.5}$ and BC exposure. MA, moving average. $PM_{2.5}$ and BC effects are scaled to 10 and 1 μg/m^3, respectively.

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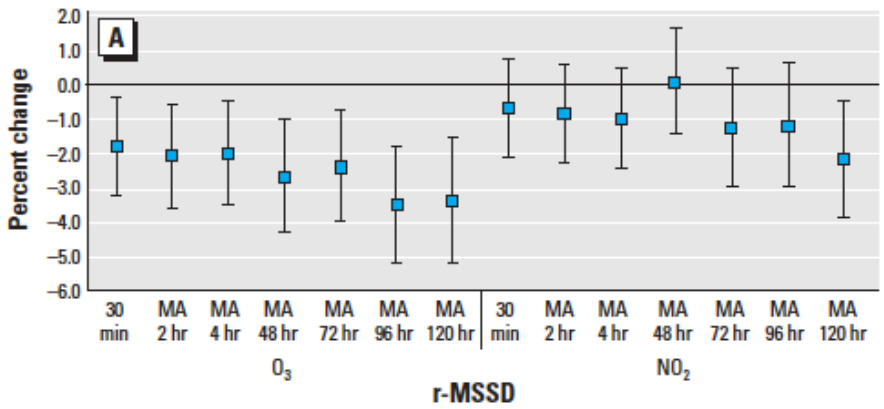


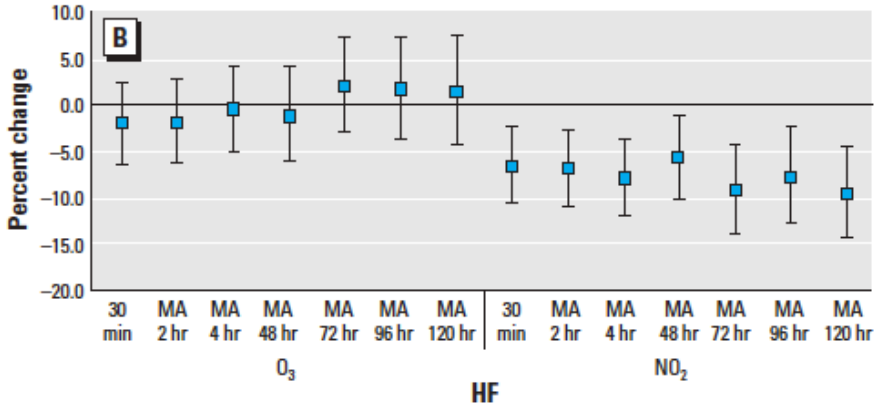


Figure 3. Percent change (95% CI) in r-MSSD (msec; *A*) and HF (msec^2; *B*) associated with different averaging times of O_3 and NO_2 exposure. MA, moving average. O_3 and NO_2 effects are scaled to their IQR.

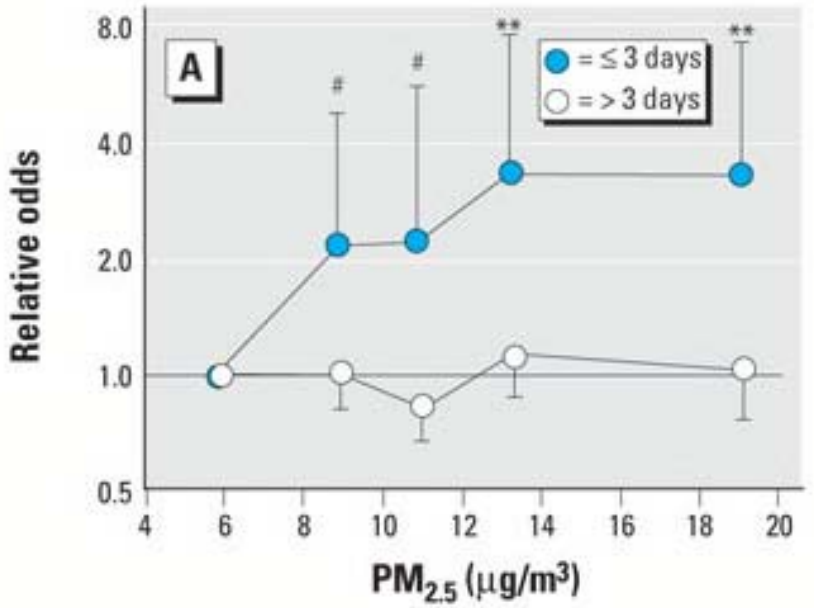
Table 4. Percent change in r-MSSD and in HF for the 72-hr mean in two-pollutant models.

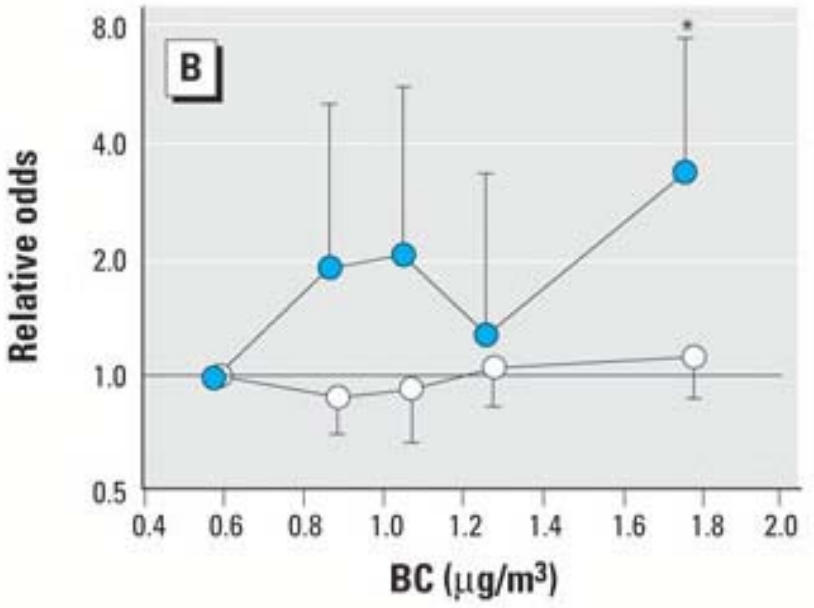
Variable (72-hr mean)	Percent change (95% CI)	
	$PM_{2.5}$	BC
r-MSSD		
NO_2	1.16 (–0.97 to 3.34)	2.27 (0.00 to 4.59)
$PM_{2.5}$ or BC	–2.32 (–3.41 to –1.21)	–5.53 (–7.71 to –3.29)
O_3	–1.13 (–2.92 to 0.69)	–2.50 (–4.11 to –0.86)
$PM_{2.5}$ or BC	–1.71 (–2.71 to –0.70)	–4.06 (–5.81 to –2.28)
HF		
NO_2	–7.63 (–13.44 to –1.44)	1.06 (–5.61 to 8.21)
$PM_{2.5}$ or BC	–2.38 (–6.49 to 1.91)	–15.36 (–20.99 to –9.32)
O_3	6.89 (0.99 to 13.15)	1.81 (–3.33 to 7.23)
$PM_{2.5}$ or BC	–7.09 (–10.65 to –3.39)	–14.72 (–19.22 to –9.97)

Pollutant effects are scaled to IQR.

Relative Odds of Ventricular Arrhythmia

ICD Cohort - Boston, MA Airshed





- Ventricular arrhythmia detection more likely during a time of electrical instability.
- Association with black carbon (BC) suggest traffic exposure

Dockery et al. EHP 2005

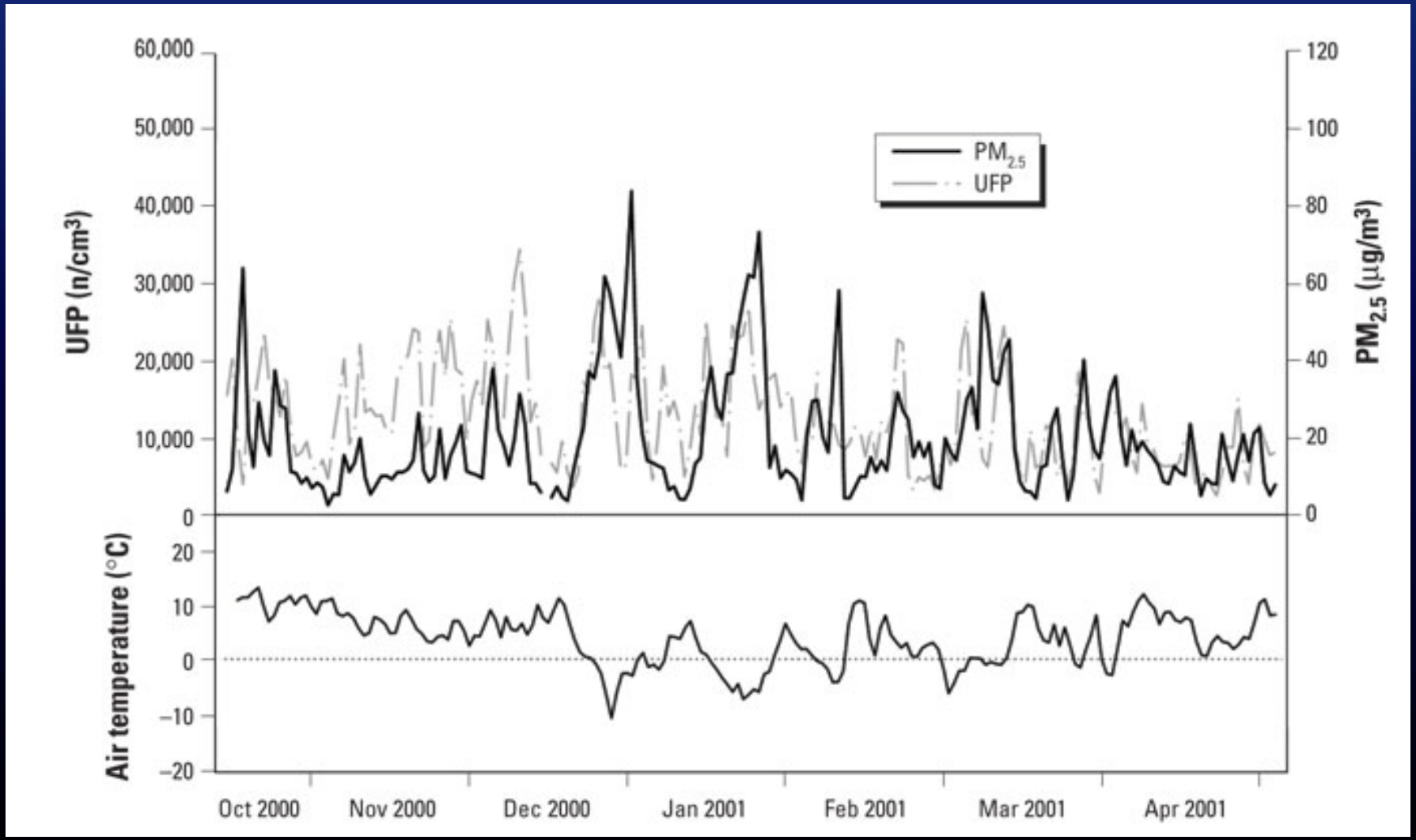
PM Affects Cardiac Repolarization

Cohort with Heart Disease – Erfurt, Germany

- 56 patients with pre-existing heart disease
- Repolarization changes changes are related to hourly measurements of ambient air pollution:
  - Sulfur dioxide, ozone, CO, NO, NO_2
  - Particle number, $PM_{2.5}$
  - SO_4
  - Organic carbon, elemental carbon
  - Temperature, barometric pressure, humidity

