

Interface of Health Effects caused by the CardioMetabolic Syndrome and Exposures to Air Pollutant Mixtures

Jack R. Harkema

April 10, 2013

SOT Webinar



MICHIGAN STATE

U N I V E R S I T Y



Current News: China's Air Pollution Problem

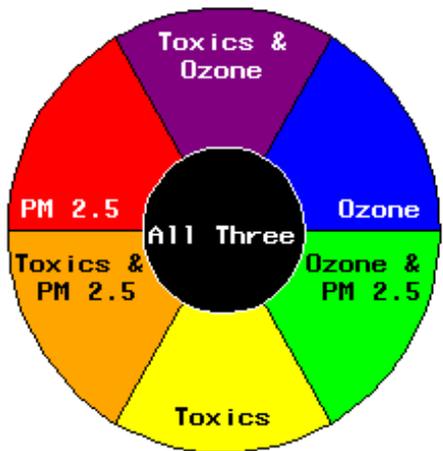
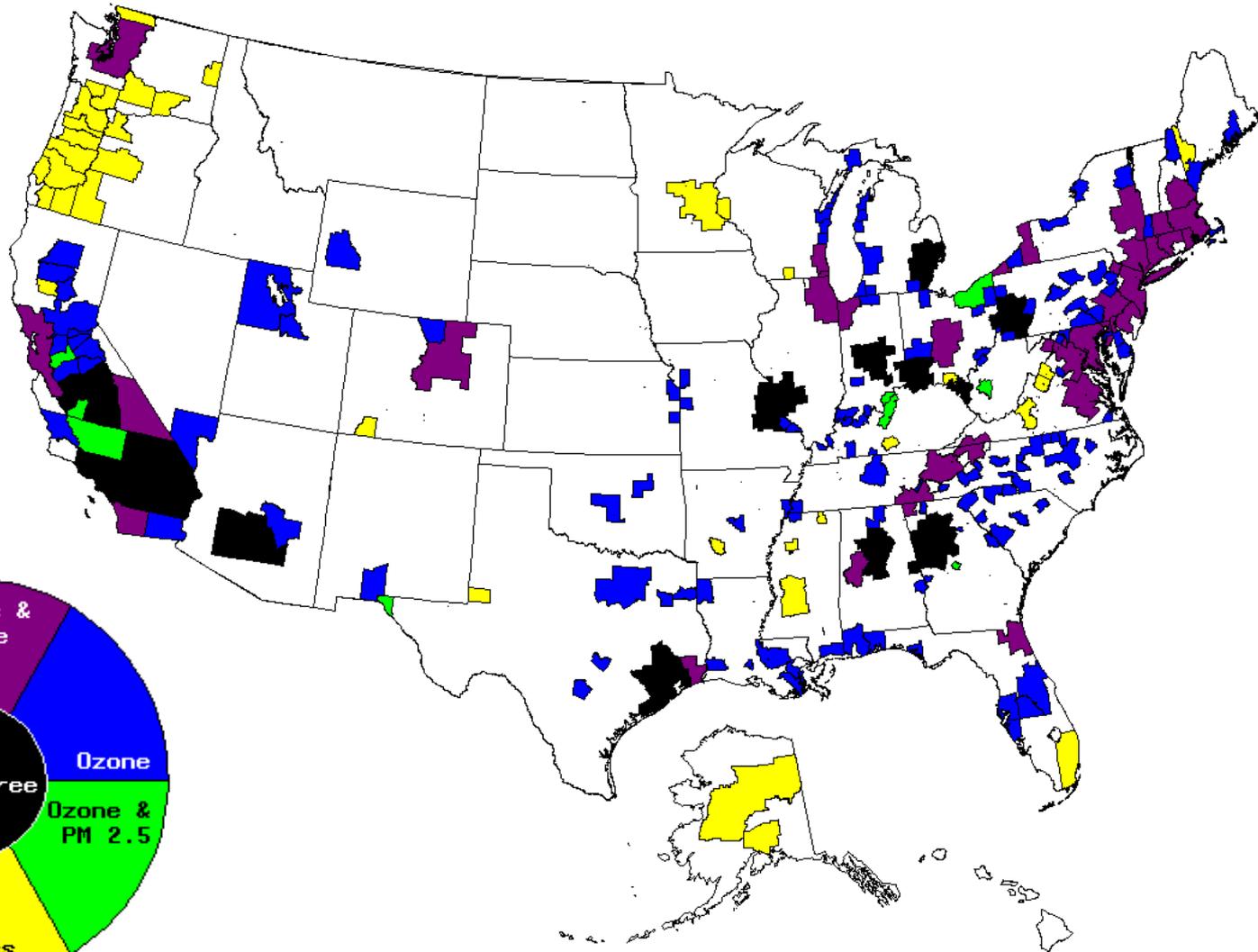


Pollution readings from the US Embassy (upper) and the local government shows hazardous levels of air pollution in Beijing on January 23, 2013. At the height of recent pollution, Beijing authorities said readings for PM2.5 -- particles small enough deeply to penetrate the lungs -- hit 993 micrograms per cubic meter, almost 40 times the World Health Organization's safe limit. (Mark Ralston/AFP/Getty Images)



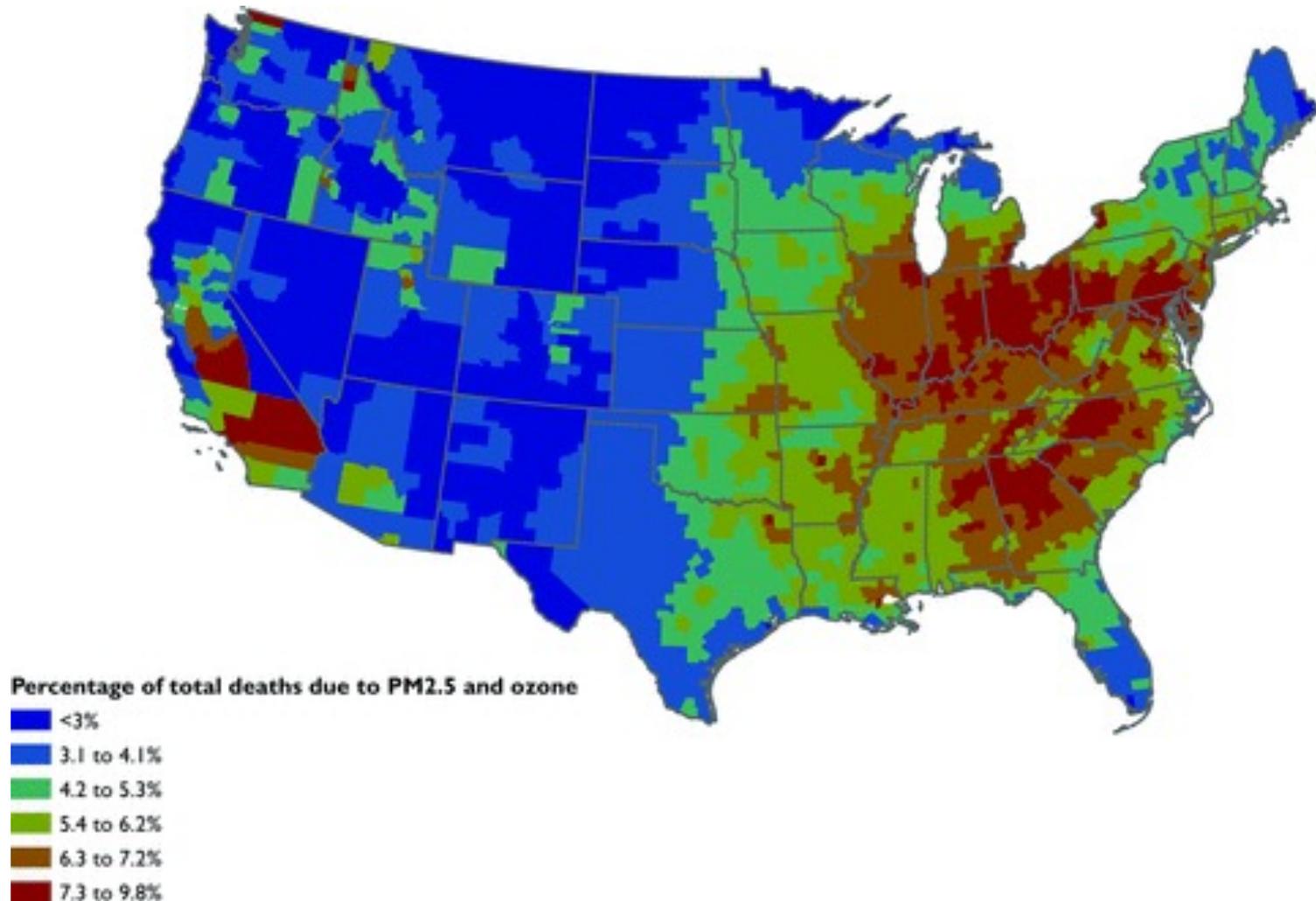
This combination of photos shows the Beijing skyline during severe pollution on January 14, 2013, and the same view (click to fade) taken during clear weather on February 4, 2012. (Ed Jones/AFP/Getty Images)

Multipollutant approaches take into account that humans and ecosystems are exposed to many air pollutants at the same time



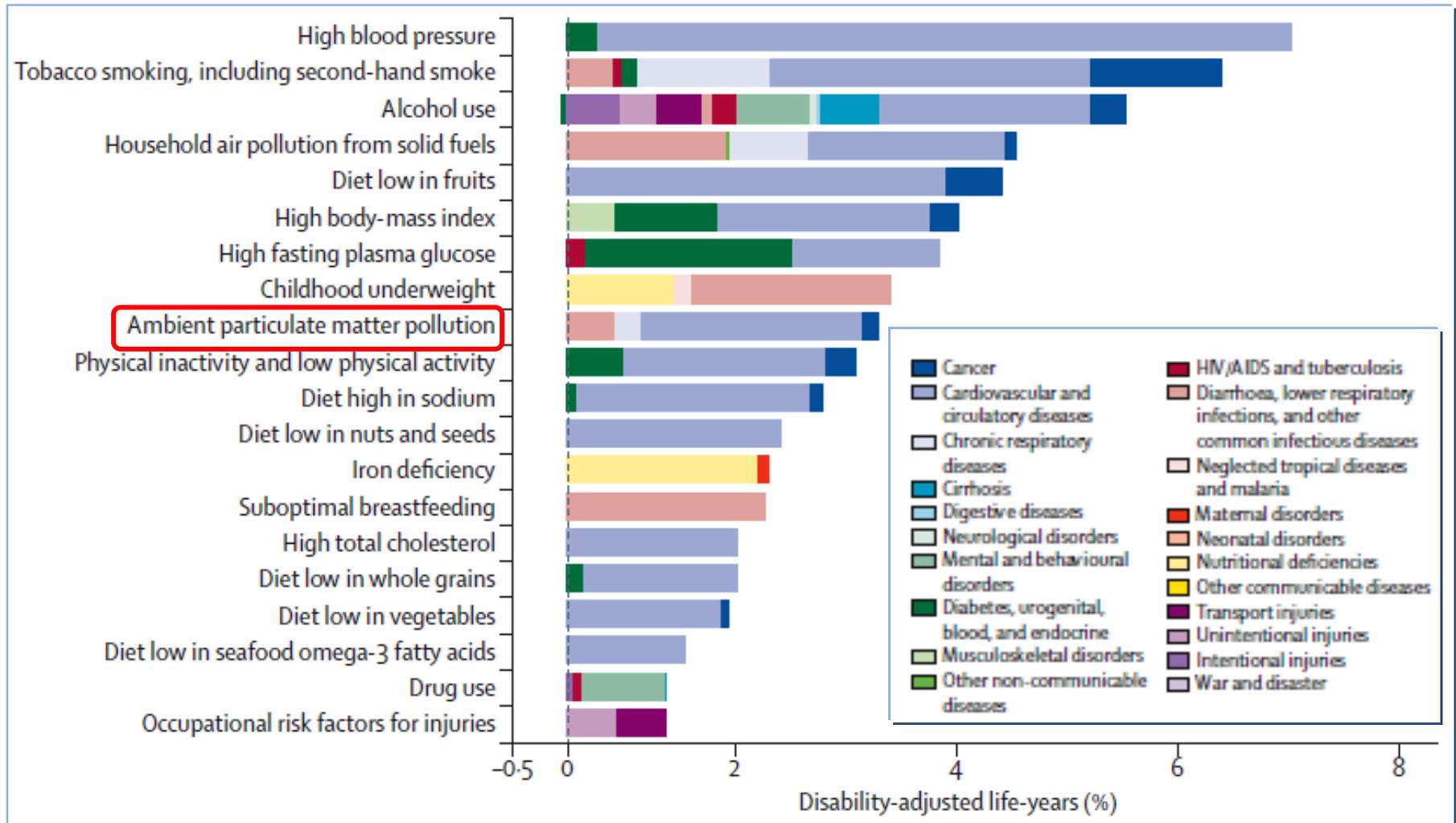
Slide from Dr. Dan Costa

National Public Health Burden Associated with Exposure to Ambient PM_{2.5} and Ozone



Fann *et al.* Risk Analysis. 32: 81-95, 2012

Global Burden of Disease: WHO Dec 2012



Annual PM-related deaths: 3.2 million

Annual world % of all DALY: 3.1%

CV population attributable factor: 22%

Lancet 2012; 380:2224-60

Recent History of Air Pollution Research

Time	Pollutants	Health Effects
1990-2000	Gases (O₃)	Respiratory
2000-2010	Particulate Matter (PM)	Cardiovascular
2010 - 2020	Multipollutants	Whole Body

2004 NRC Report:

“Air Quality Management in the United States”

Recommendation: Address multiple pollutants in the NAAQS review and standard setting process

“Although the committee does not believe that the science has evolved to a sufficient extent to permit the development of multipollutant NAAQS, it would be scientifically prudent to begin to review and develop NAAQS for related pollutants in parallel and simultaneously”

EPA Multipollutant Science and Risk Analysis Workshop: *February 22-24, 2011, Chapel Hill, NC*

“...discuss [the] challenges, along with opportunities and future research needs related to multipollutant approaches for the evaluation of health risks associated with exposures to air pollution.”