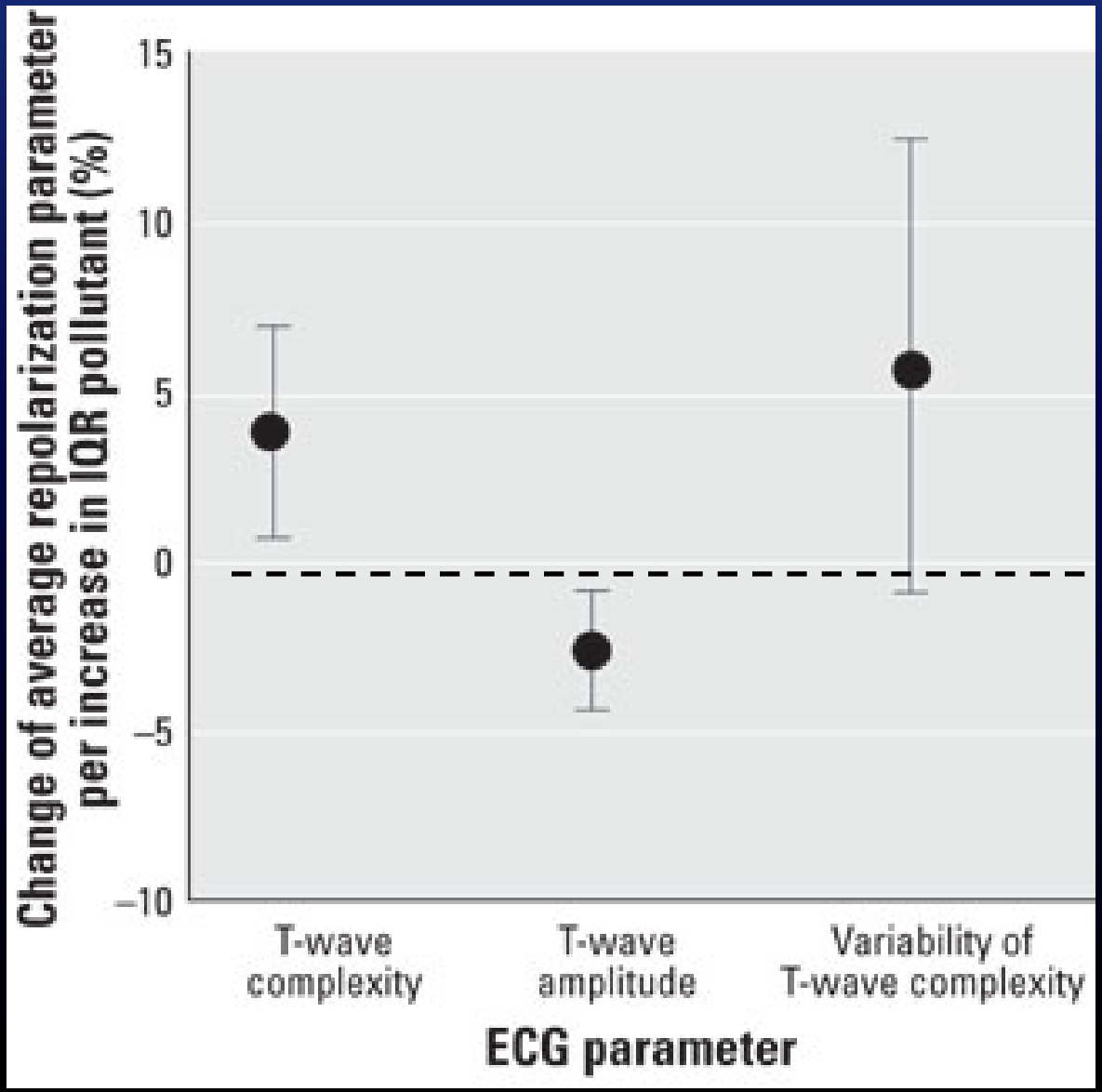
Henneberger et al. EHP 2005

Time Series of $PM_{2.5}$, UFP & Temperature



Henneberger et al. EHP 2005

PM Affects Cardiac Repolarization



- Acute effect of inhaled ambient PM on ventricular repolarization is a potential mechanism for the PM exposure and cardiovascular disease relationship.
- The time-course of PM effects has not been established.

Henneberger et al. EHP 2005

WHO Is Susceptible?

"The moral test of a government is how it treats

those who are at the dawn of life,
the children;

those who are in the twilight of life,
the aged;

and those who are in the shadow of life,
the sick, the needy, and the handicapped."

Hubert Humphrey, 1976

There Are Many Kinds of Susceptibility, Depending on the End Point

- People with cardiovascular disease may be sensitive to PM if death is the end point.
- People with certain kinds of lung disease may be sensitive if hospitalization for asthma or other respiratory diseases is the end point.
- Pregnant women or growing children may be sensitive if reproductive outcomes or lung growth is the end point.

Data are consistent for increased effect in people who have:

- Lung Disease (e.g asthma, COPD)
- Diabetes
- Heart Failure
- Coronary artery disease

It is also consistent for:

- Unborn children (pregnant mothers)
- Very young, very old

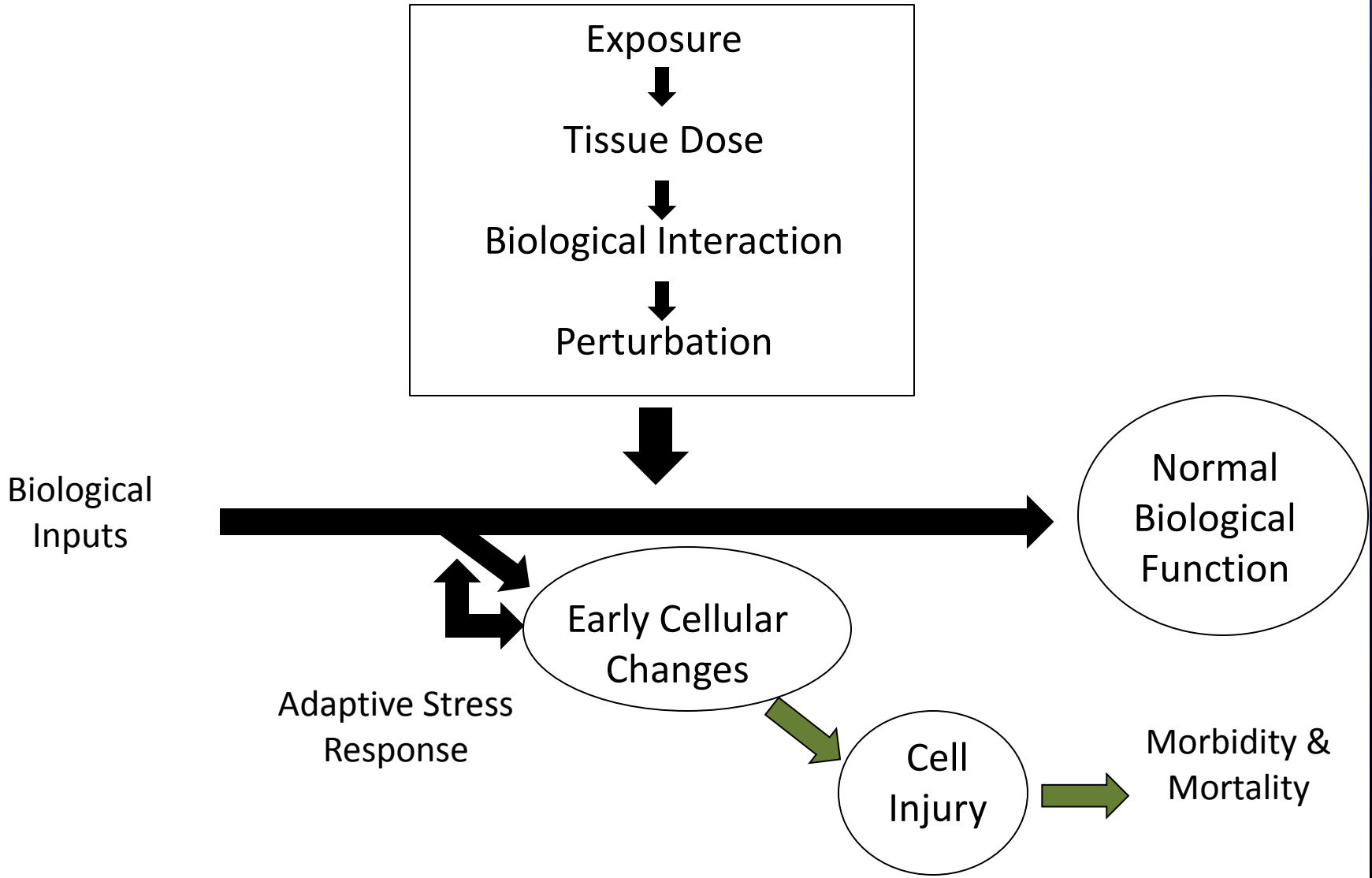
Data are inconsistent for people who have:

- Peripheral vascular disease?
- Cerebrovascular disease?
- Hypertension?

Not yet studied:

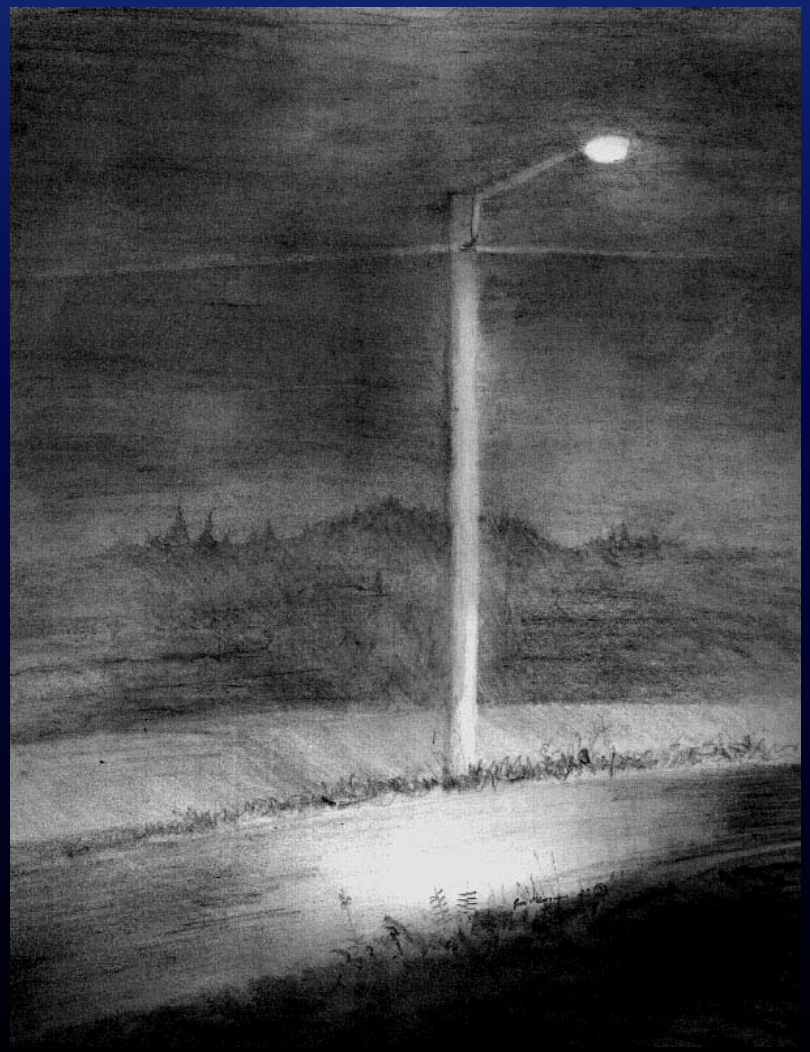
- Alzheimer's disease and other dementias
- Peripheral neuropathies, especially those with episodic or autoimmune features (ALS, MS, etc)
- Endocrine disorders other than diabetes

Toxicity Testing in the Twenty-First Century



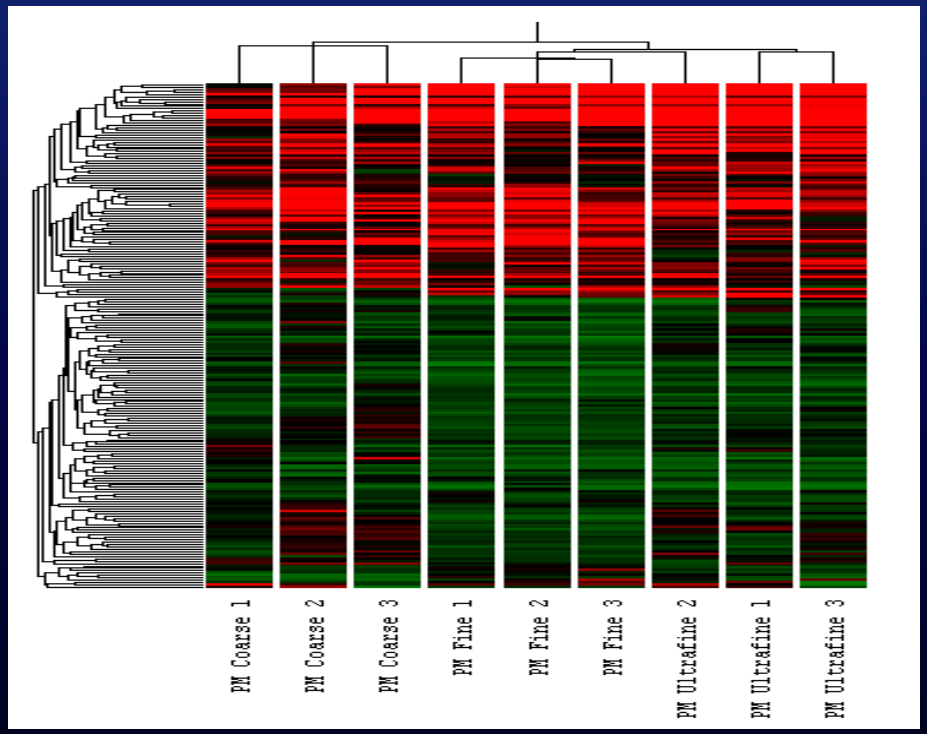
Adapted from Andersen et. al. 2005 and Tox Testing in the 21st Century

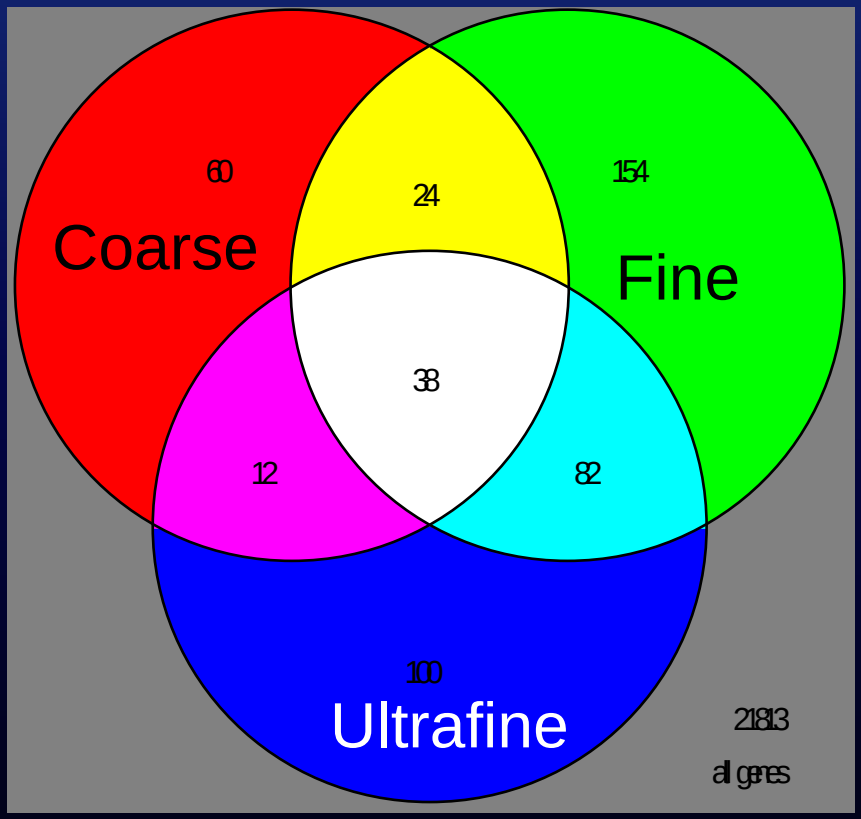
Looking Under the Lamp-post



- 22,000+ sequences on a 1.8 x 1.8 cm chip
- Hybridization with fluorescent cRNA probes
- Quantification with laser scanner
- Analysis of individual genes or biologic pathways

Genes Uniquely Expressed in Lung Cells Exposed to Coarse, Fine, or Ultra-Fine PM



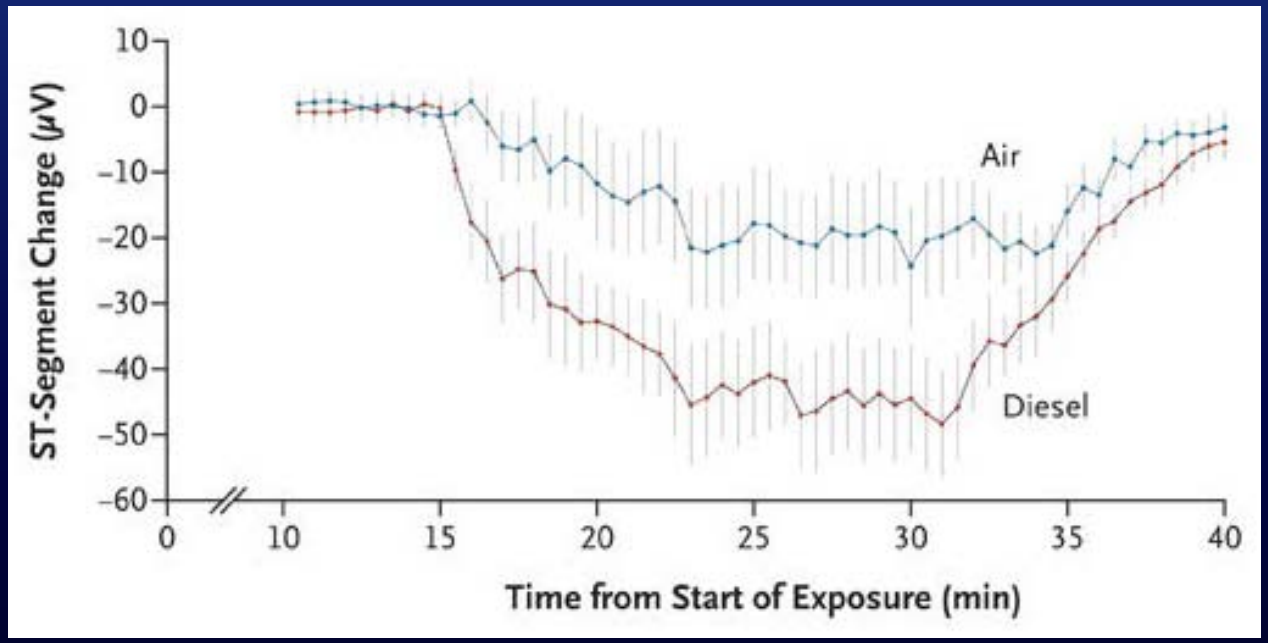


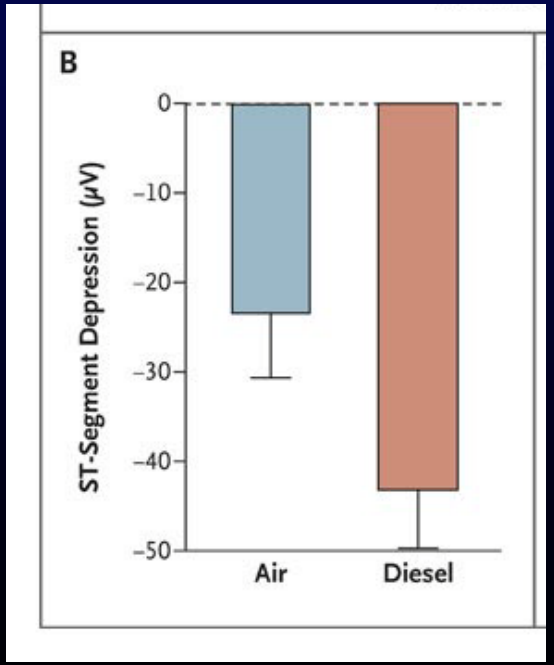
Identifying biomarkers of effect and susceptibility

What Do We Know About PM Components Today?