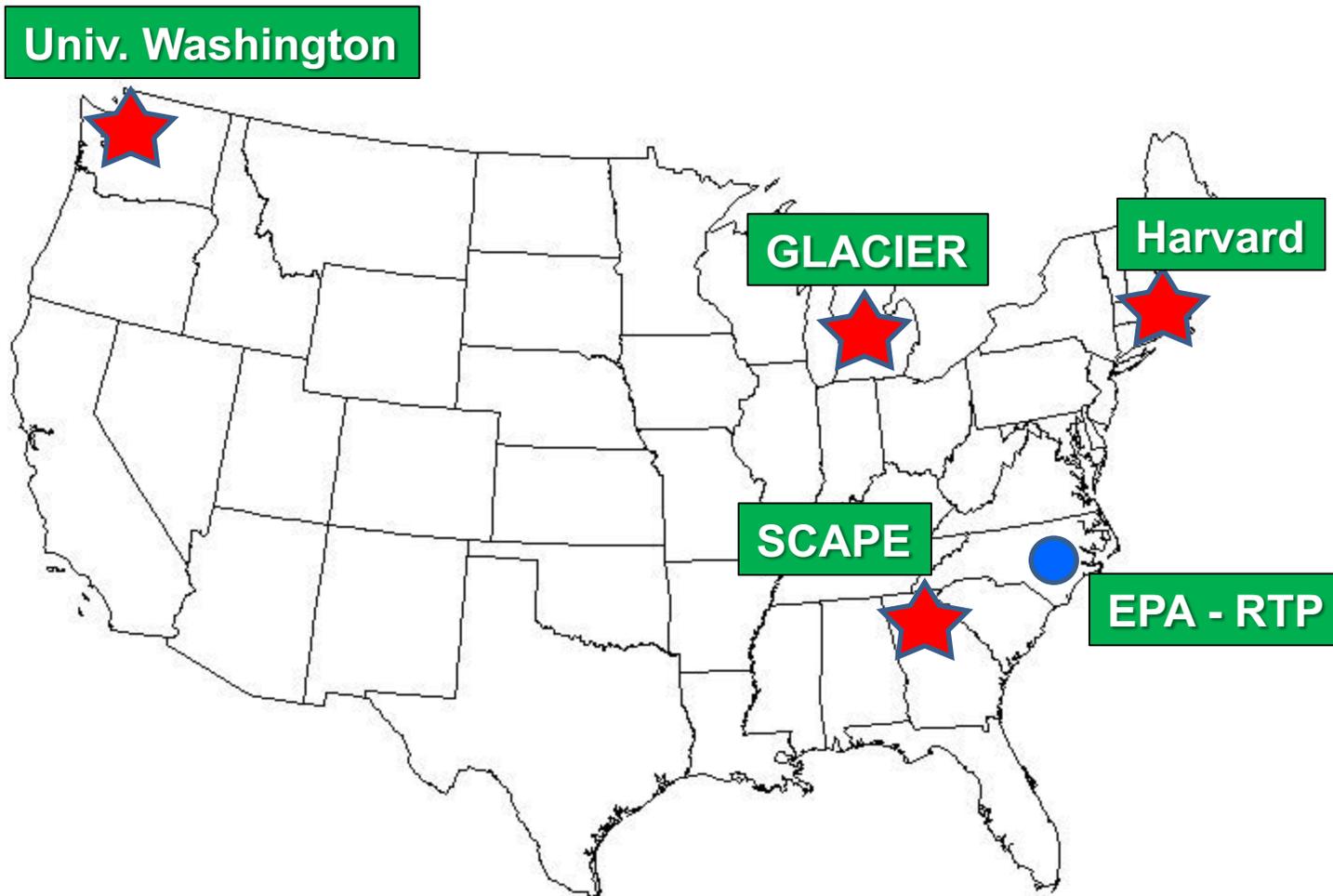
For the purpose of the workshop, they generally used Dan Greenbaum’s definition of multipollutant:

“a discrete and perhaps manageable set of compounds (i.e., the criteria pollutants and a subset of priority air toxics).”

Outline

- **EPA-Funded, University-based Clean Air Research Centers (CLARCs)**
- **Interface of two global health problems — the CardioMetabolic Syndrome (CMS) and Air Pollution**
- **Initial results of inhalation toxicology studies from the Great Lakes Air Center for Integrated Environmental Research (GLACIER, one of the CLARCs)**

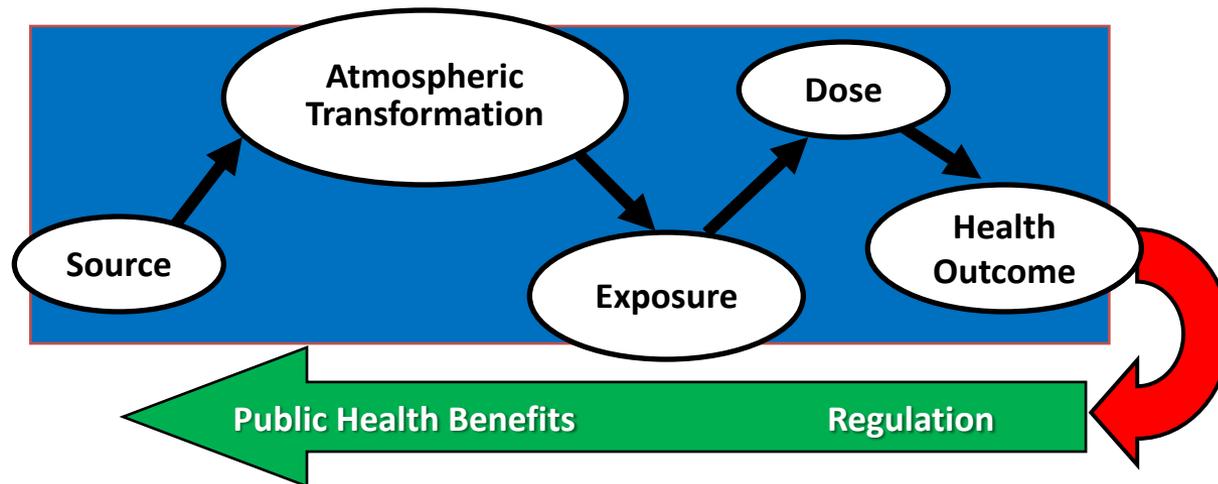
Clean Air Research Centers



Clean Air Research Centers

Key Objectives:

- Research health effects of exposure to particulate matter (PM), ozone, and other air pollutants, both singularly and in multipollutant atmospheres.
- Take an integrated approach to their study designs.



- Consider social factors (e.g. where people live) when studying health effects to air pollution sources (e.g. traffic)

Our Center Objective

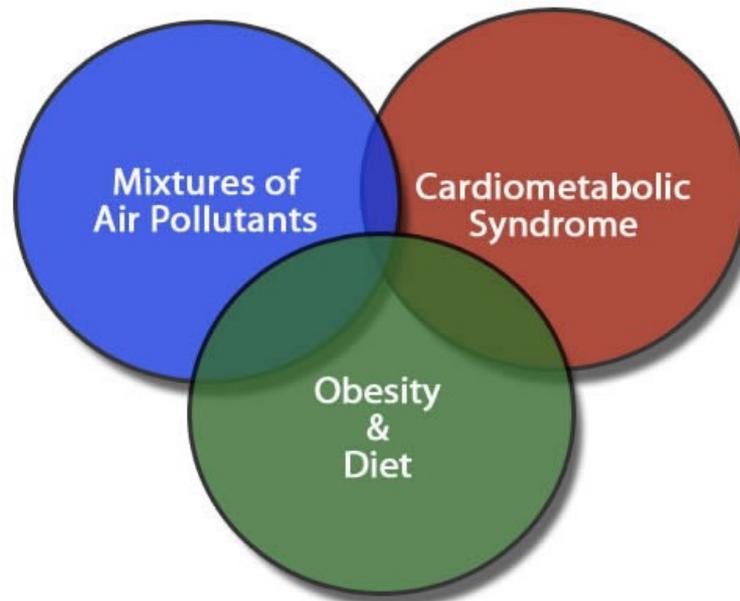


Explore and elucidate one of the most prevalent and important global health-environment interfaces:

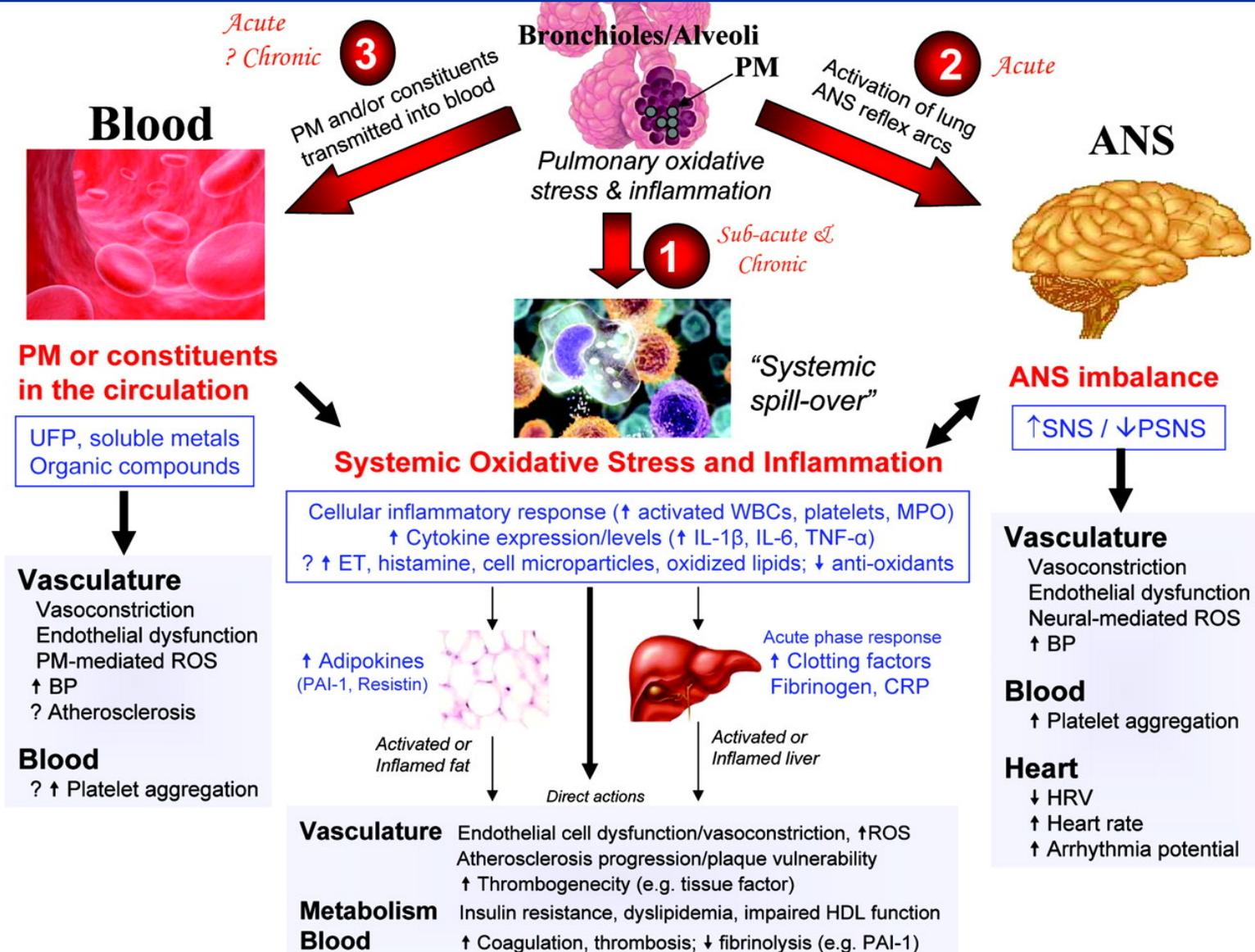
Inter-relationships between facets of the cardiometabolic syndrome and air pollution



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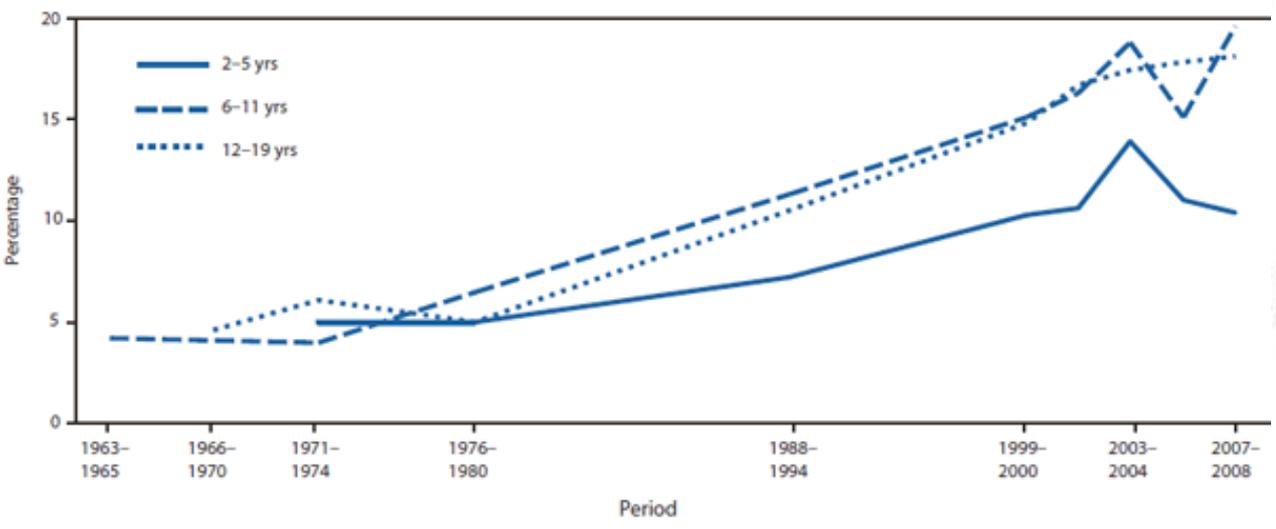
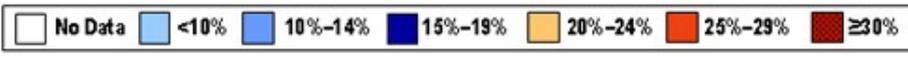
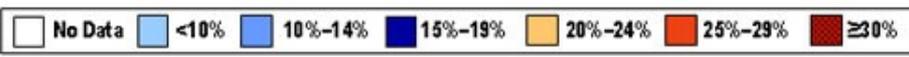
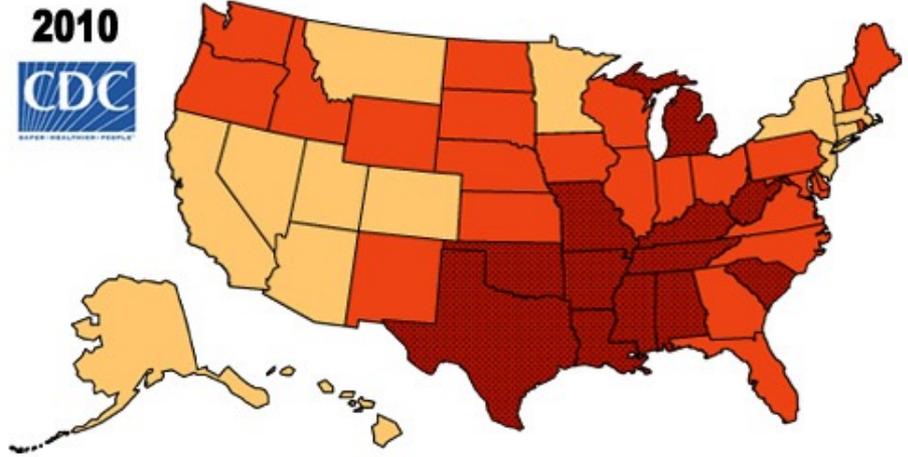
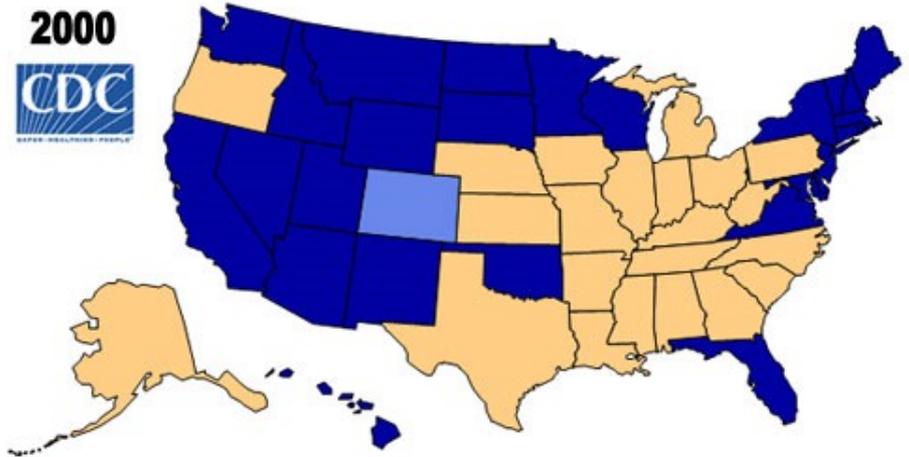
Biological pathways linking PM exposure with cardiovascular diseases



Who are susceptible to the health effects of air pollution?