- It seems that nearly every component that has been tested in toxicology studies causes effects.
- No “silver bullet” to which all PM effects can be related.
  - May be why mass seems to be a consistent metric in epidemiology studies
- This has important implications for design of future studies
  - Multi-pollutant studies

Ischemic Effects of Diesel-Exhaust in Men with Coronary Heart Disease





Mills et al. 2008

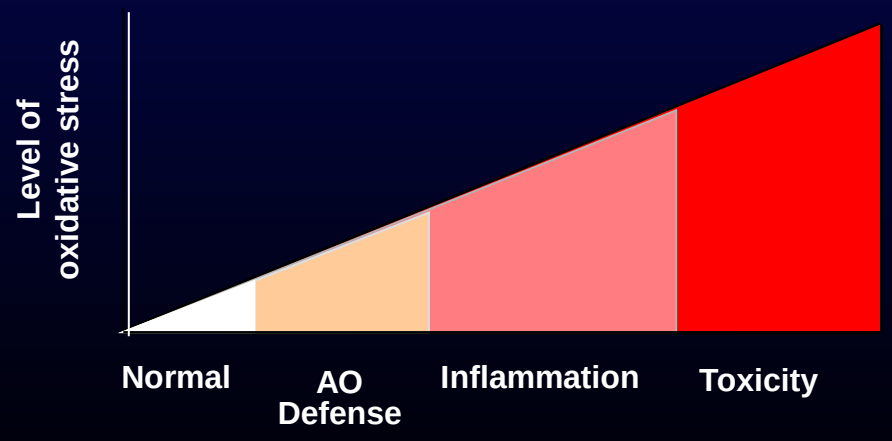
Perhaps Many PM Components Affect Cells the Same Way

How to explain similar PM-associated mortality and morbidity in cities with very different chemical composition?

Hypothesis:

- Organic chemical components and transition metals associated with PM contribute to adverse cardio-respiratory effects based on their ability to induce oxidative stress.
- Oxidative stress is responsible for the development of inflammation in the lung and cardiovascular system,
- A failure in antioxidant defense plays a role in the susceptibility to PM-induced adverse health effects.

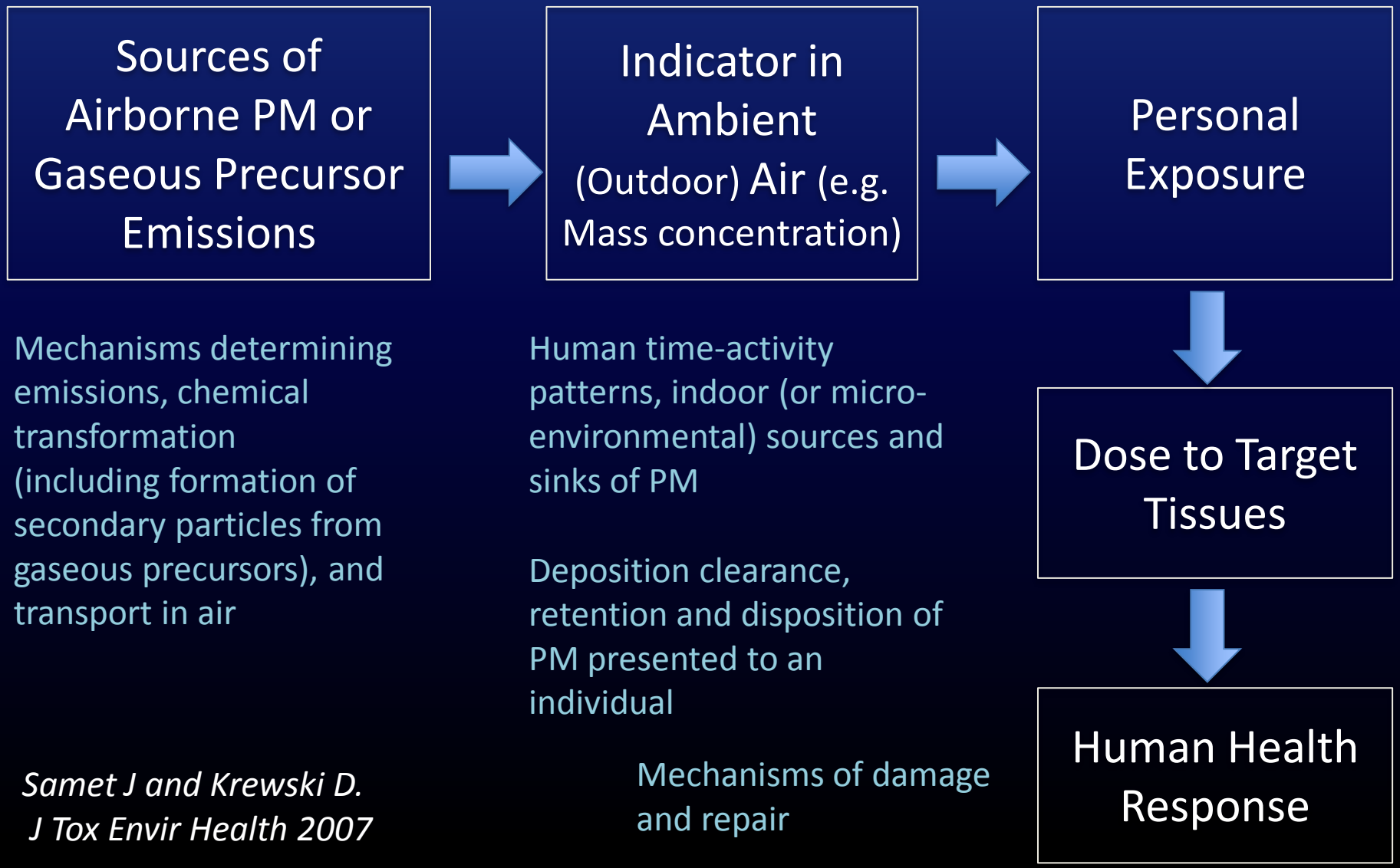
Hierarchical model of oxidative stress:



Nel et al., 2006

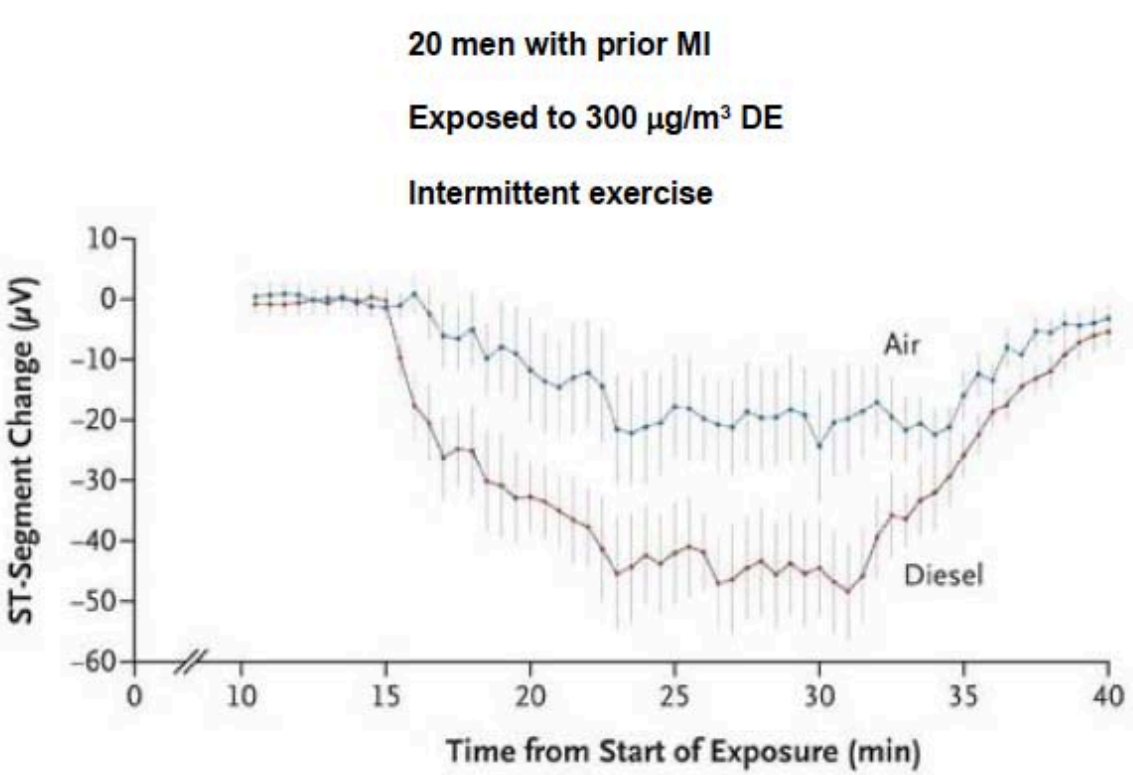
NRC Five-Stage Framework:

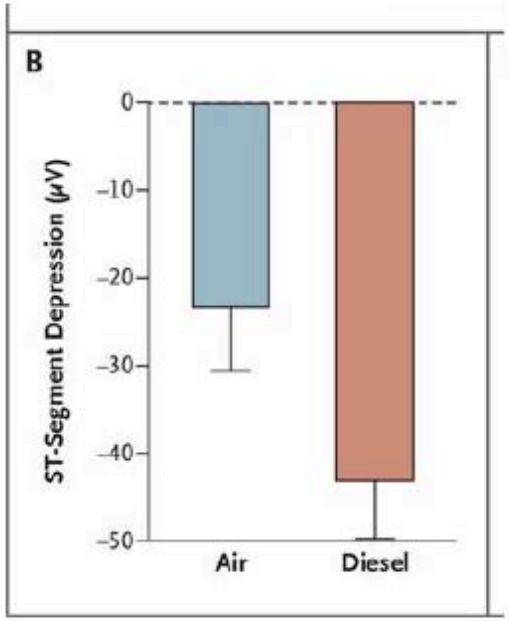
Integrating Particulate Matter Research (NCR, 1998)