- **Those with chronic pre-existing diseases**
 - Respiratory diseases (asthma, COPD)
 - Cardiovascular diseases (atherosclerosis)
 - **Diabetes, obesity, metabolic syndrome**
- **Children and older adults**
- **Those with specific polymorphisms**
- **The unborn fetus**
- **Those with low socioeconomic status**

Increased Prevalence of Obesity



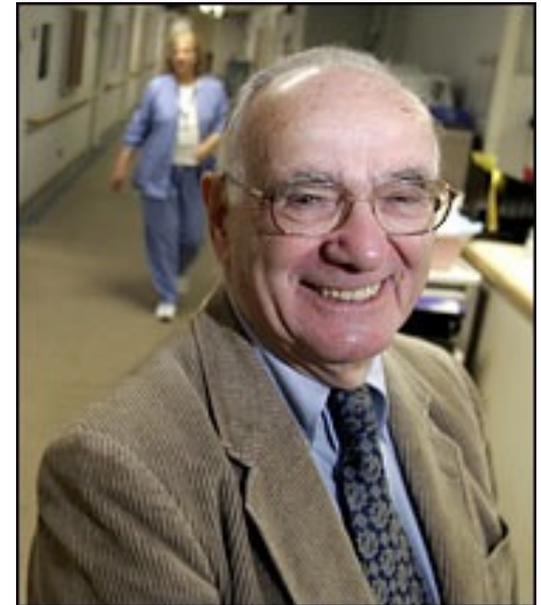
© 2008
 caglecartoons.com



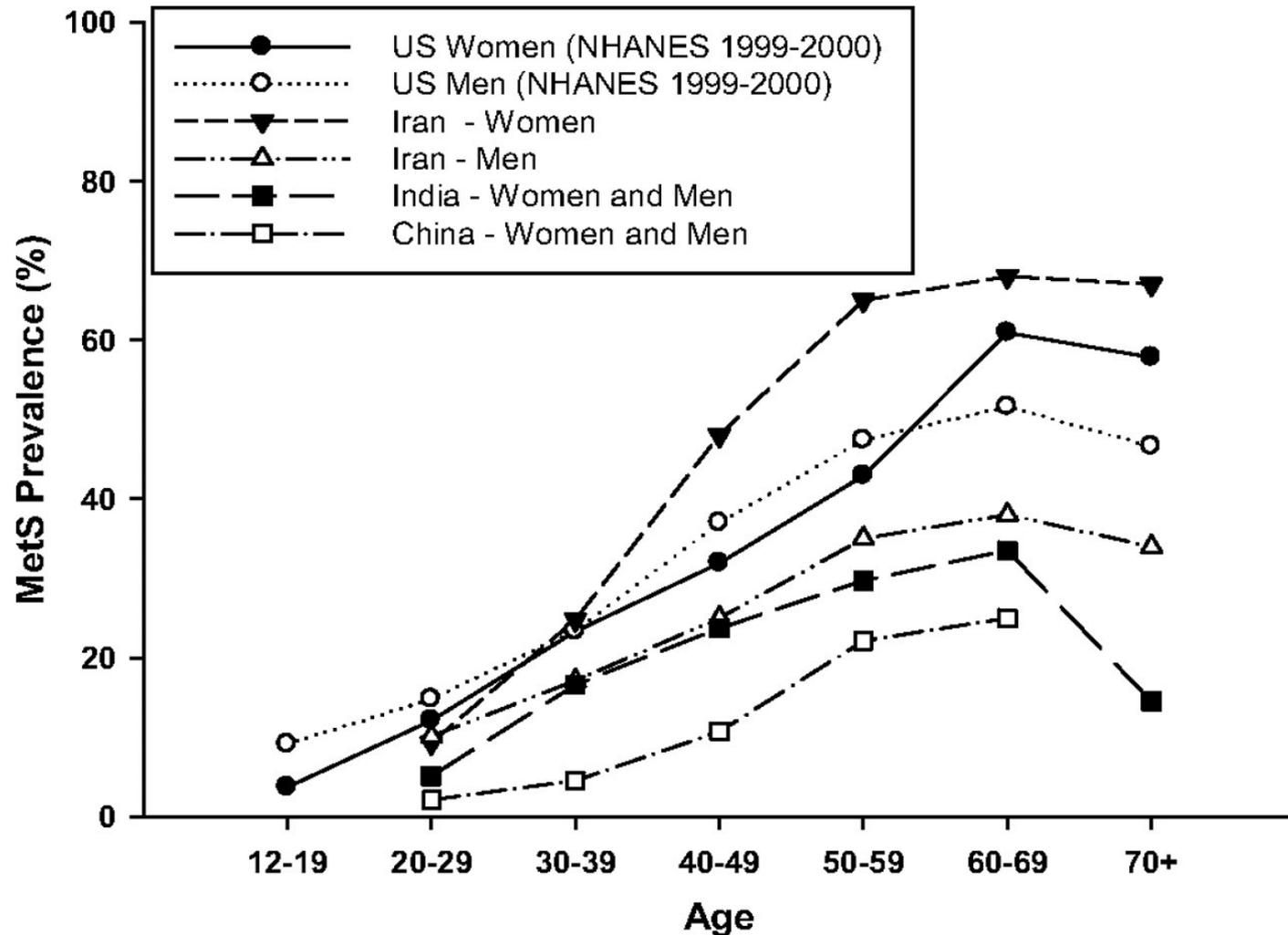
CHILDHOOD OBESITY EPIDEMIC..

The Metabolic Syndrome

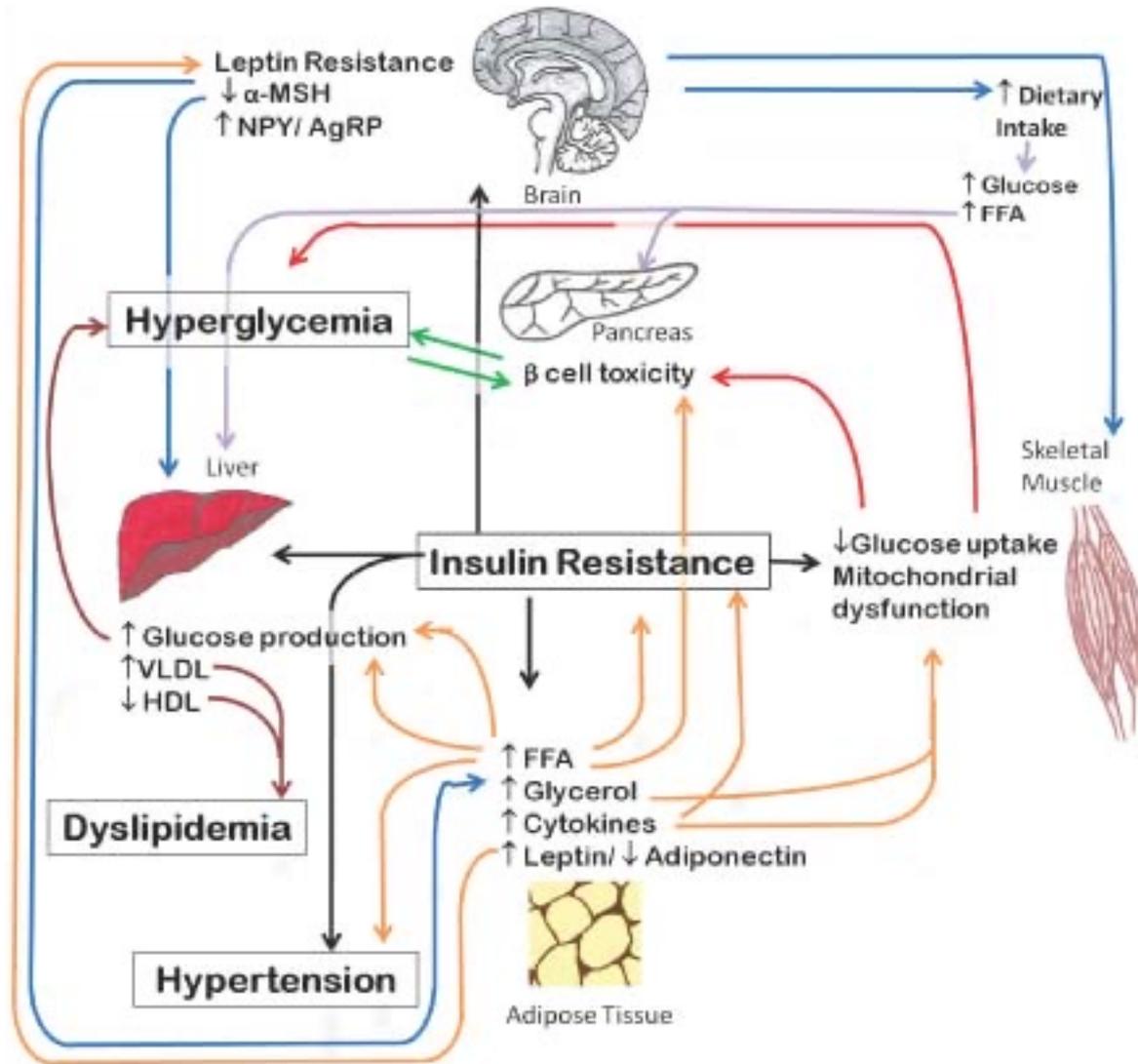
- Cluster of Risk Factors for CVD and Diabetes: Central Obesity; Dyslipidemia; Hyperglycemia; Hypertension; Insulin Resistance
- Dr. Gerald Reaves, Stanford University, 1988 Banting Lecture
- *Syndrome X, Insulin Resistance Syndrome, **CardioMetabolic Syndrome***
- Increased risk of heart attack (2X), stroke (2X), and diabetes (5X)
- 20-25% of world population



Prevalence of the MetS Across Age Groups and Gender in Various Countries

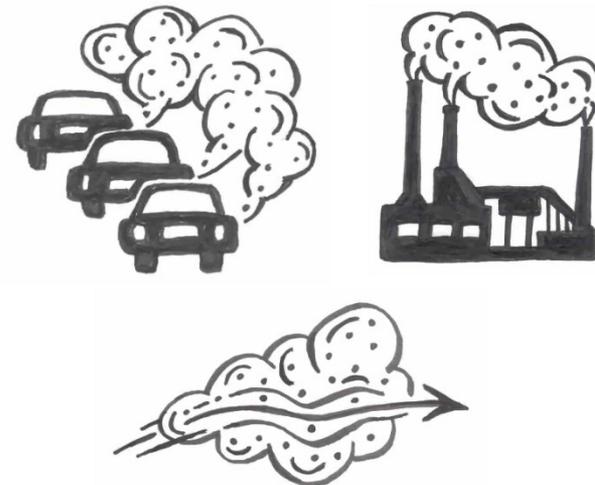


Insulin Resistance in Obesity as the Underlying Cause for the Metabolic Syndrome

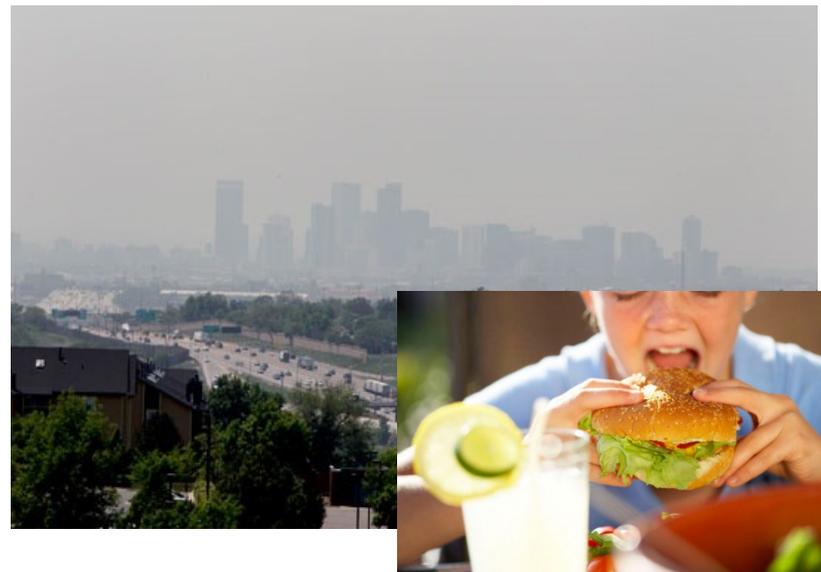


Our Current Research Questions

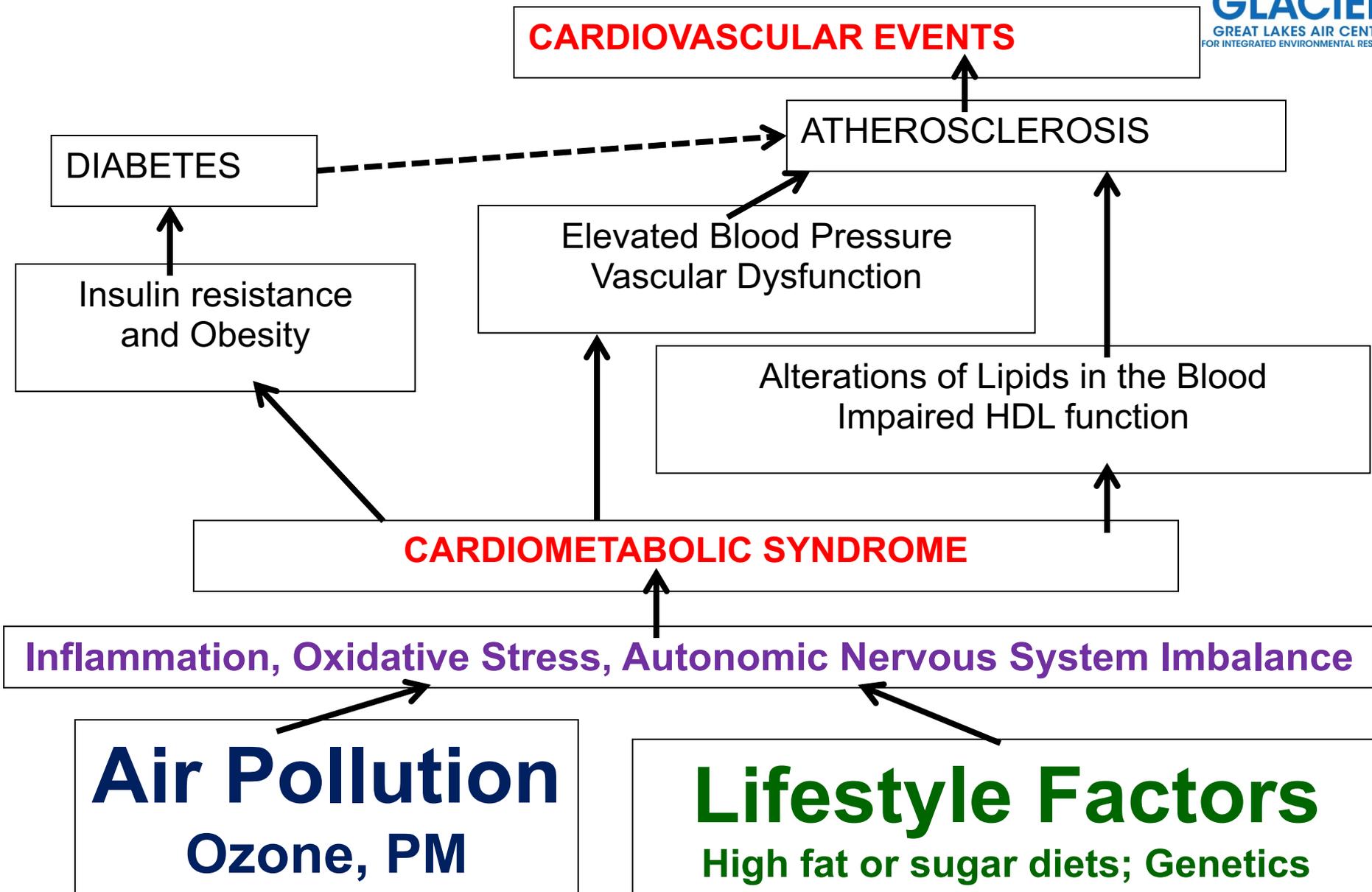
Q1. What multipollutant atmospheres in the Great Lakes Region adversely affect human health?



Q2. Does diabetes, obesity, or unhealthy diets make people more susceptible to the health effects of air pollution?



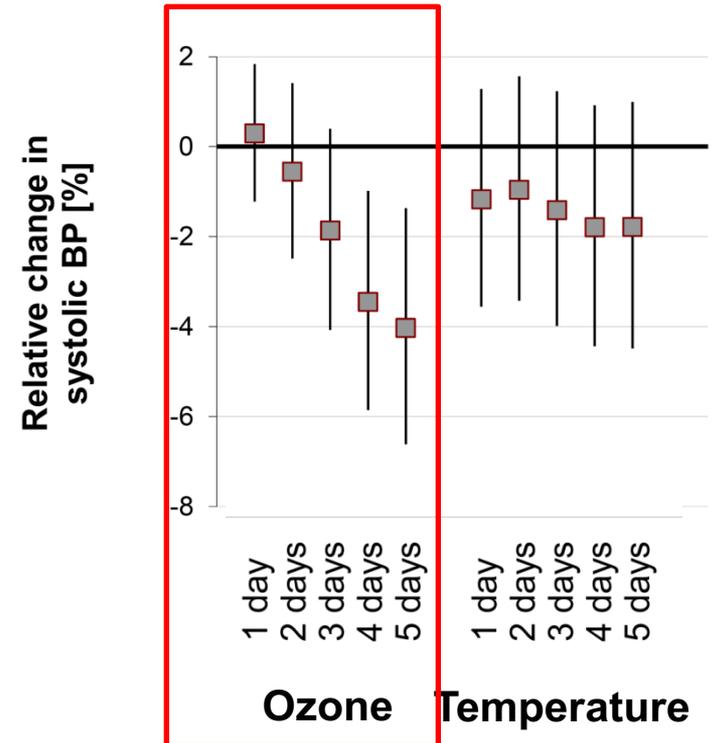
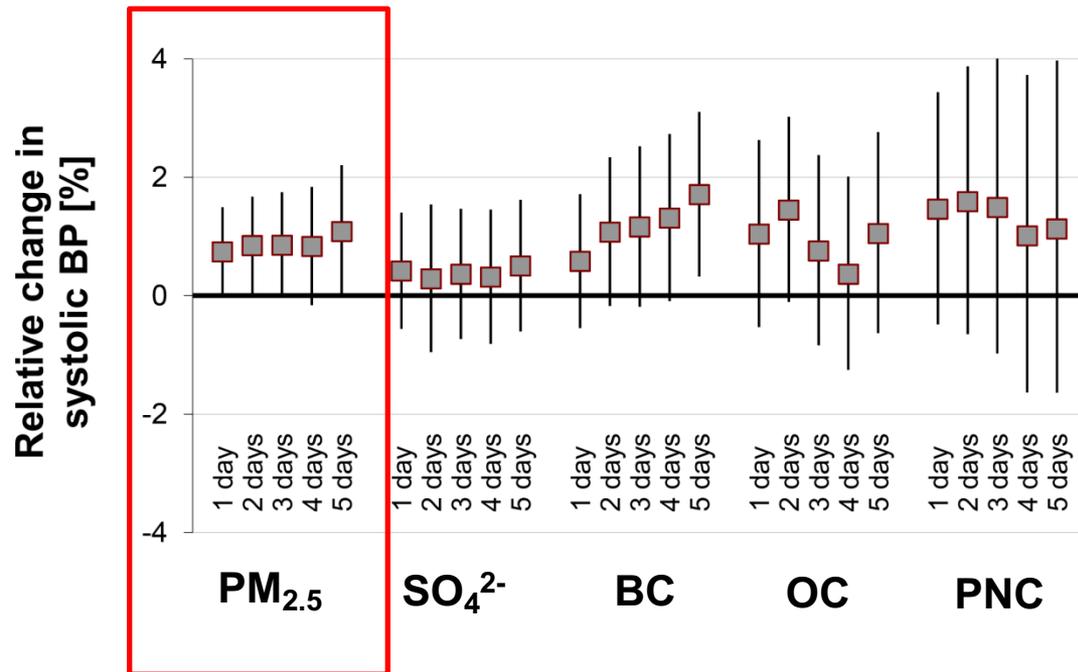
Proposed Pathogenesis



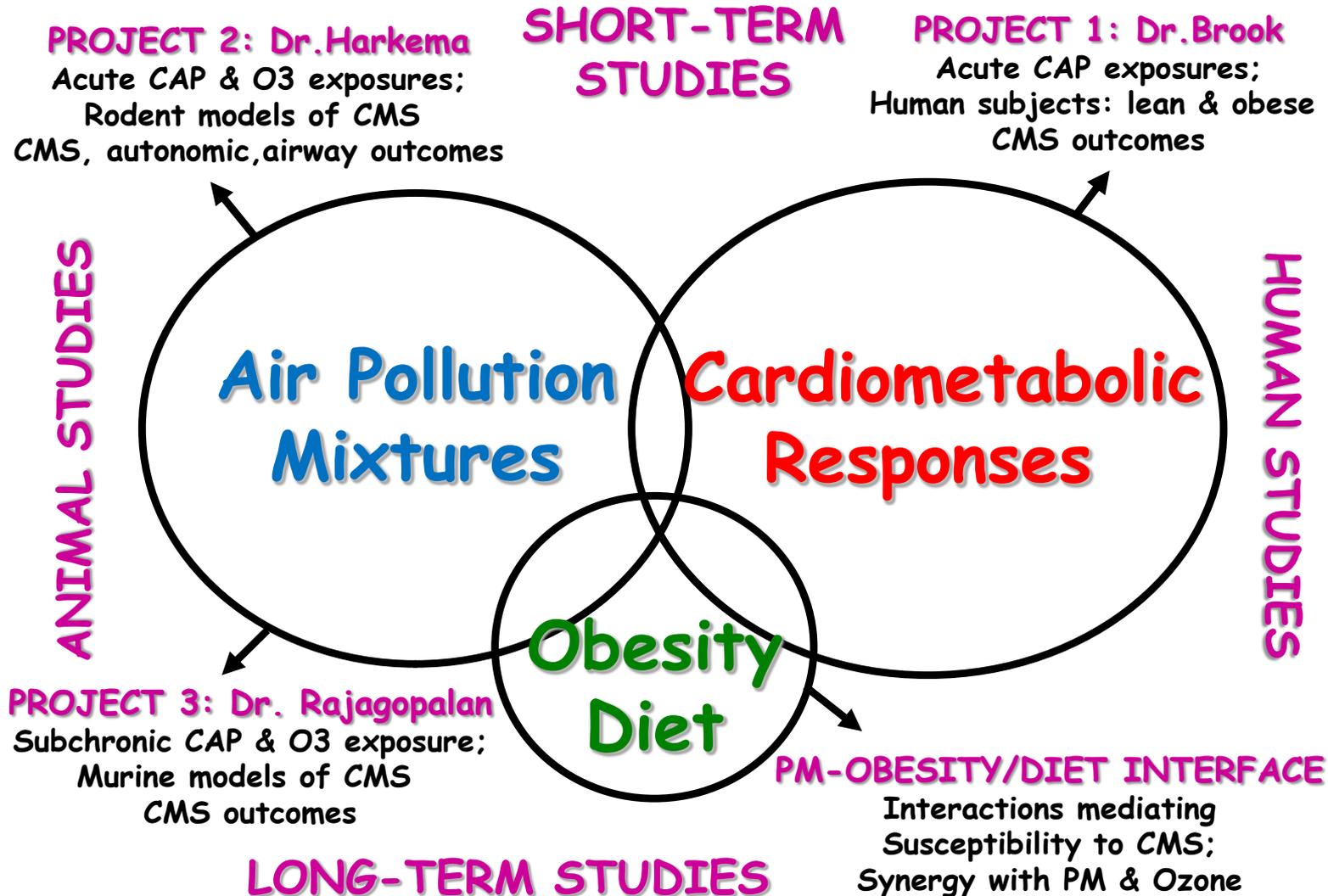
Opposing Effects of Particle Pollution, Ozone and Ambient Temperature on Arterial Blood Pressure

Hoffmann et al. *Environ Health Perspect*, 2012, 120:241

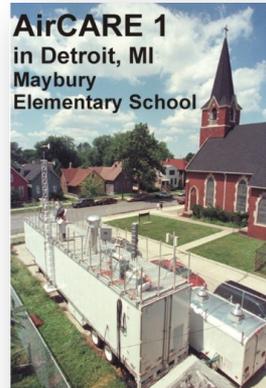
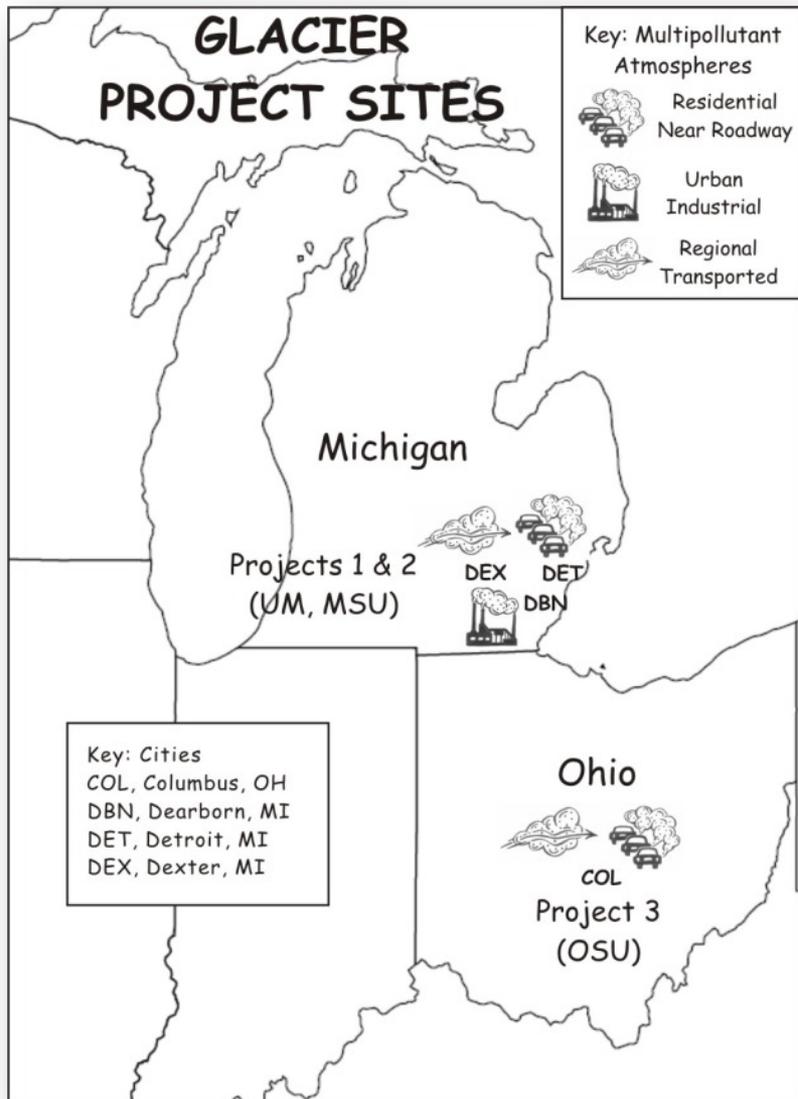
- **Panel study in 70 subjects with type 2 diabetes mellitus**
- Applied linear mixed models to investigate associations
- Interquartile increase in **PM** associated with **increased blood pressure**
- Interquartile increase in **Ozone** associated with **decreased blood pressure**



Center Projects



Human and Animal Exposures to Multi-pollutant Atmospheres



To provide insights into the health effects of PM, O₃, and their coexposures in a multipollutant context.

Cardio-metabolic Effects of Exposure to Differing Mixtures and Concentrations of Coarse and Fine Concentrated Ambient Particles in Obese and Lean Adults

**Robert Brook, MD¹, Elif Oral, MD¹
Marianna Kaplan, MD¹ and Jesus Araujo, MD²**

¹The University of Michigan, Ann Arbor, MI

²University of California, Los Angeles, CA

PROJECT 1: Reduced insulin sensitivity in human subjects with 5-day ambient PM_{2.5} exposure

Sci Total Environ. 2013 Mar 15;448:66-71



OUTCOME	β^*	95% CI	p
SDNN (msec) [HEART RATE VARIABILITY]	-13.1	-25.3 to -0.9	0.035
†HOMA-IR [METABOLIC INSULIN SENSITIVITY]	0.7	0.1 to 1.3	0.023

† Homeostasis model assessment of insulin resistance : [glucose (mg/dL) x insulin ($\mu\text{U}\cdot\text{ml}^{-1}$)]/405
(Lower values denote better metabolic insulin sensitivity)

Autonomic imbalance may be the mechanism linking PM to insulin resistance

SDNN was inversely associated with HOMA-IR ($\beta=-0.13$ per 10 msec HRV change, $p=0.035$).

***BMI and/or age-adjusted (per 10 $\mu\text{g}/\text{m}^3$ of 5-day PM_{2.5} average)**

Project 3: Long-term Animal Studies



Long-term Metabolic Consequences of Exposures to Multipollutant Atmospheres in the Great Lakes Region

Sanjay Rajagopalan, MD and Qinghua Sun, MD

The Ohio State University, Columbus, OH

Project 3: Aim 1

Hypothesis: Near-roadway CAP exposure promotes development of obesity and insulin resistance.