Samet J and Krewski D.
J Tox Envir Health 2007

Diesel-Related PM is Associated with Increased Ischemia

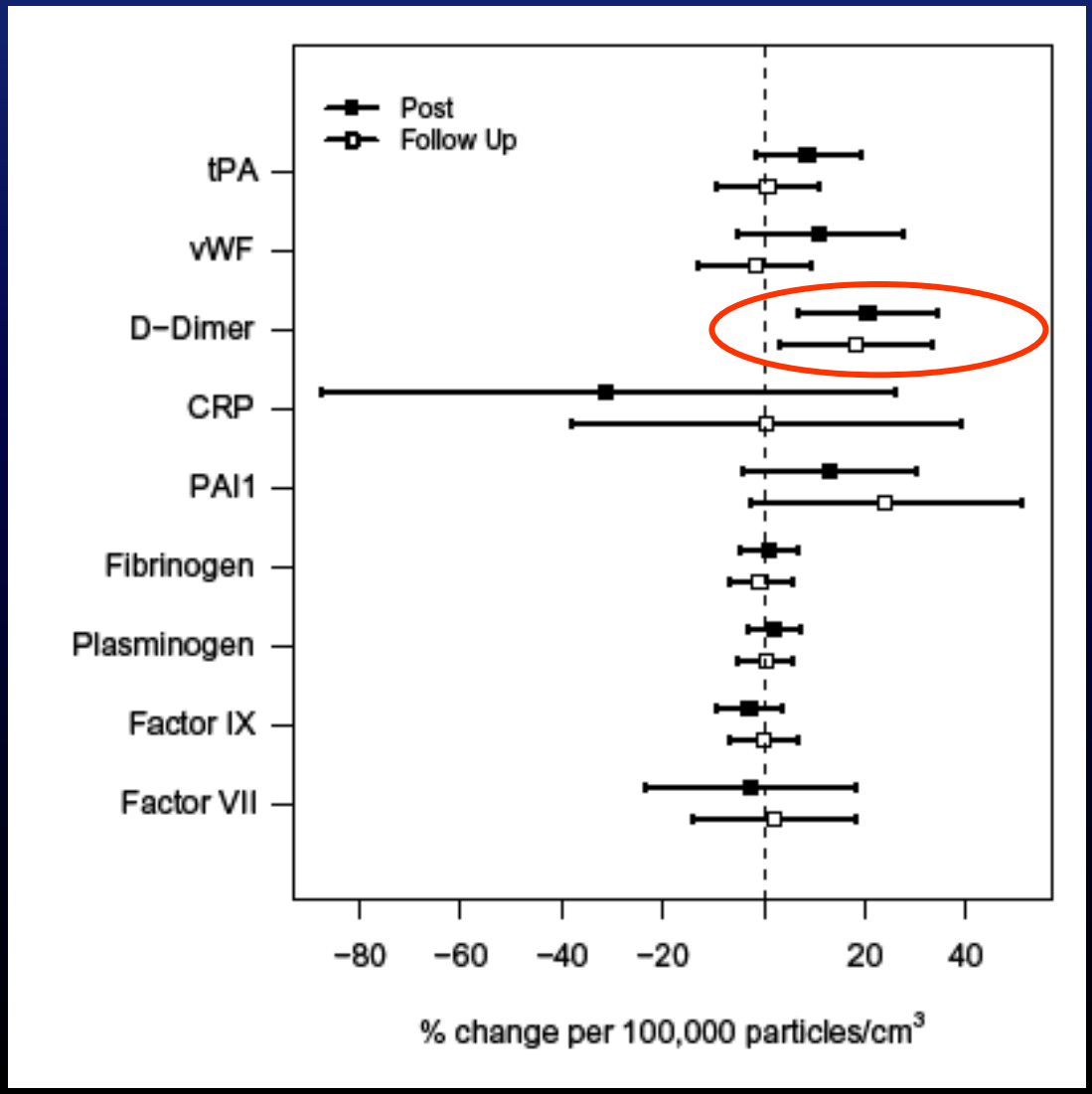




Mills et al., 2008

Ultrafine CAPS Causes Increased d-Dimer in Blood

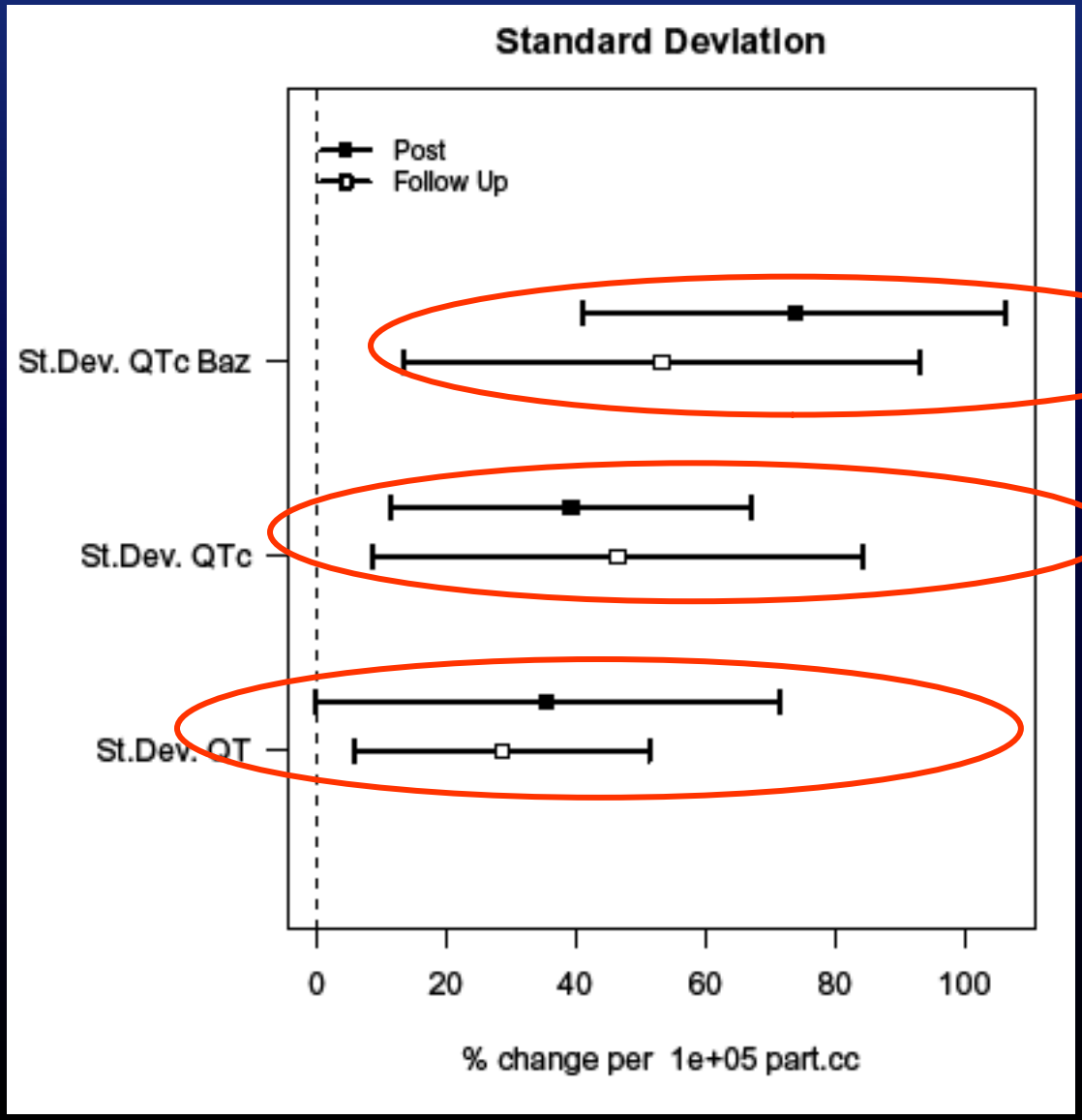
Chapel Hill, NC Airshed



Samet et al., 2008

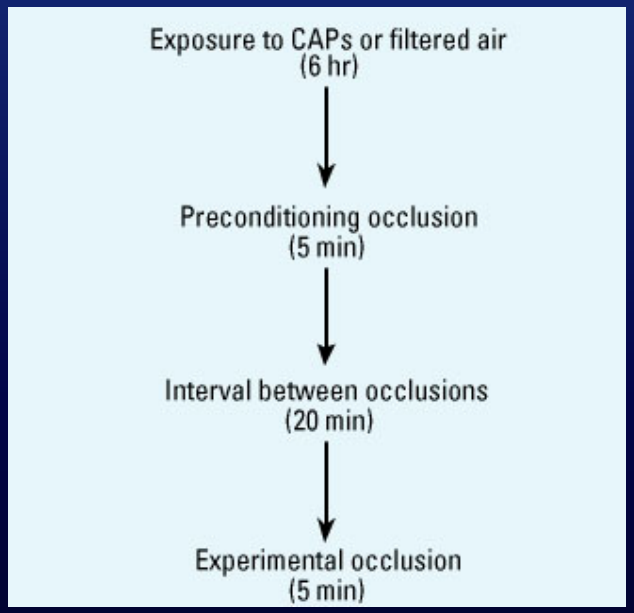
Ultrafine CAPS Causes Increased QT Variability