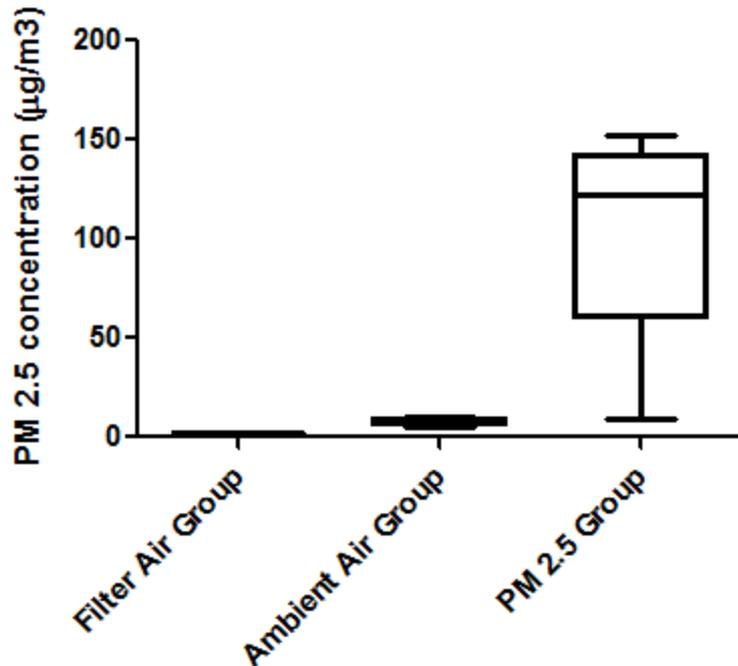
**Design: C57Bl/6 model fed normal chow or high-fat chow and exposed to FA/CAP for 12 or 18 weeks.
KKAy mice exposed to CAP over 8-10 weeks**

- **To assess effects of multi-pollutant CAP (regional vs. near-roadway) on glucose and insulin homeostasis, inflammation and insulin signaling pathways.**
- **To identify inflammatory chemokine mediators.**
- **To investigate temporal response of multi-pollutant CAP and CMS effects.**

**KKAy Mice = Heterozygous for the yellow spontaneous mutation (Ay).
Progressively develop insulin resistance, obesity over 6-12 weeks**

Effect of Regional CAP Exposure in a Model of Genetic Type II DM (KKAy Mouse Model)

EXPOSURE CONCENTRATIONS
(Columbus Regional:12/28/2011-02/28/2012)

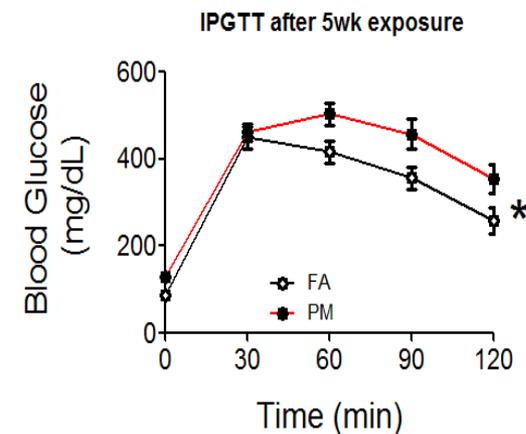
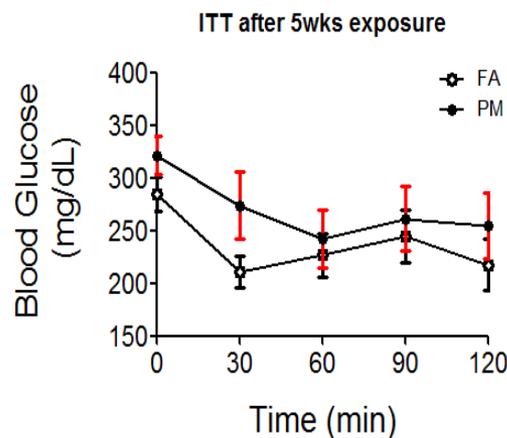
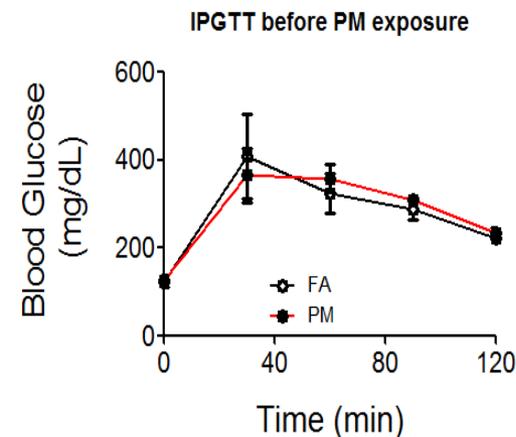
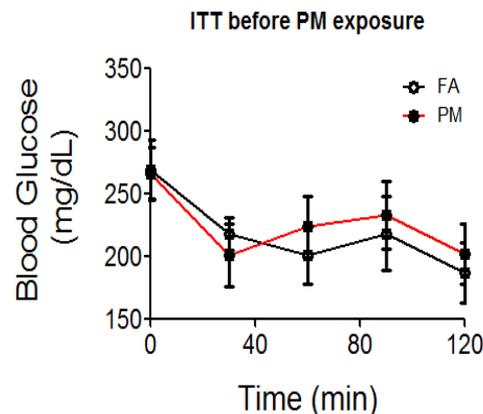
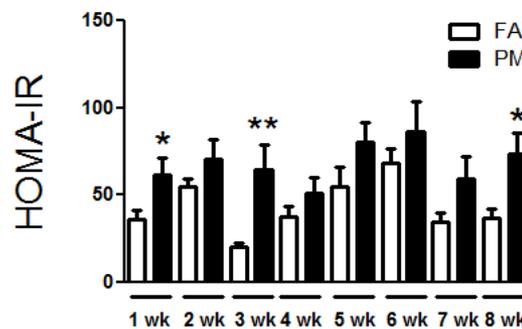
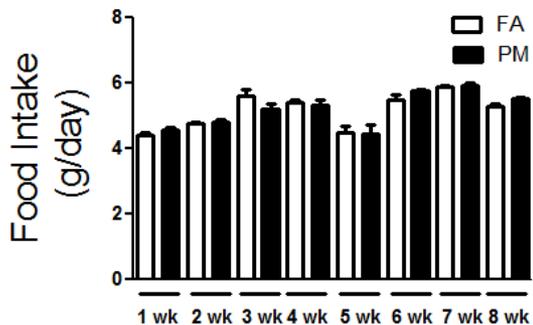
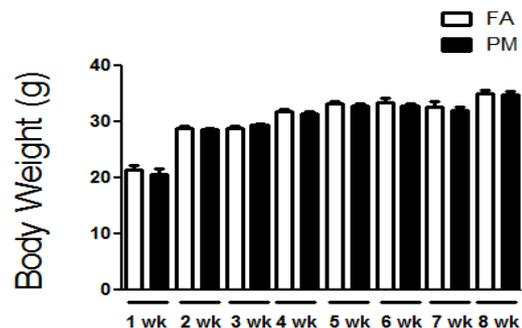


Ambient	FA	CAPS
8.27 µg/m ³	1.51 µg/m ³	102.9 µg/m ³

Enrichment Factor = 12.22

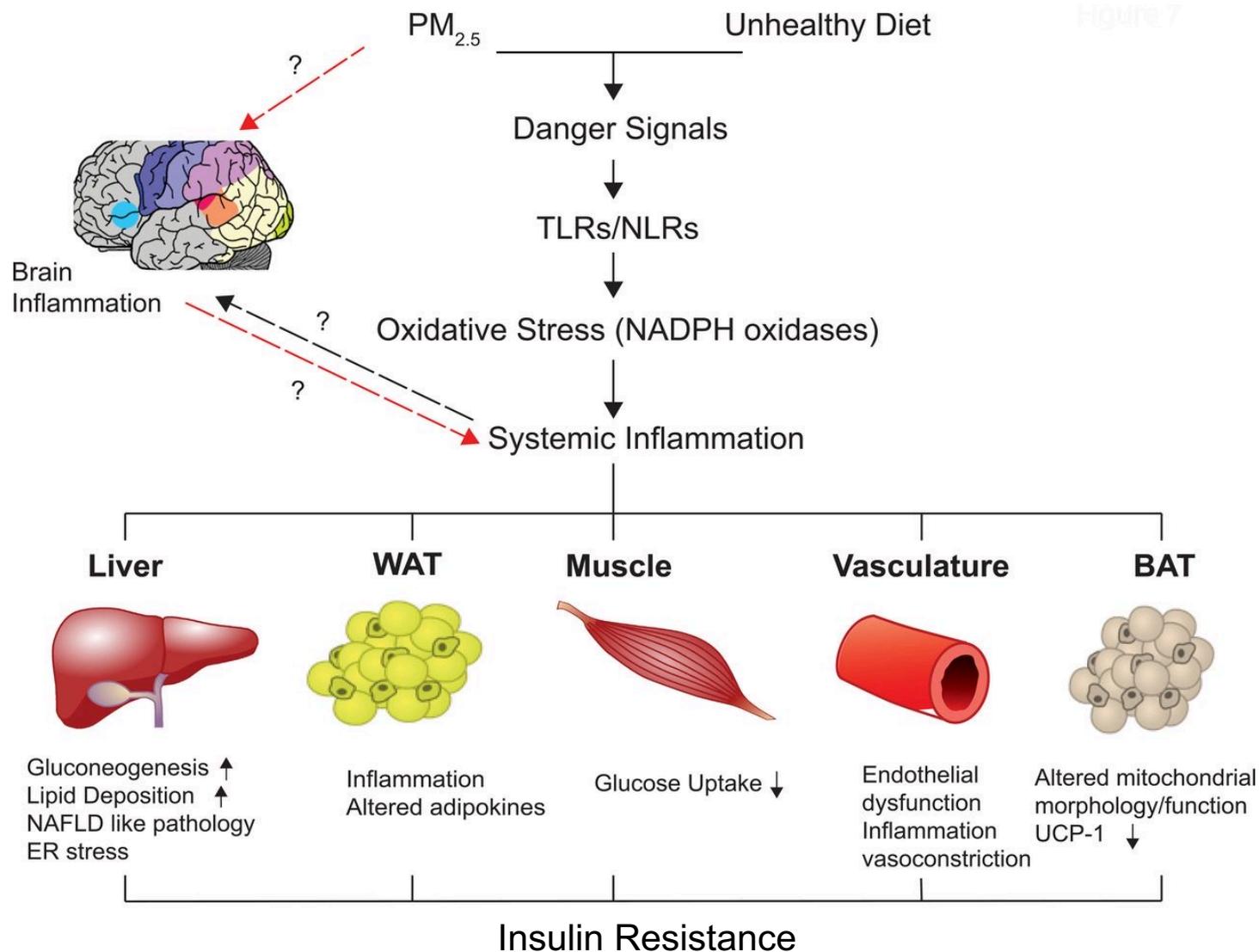
4-5 wk-old KKAy mice exposed to FA or CAP (normal diet)

Regional CAP Exposure and Insulin Resistance Measures in Genetic Type II DM (KKAy Model)



*P<0.05, **P<0.01, ***P<0.001 vs respective FA group.

Hypothesis for Air Pollution-Mediated Type 2 DM/Insulin Resistance



Project 2: Short-Term Animal Studies



Cardiometabolic, Autonomic, and Airway Toxicity of Acute Exposures to PM_{2.5} from Multipollutant Atmospheres in the Great Lakes Region

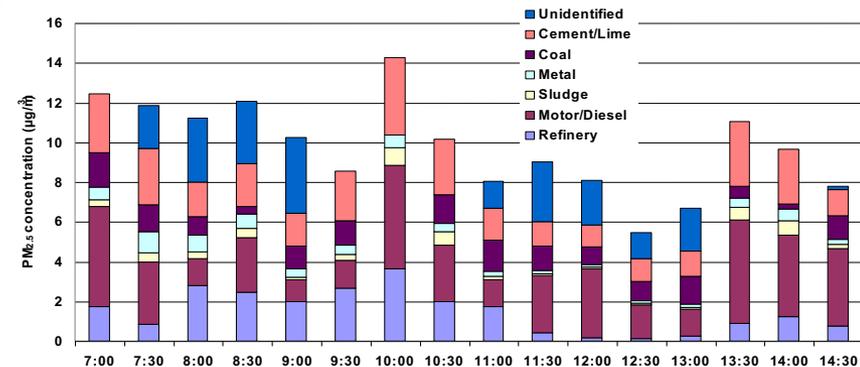
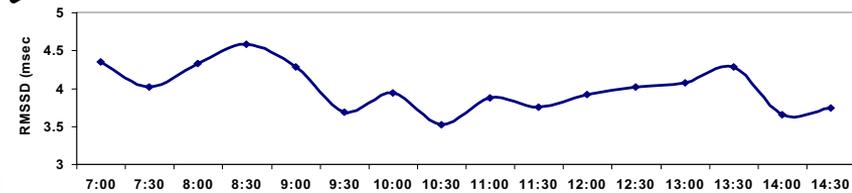
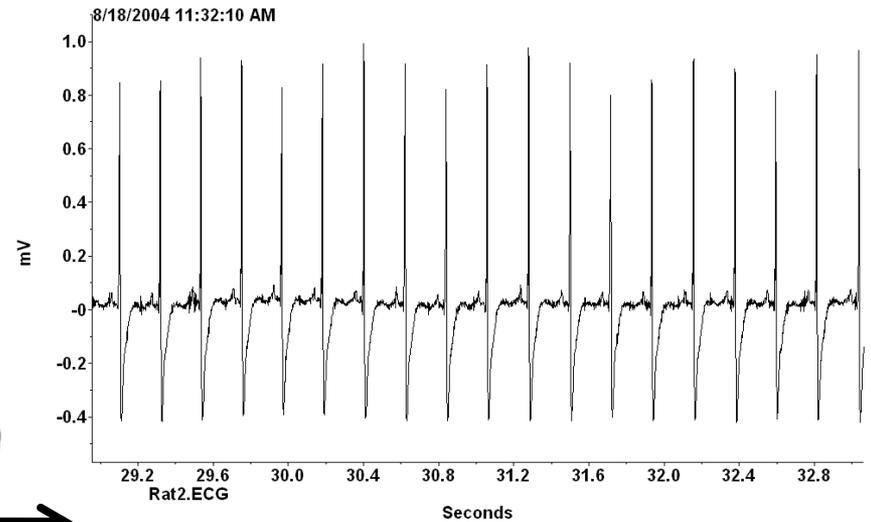
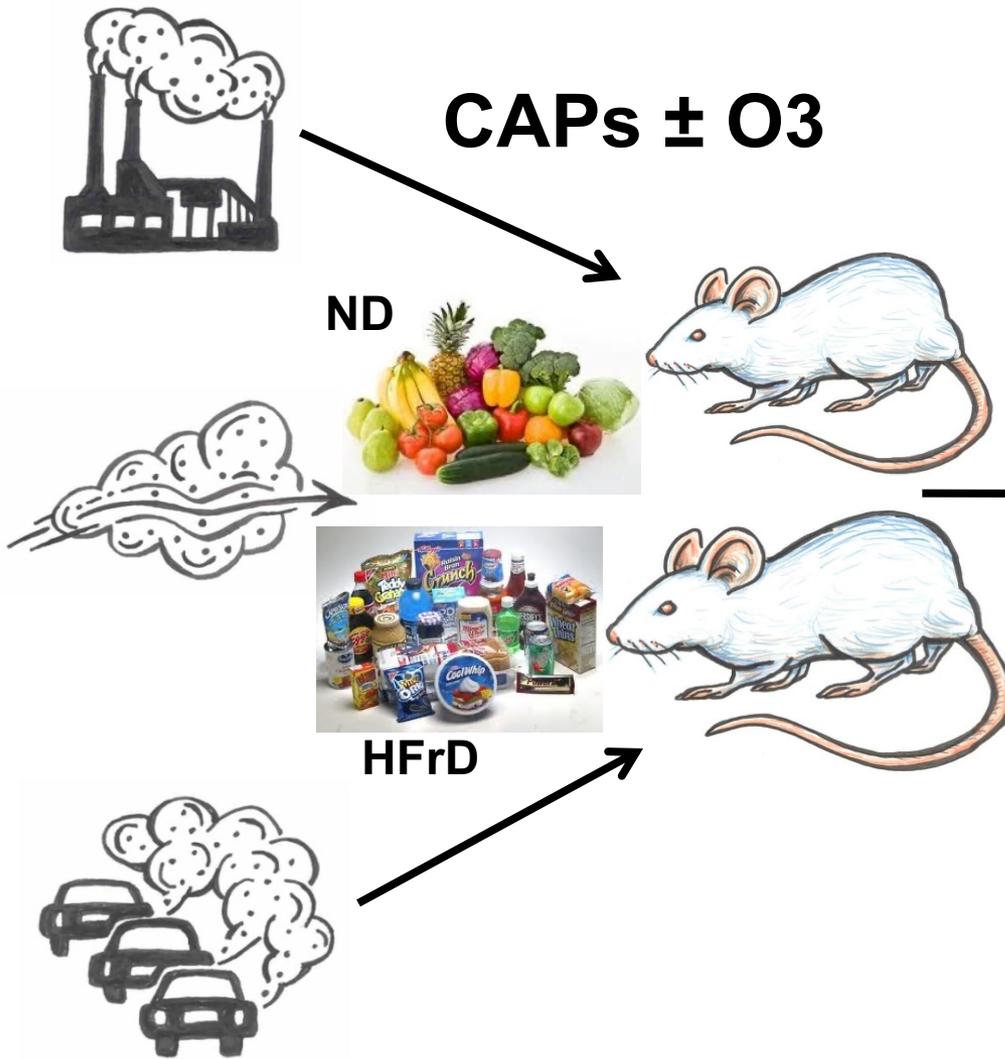
Jack Harkema, DVM, PhD¹, Greg Fink, PhD¹

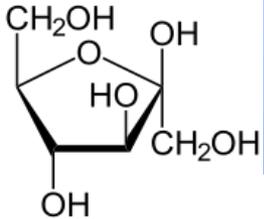
**James Wagner, PhD¹, Masako Morishita², Tim Dvonch²,
Cathie Spino², and Bhramar Mukherjee²**

¹Michigan State University, East Lansing, MI

²The University of Michigan, Ann Arbor, MI

Project 2: Animal Toxicology Studies





High Fructose Diet

	Normal Diet (Teklad 22/5)	60% Fructose Diet (TD.89247)
Protein (% by weight)	22.0 %	18.3%
Carbohydrate	40.6 %	60.4%
Fat	5.5 %	5.2%
Kcal/g	3.0	3.6

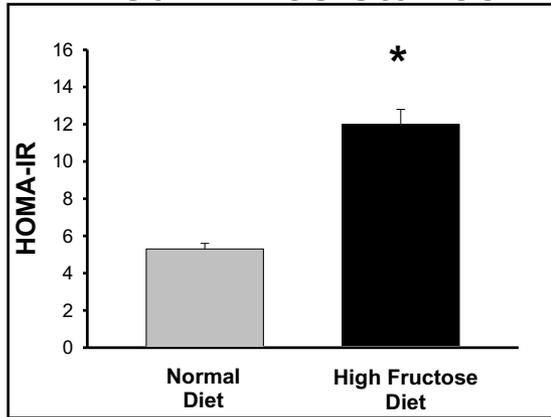


- Fructose has same chemical formula as glucose ($C_6H_{12}O_6$), but with different stereochemistry.
- Metabolism of fructose differs from glucose, and is insulin independent.
- Rats on a high fructose diet develop facets of the CardioMetabolic Syndrome in 10 weeks.

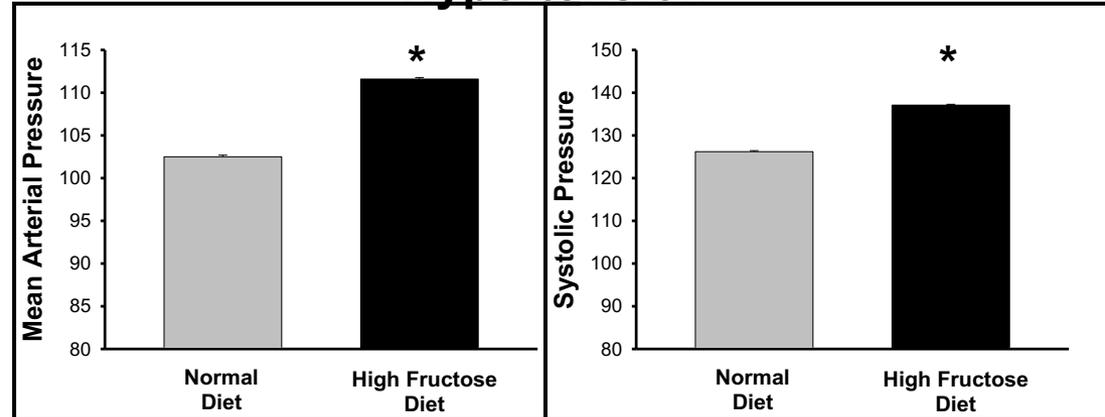
High Fructose Diet-Induced CMS

Sprague Dawley Rats; 10 weeks on High Fructose Diet

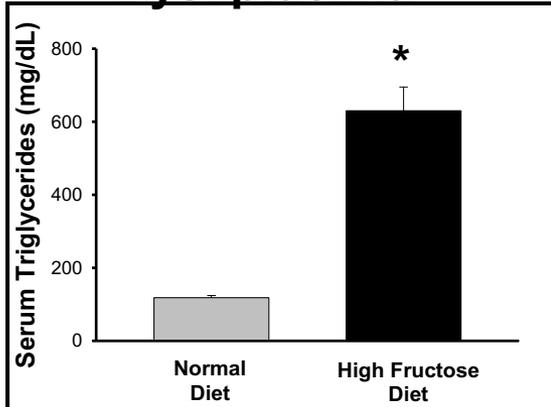
Insulin Resistance



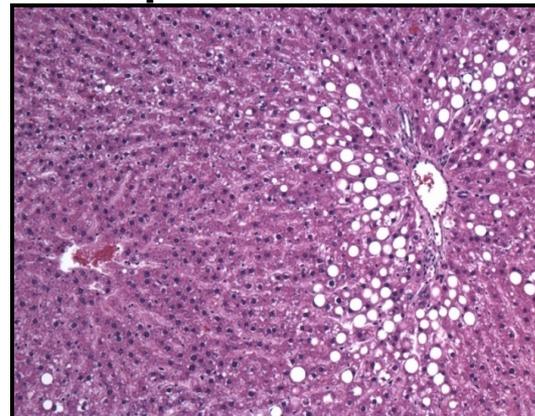
Hypertension



Dyslipidemia



Hepatic Steatosis



- Increased hepatic triglycerides
- No weight gain
- Elevated HR
- Decreased HRV

Study 1: Dearborn Study Design

	<h2>Air Pollutants</h2>			
Diet	Air	*CAPs (PM2.5)	O3 (0.5 ppm)	O3 & CAPs Mixture
Normal (ND)	8 rats	8	8	8
High Fructose (HFrD)	8	8	8	8

- Male rats on diet for 8 wks prior to and during exposure
- Daily 8h-exposures for two weeks (5 & 4 days/wk; 9 total exposure days)
- * ~400 $\mu\text{g}/\text{m}^3$ Concentrated Ambient Fine Particles (CAPs)
- Animal necropsies one day after last exposure

Urban/Industrial Exposure Site

***AirCARE 2 in Dearborn, MI**

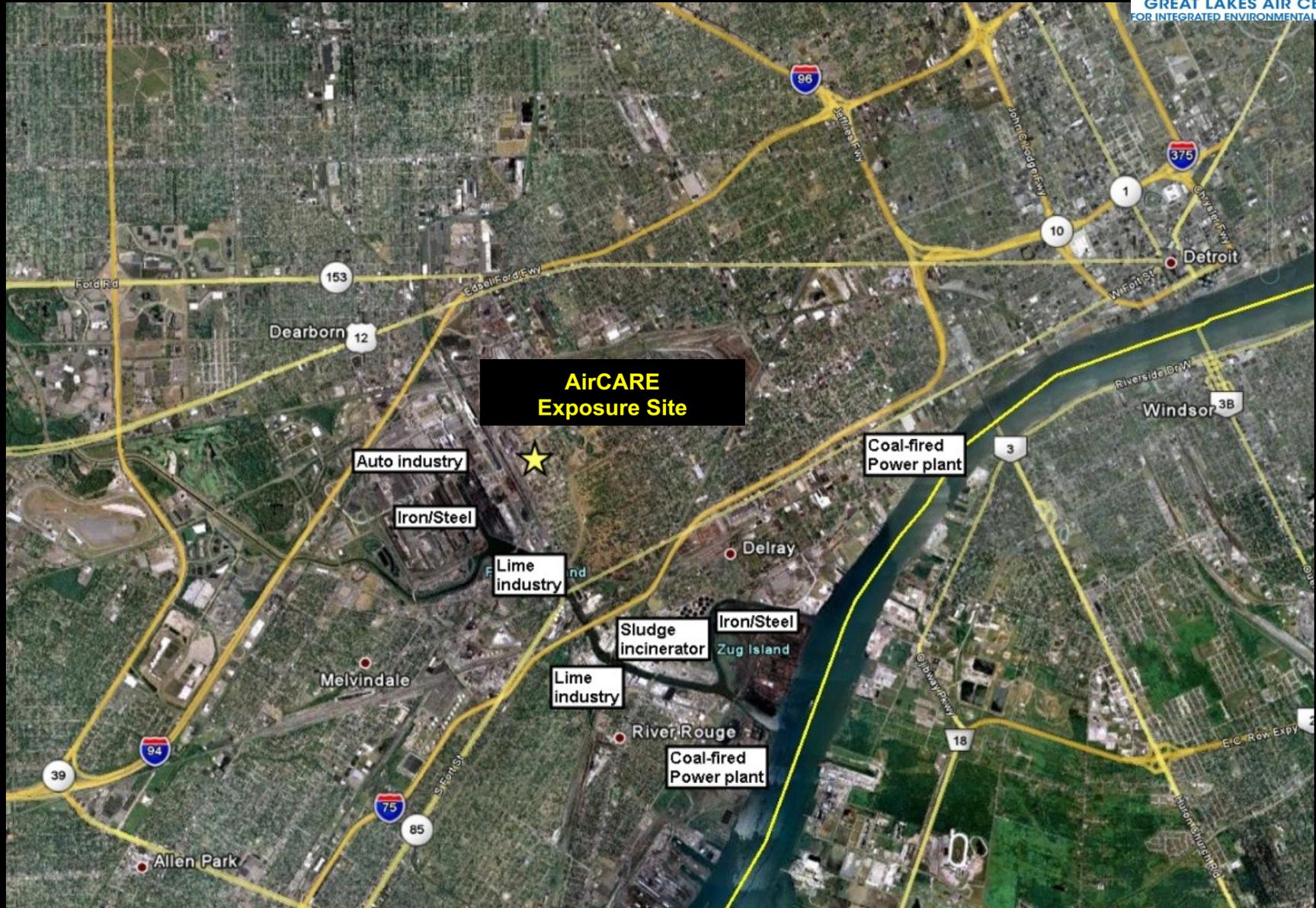
**Salina
Elementary
School**

Steel Manufacturing Plant

**Michigan Department of Environmental
Quality Monitoring Site**



Exposure Site: Urban/Industrial SE Michigan (Dearborn)

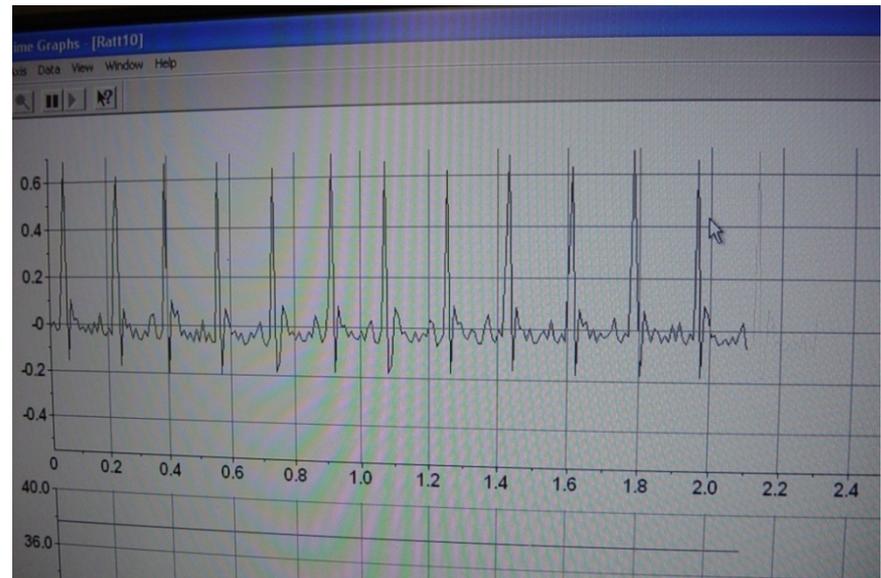


Cardiovascular Telemetry (BP, ECG)



**8 rats with implanted
telemeters in each
exposure chamber**

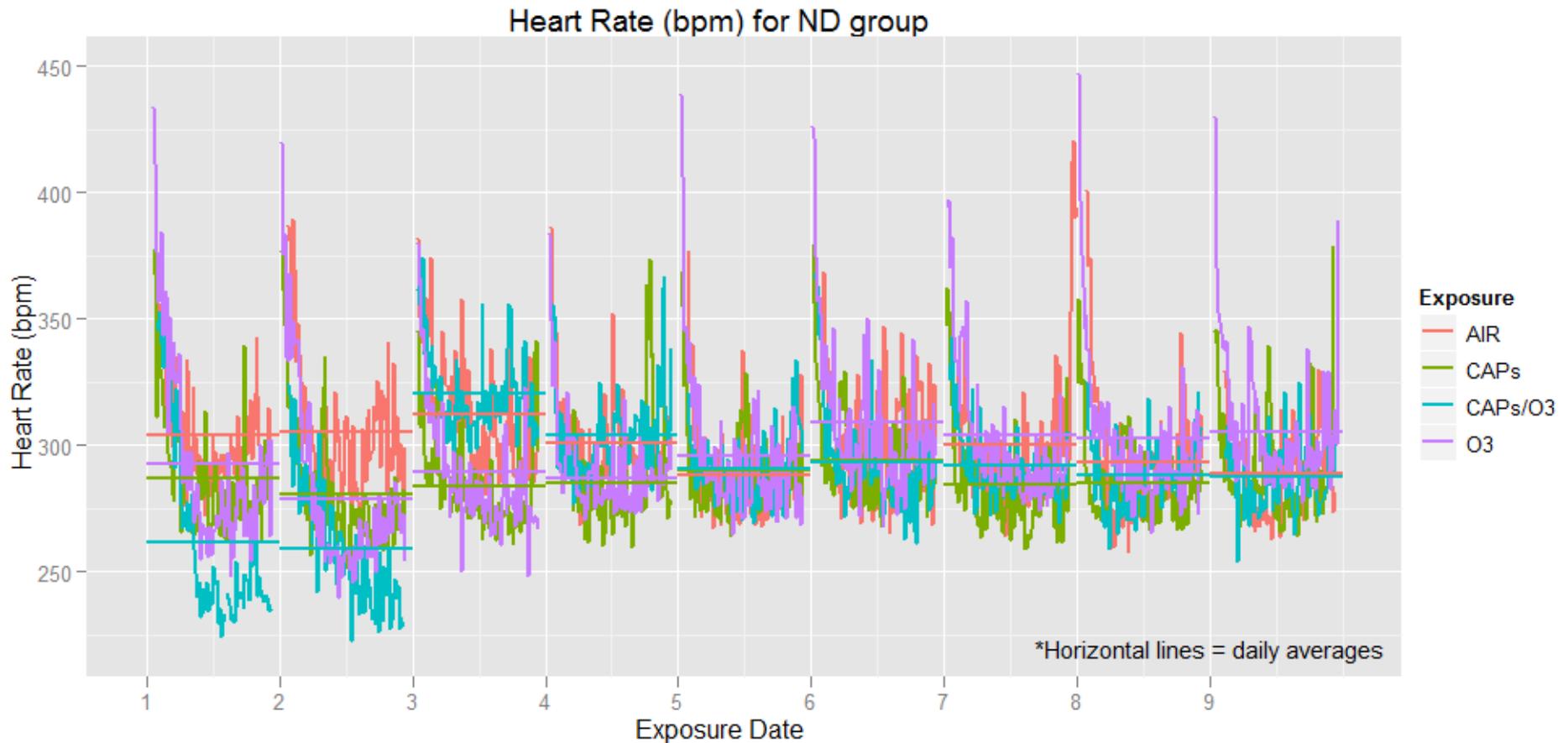
**30-second recordings
every 5 minutes during
daily 8-hour exposures**