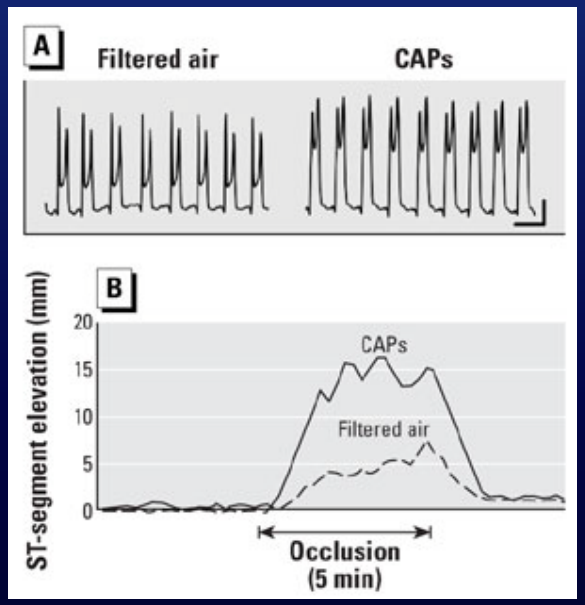
Chapel Hill, NC Airshed

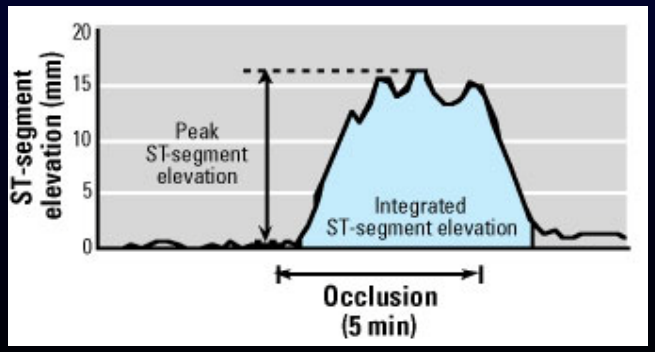


Samet et al., 2008

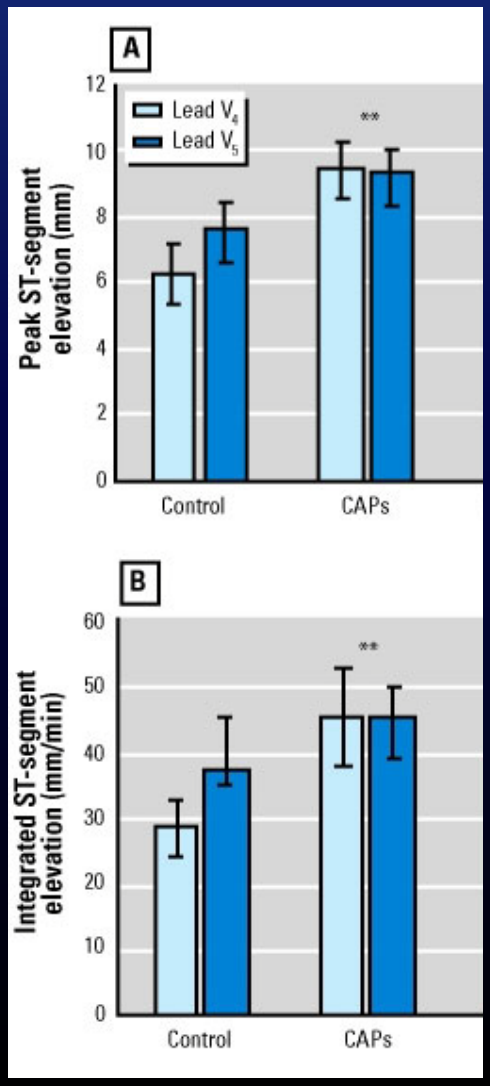
CAPs Modifies Ischemia-Induced T Wave Changes







- Implantation of balloon occluder for coronary artery occlusion
- Occlusion for 5 minutes with sham or CAPs exposure



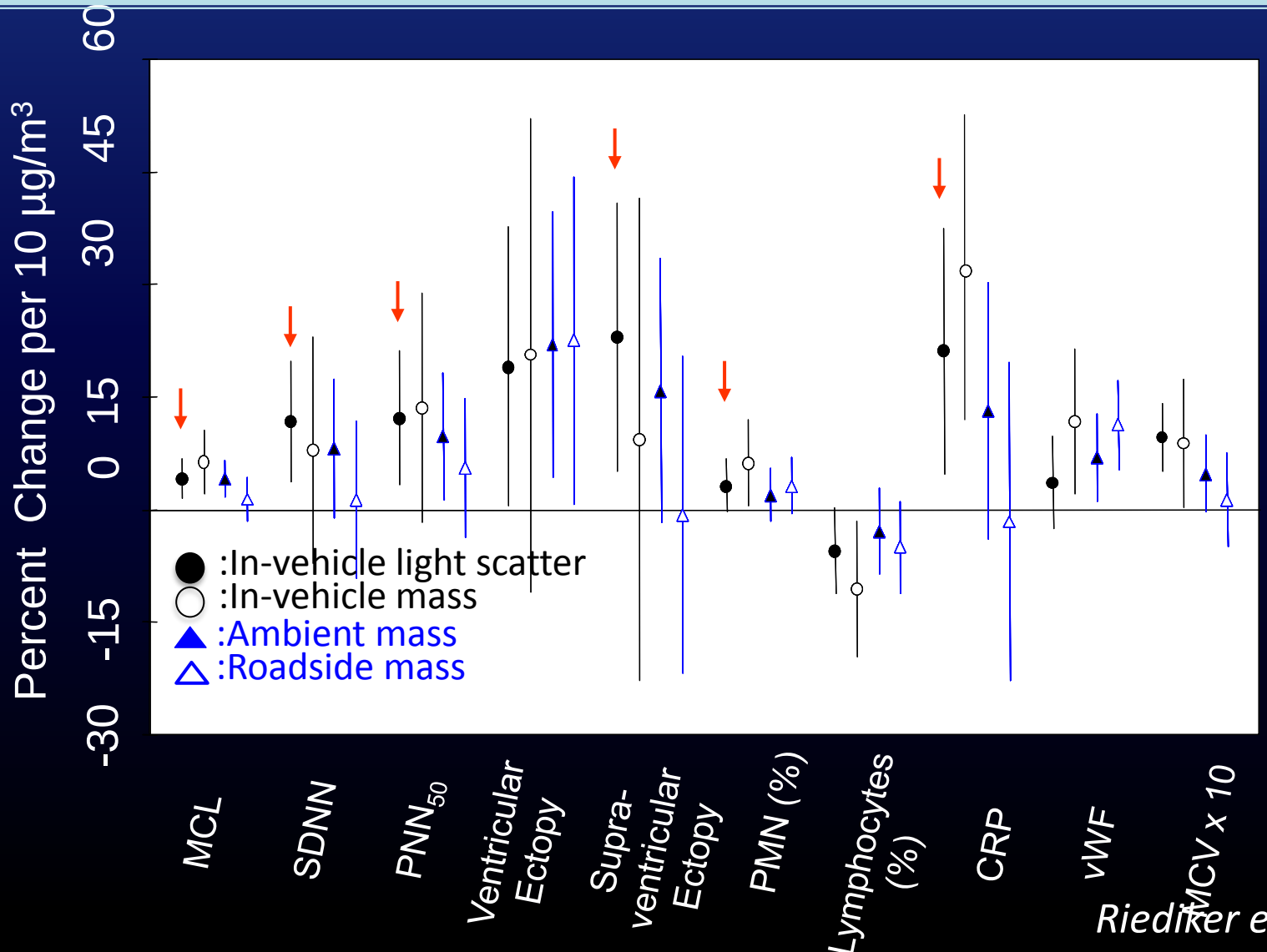
Wellenius et al. EHP 2002

PM Induced Changes in Ectopic Beats & HRV

	Effect per 10µg/m^3 $PM_{2.5}$			
Parameter	mean	slope	% change	p-value
VEB (/hour)	14.5	2.76	19.1%	0.045
SVEB (/hour)	4.48	1.03	23.0%	0.014
MCL (ms)	1001	41.9	4.2%	0.003
SDNN (ms)	129	15.2	11.7%	0.006
PNN50 (%)	43	5.28	12.2%	0.009
HF (BPM^2)	5.7	0.84	14.8%	0.019

Riediker et al. AJRCCM 2004

Cardiovascular Effects Associated with PM Derived from Mobile Sources



Riediker et al., 2004

Ambient and Traffic-Related PM can Trigger Myocardial Infarction

772 MI patients who survived 24-hours and completed interview

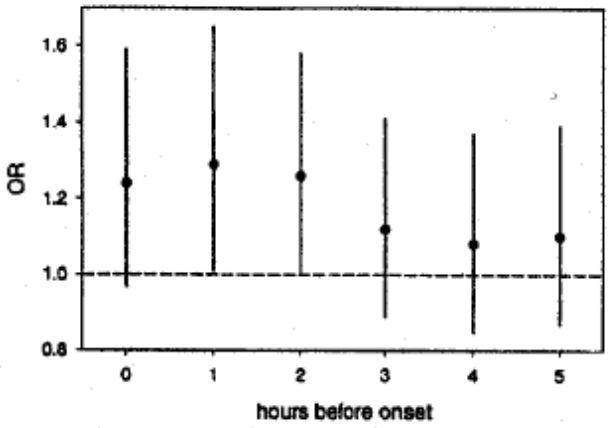
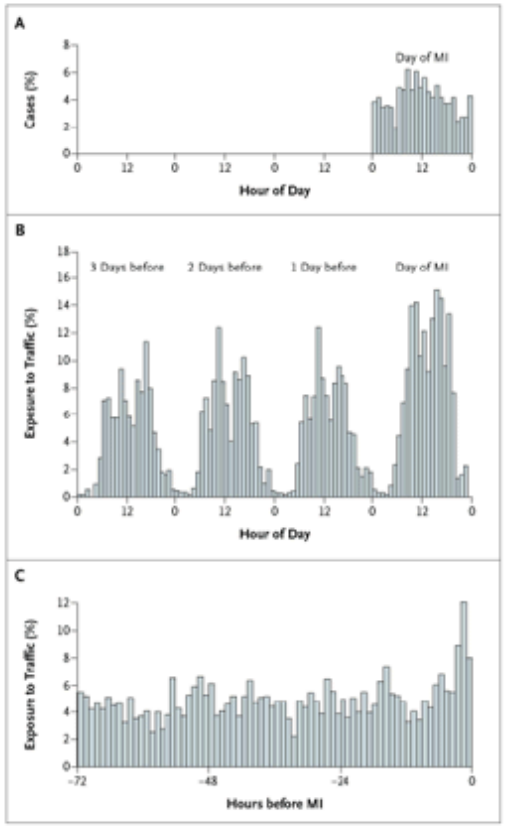


Figure 1. Univariate analyses for association between onset of MI and hourly concentrations of $PM_{2.5}$. Odds ratios and 95% CIs for an increase of 25 $\mu g/m^3$ $PM_{2.5}$.

Peters et al., 2001

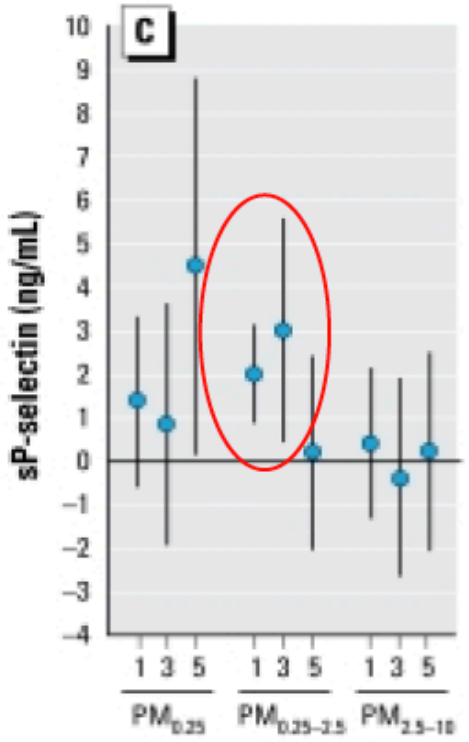
Association between MI and amount of time spent in traffic



Peters et al., 2005

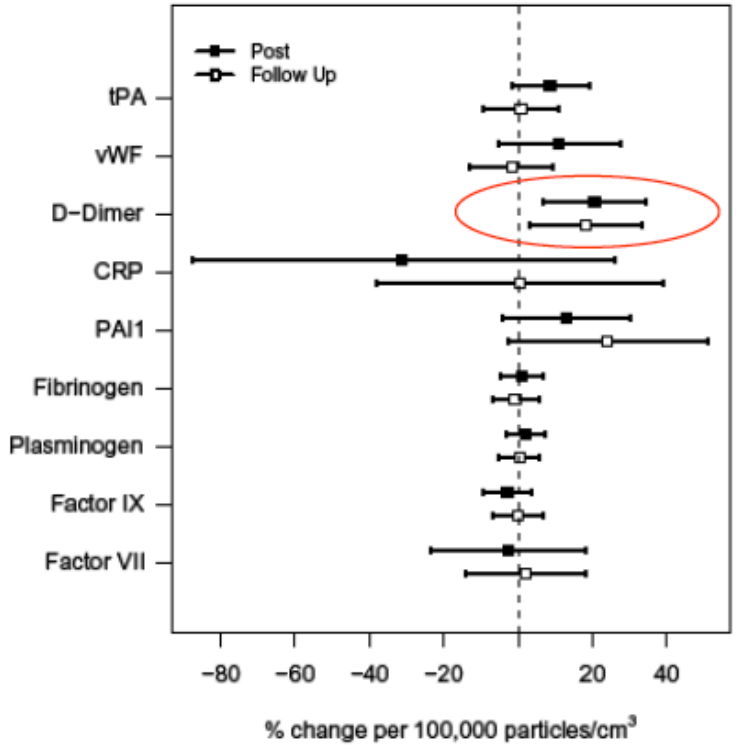
Ambient and Ultrafine PM are Pro-thrombotic

Association of PM platelet activation in people with CAD



Delfino et al., 2009

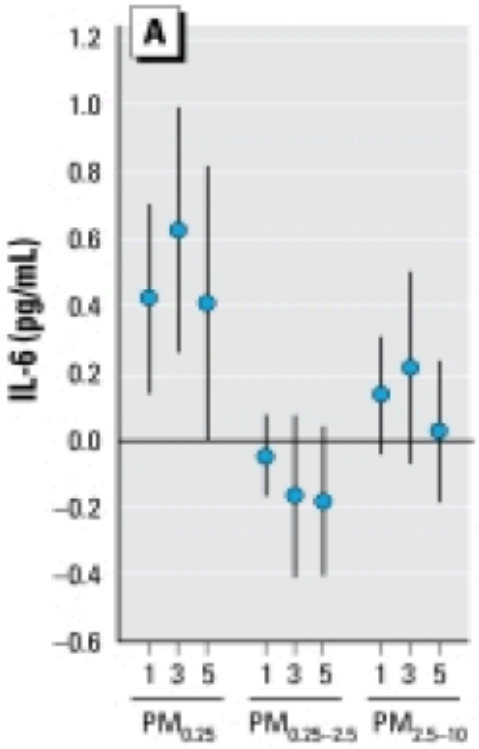
UF CAPS causes increased d-dimer formation in young healthy volunteers



Samet et al., 2008

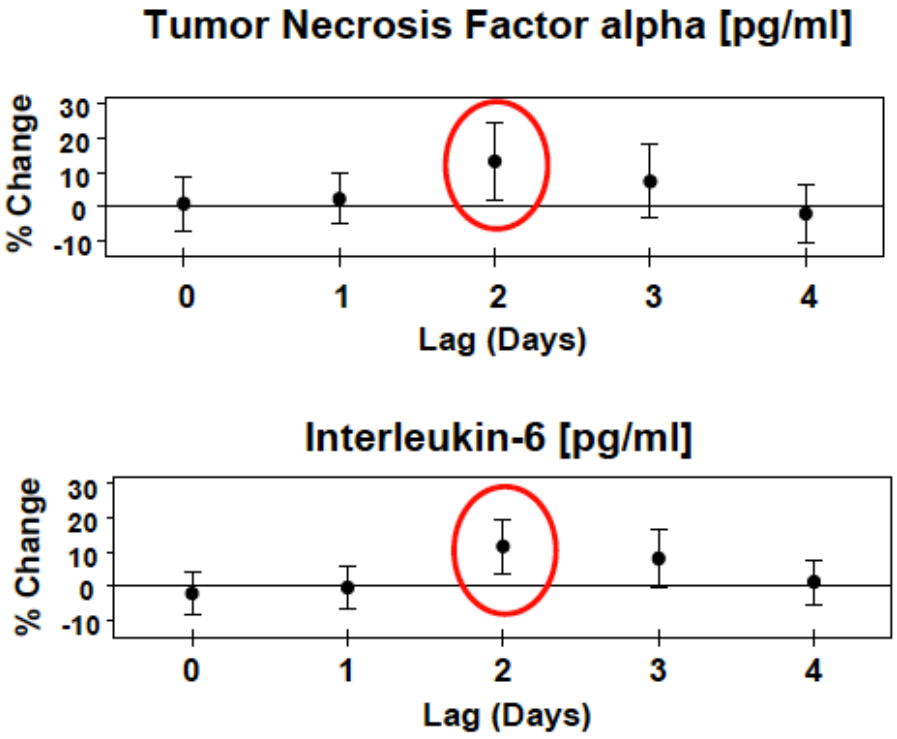
Ultrafine PM is Associated with Systemic Inflammation

Association of PM and blood cytokine levels in people with CAD



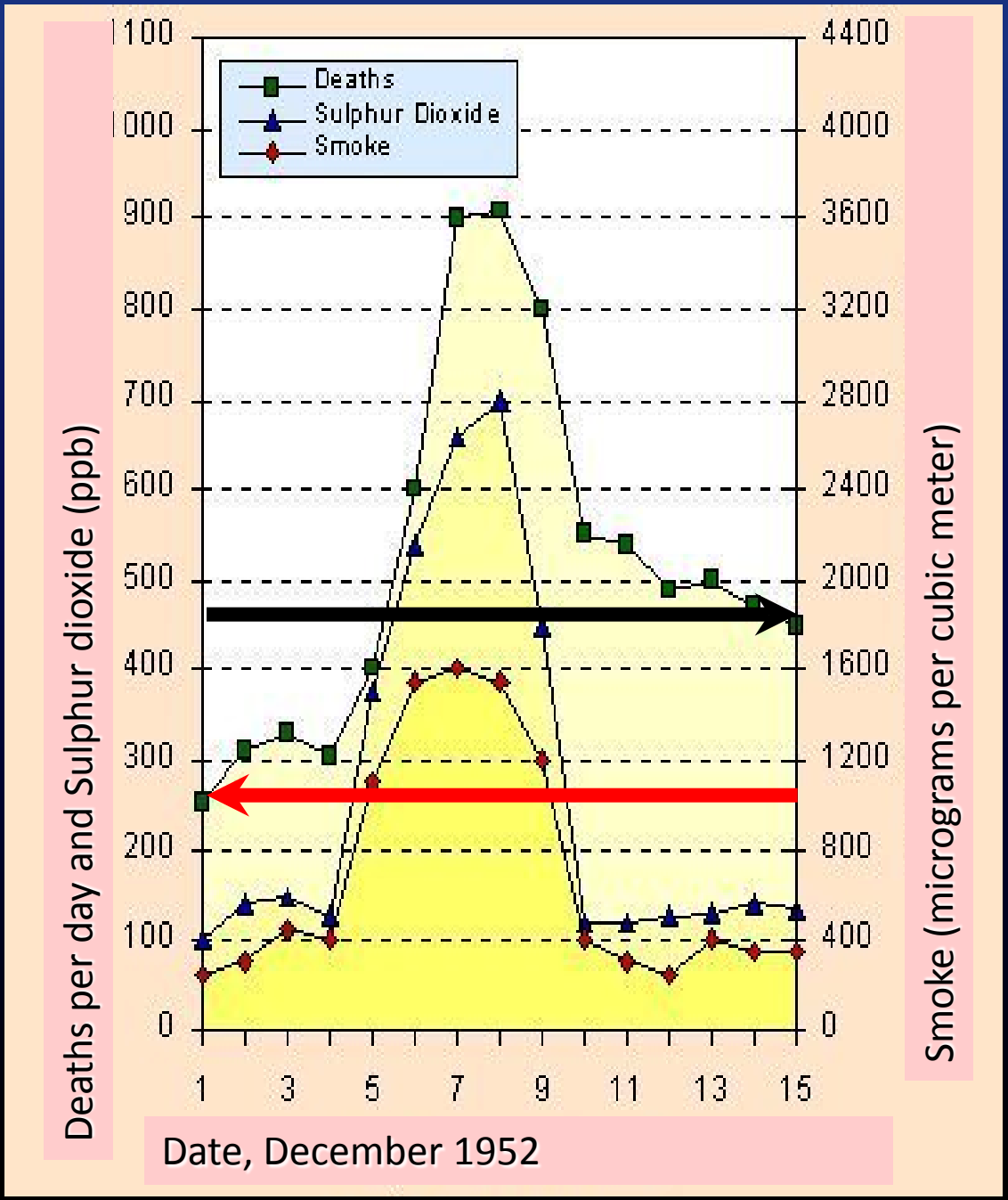
Delfino et al., 2009

Association of PM and blood cytokine levels in diabetics



Schneider et al., 2008

The Great London Smog Dec. 1952



- 12,000 excess deaths
- 2/3 >65 years old
- Increased death rates persisted through the next summer