Chamber Concentrations

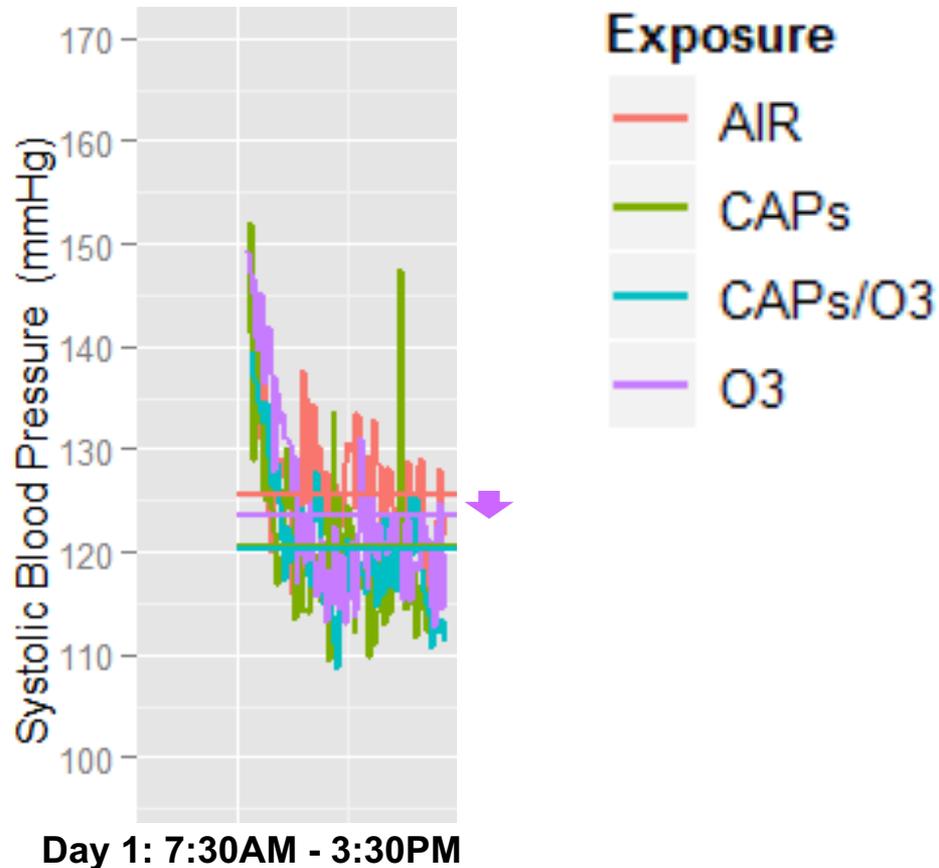
Air Pollutant	Average Daily Concentrations (Mean \pm Standard Deviation)
Ozone (O₃)	0.50 \pm .03 ppm
CAPs (PM_{2.5})	444 \pm 196 μg/m³
O₃ & PM_{2.5} Mixture	O₃: 0.49 \pm .04 ppm CAPs: 356 \pm 261 μg/m³

Effect of Repeated Exposure of Air Pollutants on HR in HFr-fed Rats

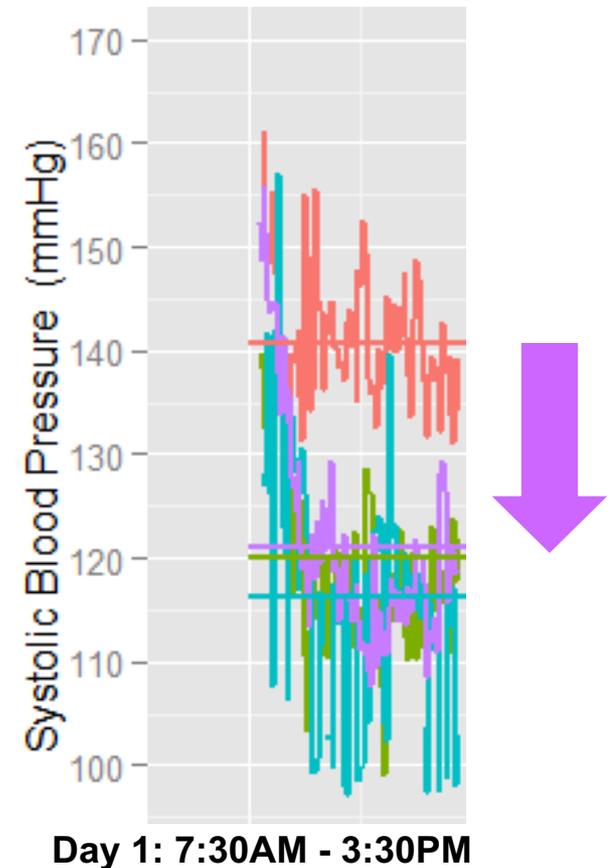


Effect of Air Pollutants/Diets on SBP

Normal Diet-Fed Rats



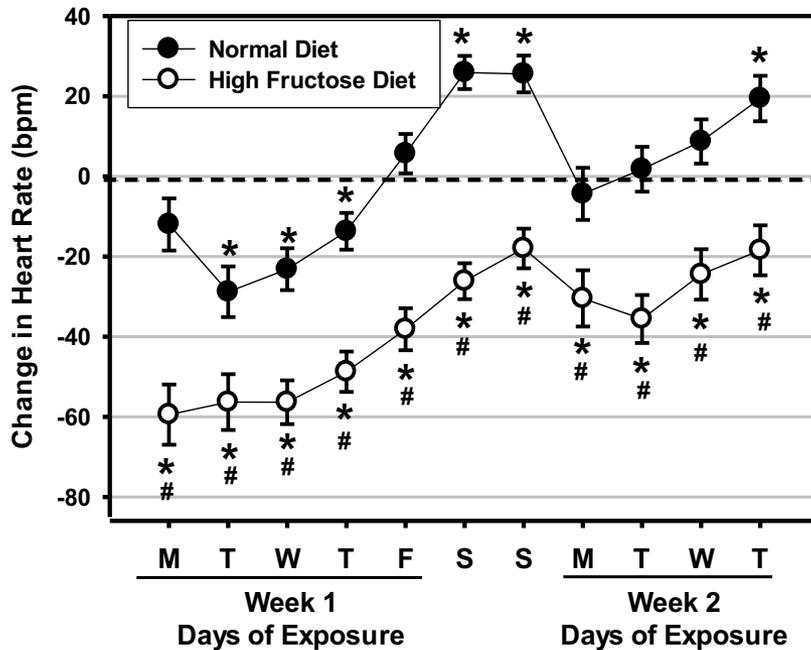
High Fructose Diet-Fed Rats



Results – Heart Rate

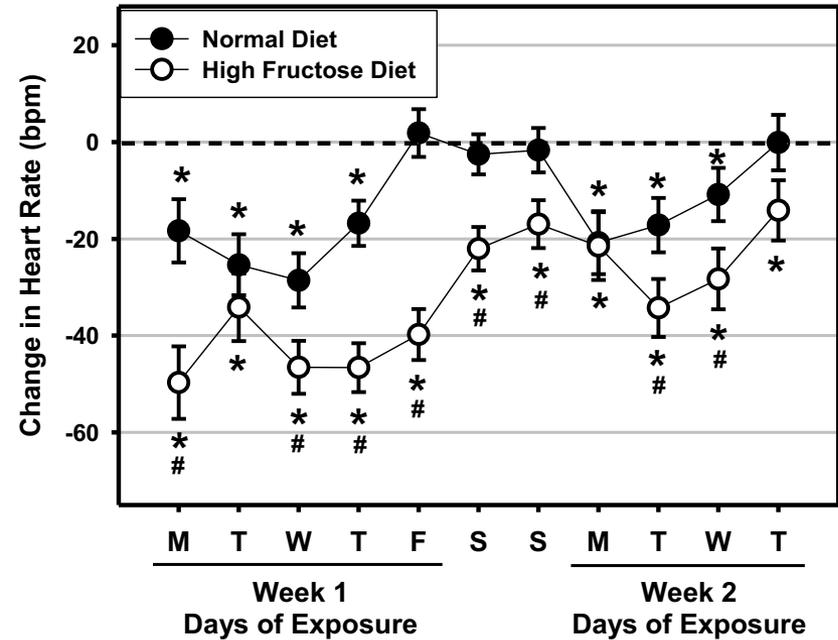
Ozone

Daily Effect of Ozone Exposure on Heart Rate
In Rats Fed Normal or High Fructose Diets



PM2.5

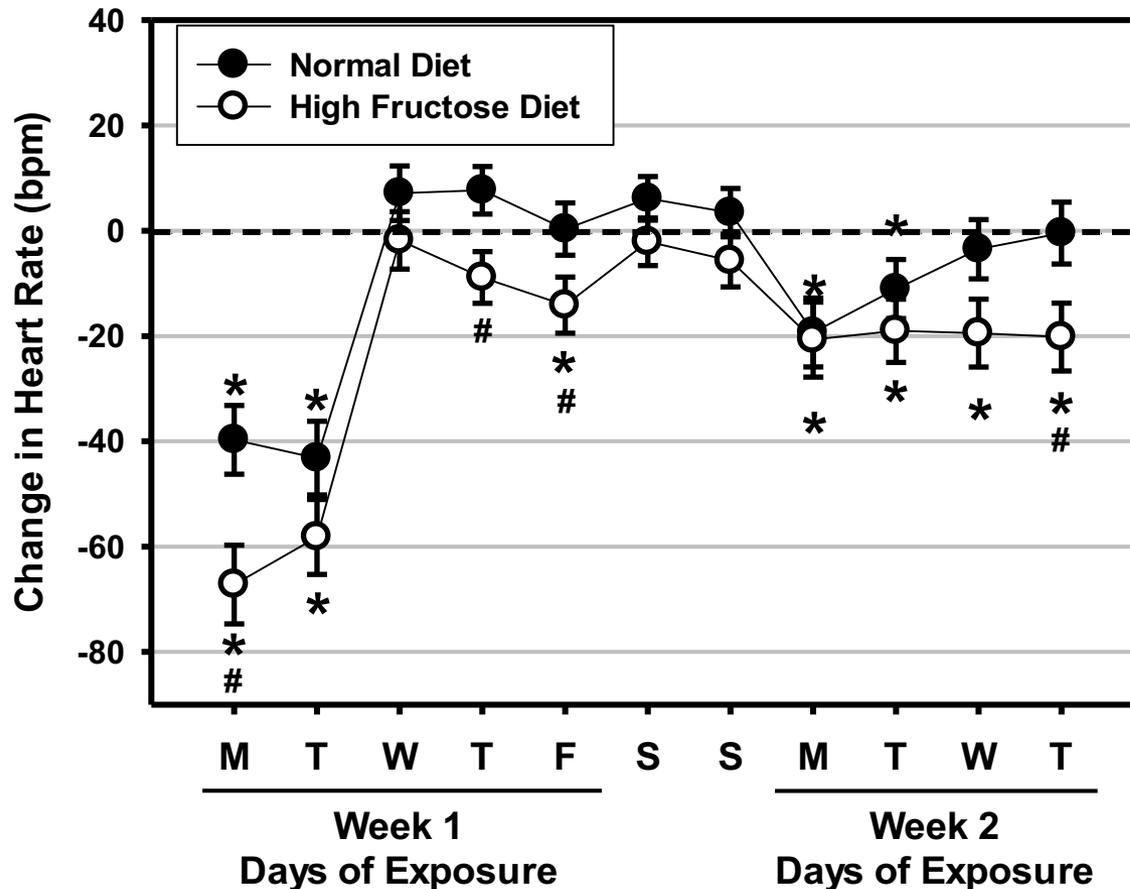
Daily Effect of CAPs Exposure on Heart Rate
In Rats Fed Normal or High Fructose Diets



Results – Heart Rate

Ozone + PM2.5

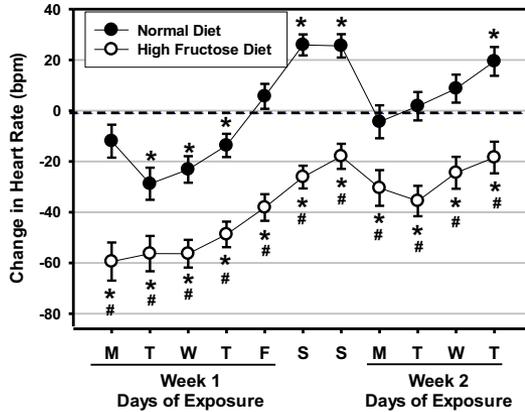
Daily Effect of Ozone+CAP Co-Exposure on Heart Rate
In Rats Fed Normal or High Fructose Diets



Results – Heart Rate

Ozone

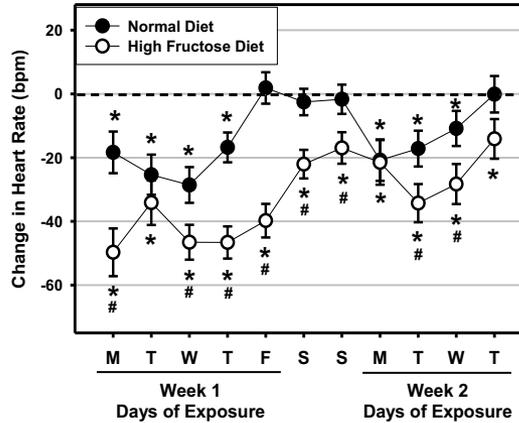
Daily Effect of Ozone Exposure on Heart Rate In Rats Fed Normal or High Fructose Diets



During Exposure

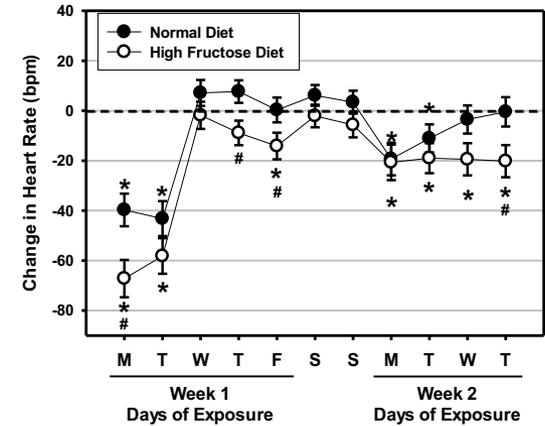
PM2.5

Daily Effect of CAPs Exposure on Heart Rate In Rats Fed Normal or High Fructose Diets



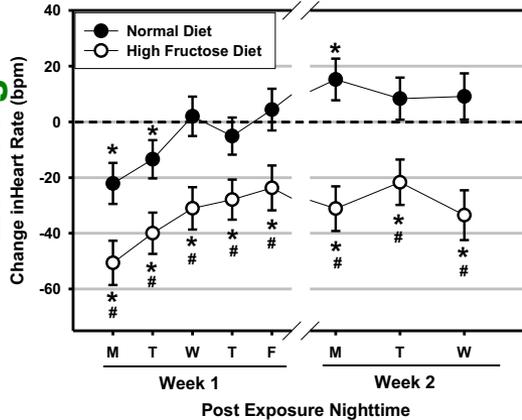
Ozone + PM2.5

Daily Effect of Ozone+CAP Co-Exposure on Heart Rate In Rats Fed Normal or High Fructose Diets