Airborne
Particulate Matter
is derived from
many different sources

Characterization of Ambient UF PM

Formation Process:
Combustion, high temp. processes and atmospheric reactions

Travel Distance:
<1 to 10s km

Atmospheric half-life:
Minutes to hours

Formed by:
Nucleation of atmospheric gases
Condensation of gases

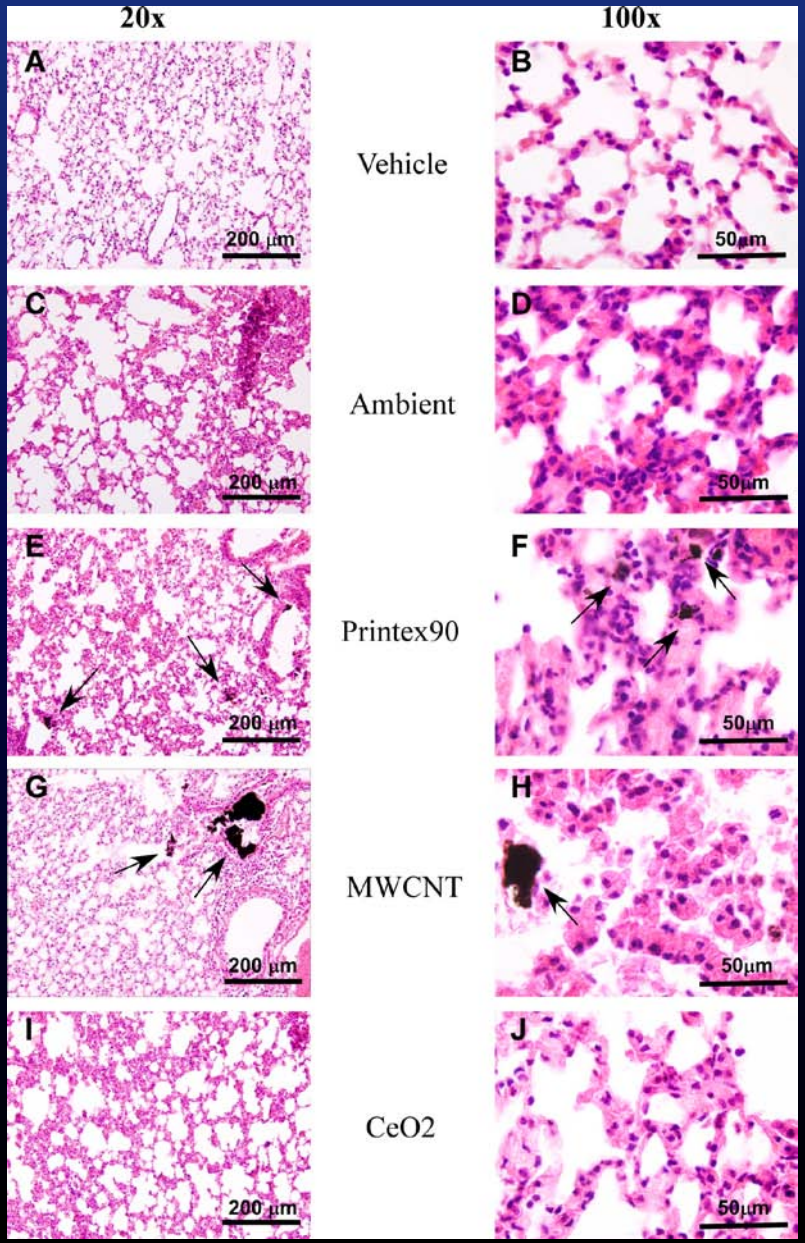
Removal Process:
Grows into accumulation mode
Diffuses to raindrops and other surfaces

Composed of:
Sulfate, EC, metal compounds, organic compounds with very low saturation vapor pressure at ambient temperature

Solubility:
Poorly characterized

Sources:
High temp. combustion, atmospheric reactions of primary gaseous compounds

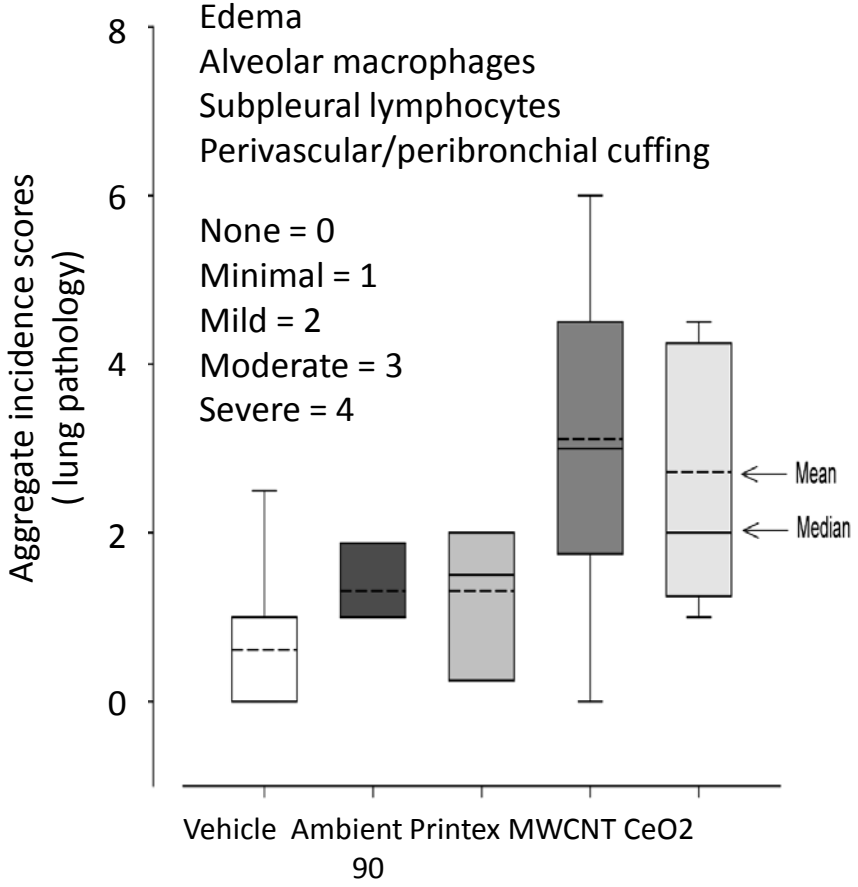
Ultrafine PM Lung Toxicity



24 hours after
100 µg intra-tracheal instillation

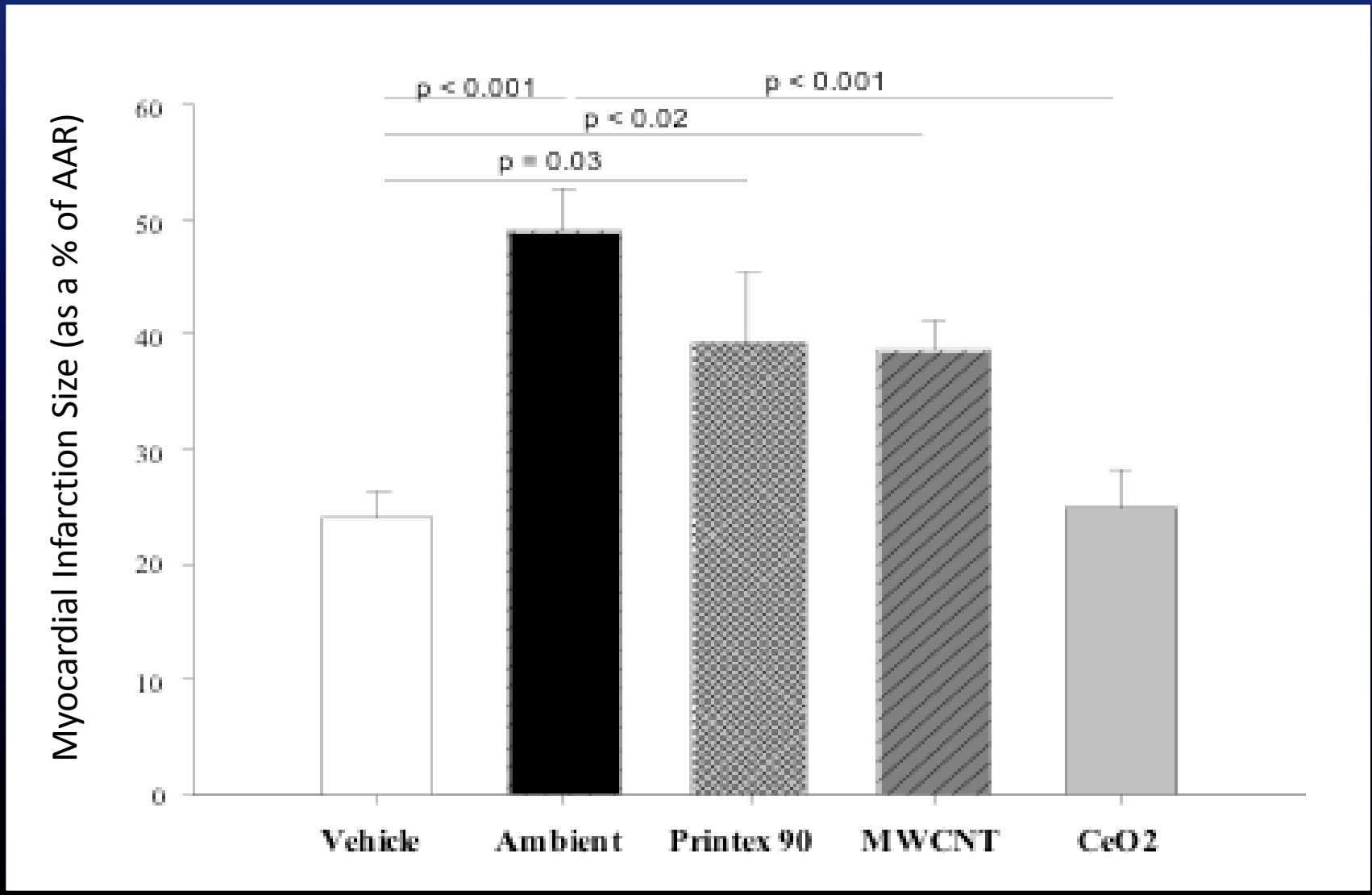
Criteria assessed:
Pneumonia/Pneumonitis
Edema
Alveolar macrophages
Subpleural lymphocytes
Perivascular/peribronchial cuffing

None = 0
Minimal = 1
Mild = 2
Moderate = 3
Severe = 4



Ultrafine PM I/R Injury

Murine model of I/R injury



Cellular and Organ Toxicology

California Freeway Study

Mean incidence of supraventricular ectopic beats (SVEBs) before, during, and after exposure