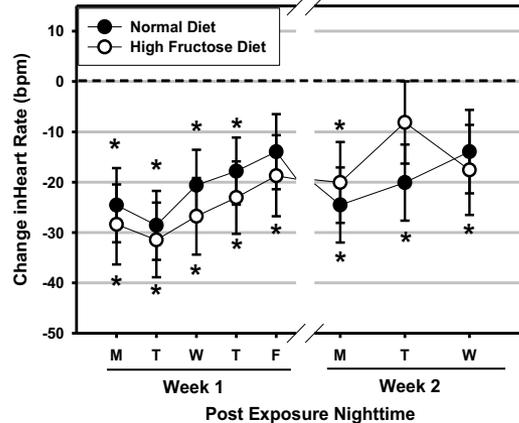


Post Exposure Evening

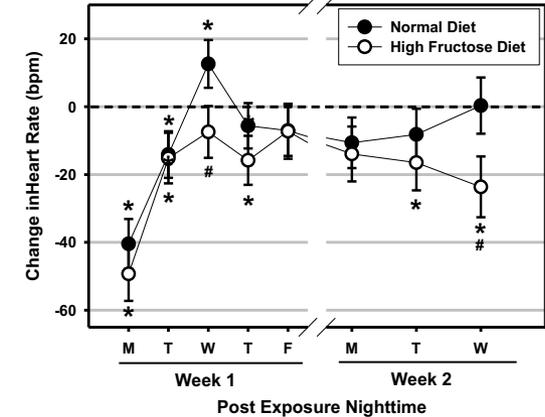
Nightly Postexposure Effect of Ozone Exposure on Heart Rate In Rats Fed Normal or High Fructose Diets



Nightly Postexposure Effect of CAP Exposure on Heart Rate In Rats Fed Normal or High Fructose Diets



Nightly Postexposure Effect of CAP + Ozone Co-Exposure on Heart Rate In Rats Fed Normal or High Fructose Diets



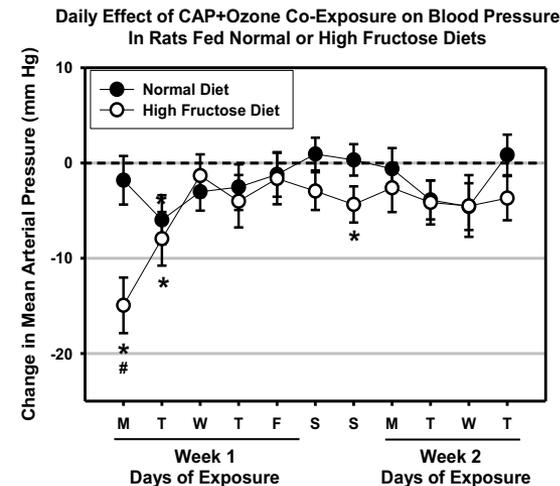
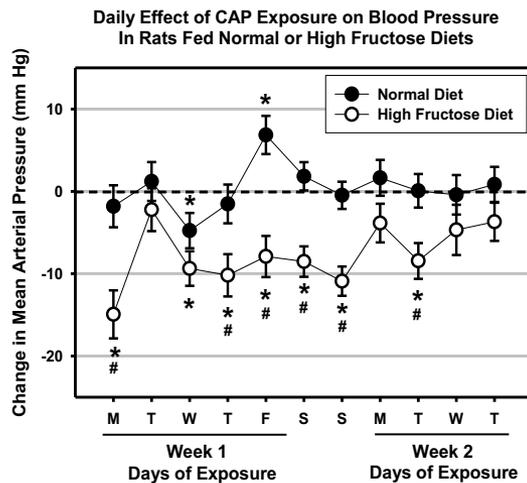
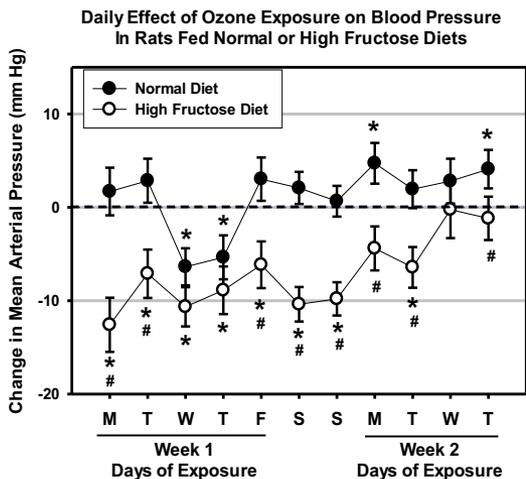
Results – Blood Pressure

Ozone

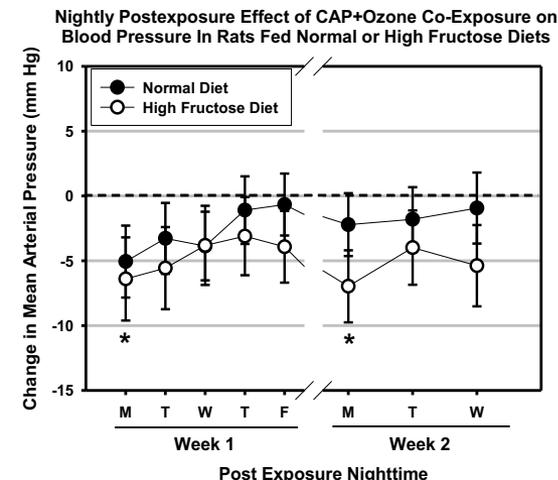
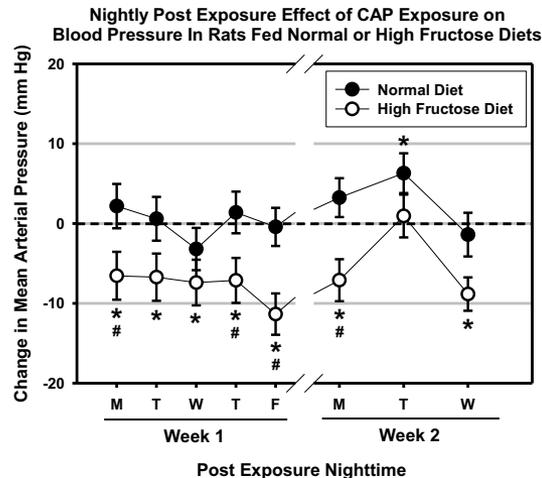
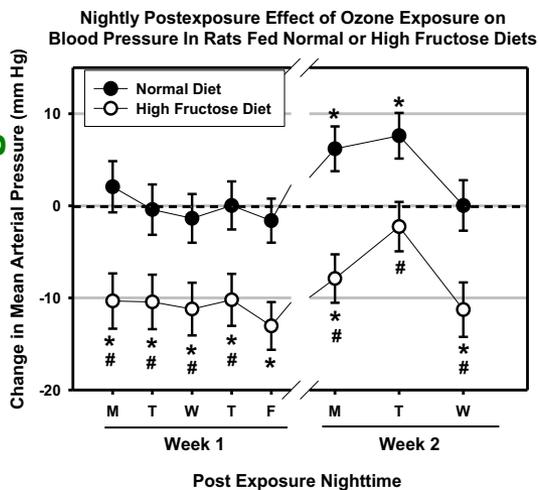
PM2.5

Ozone + PM2.5

During Exposure

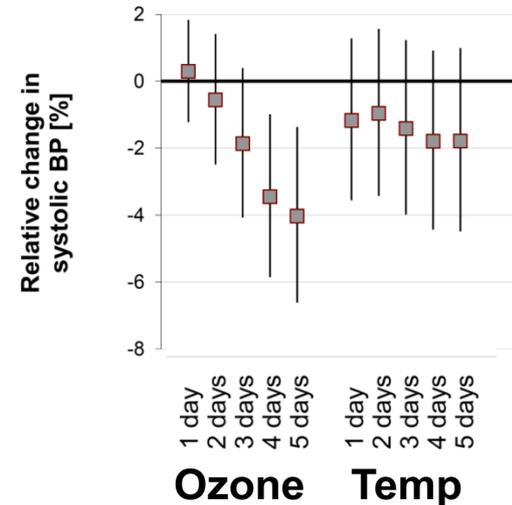


Post Exposure Evening



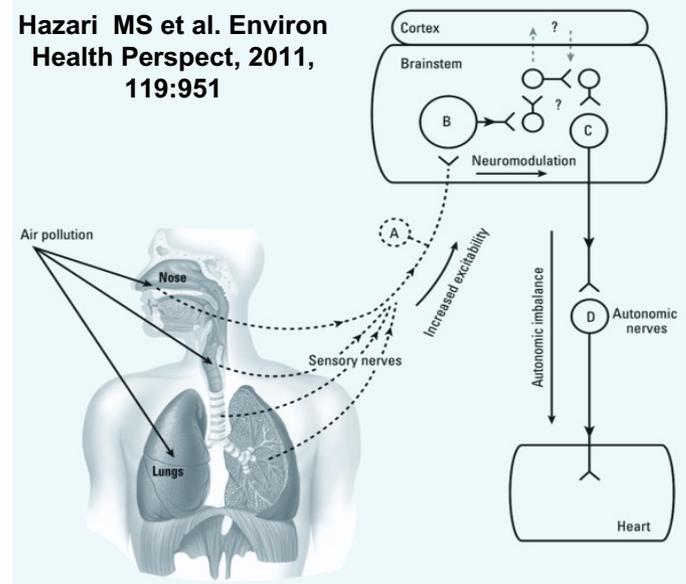
How do air pollutants cause a drop in HR and BP?

- **Trigemino-cardiac reflex (TCR) causes bradycardia (increased parasympathetic activity) and is the most powerful autonomic reflex in the body.**
- **Irritants induce stimulation of airway sensory nerves and transient receptor potential channels (TRPs; e.g., TRPA1)**
- **Does O₃ and/or CAPs cause a drop in HR and BP through TCR and/or TRPs?**
- **What are the mechanism(s) underlying HFrD enhancement of the exposure-induced bradycardia and hypotension?**

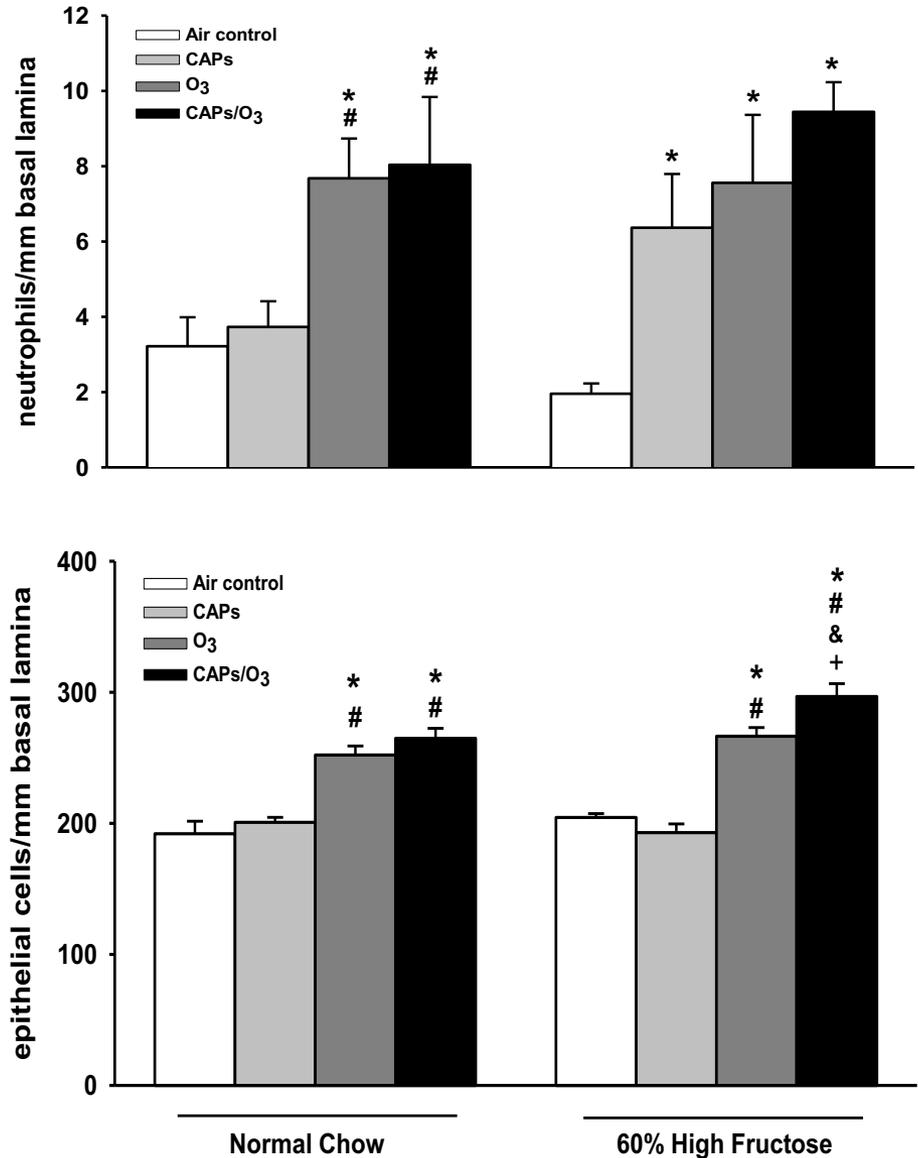
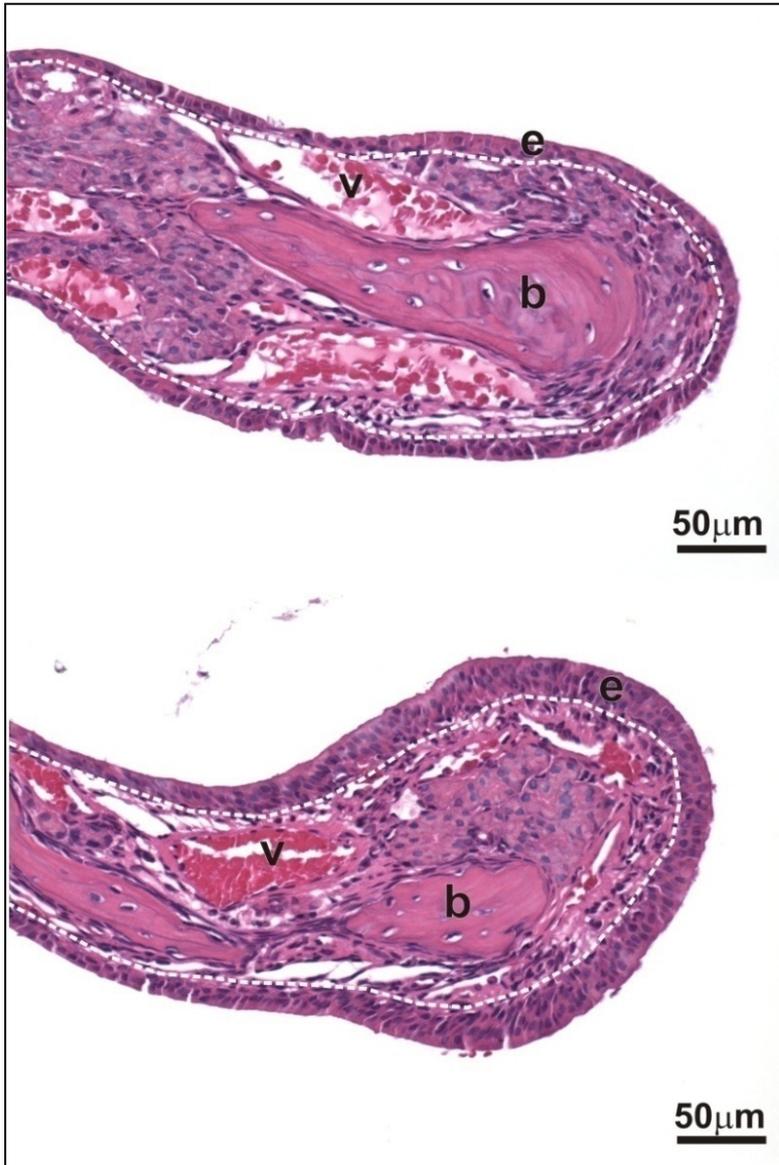


Ozone Temp
Hoffmann et al. Environ Health Perspect, 2012, 120:241

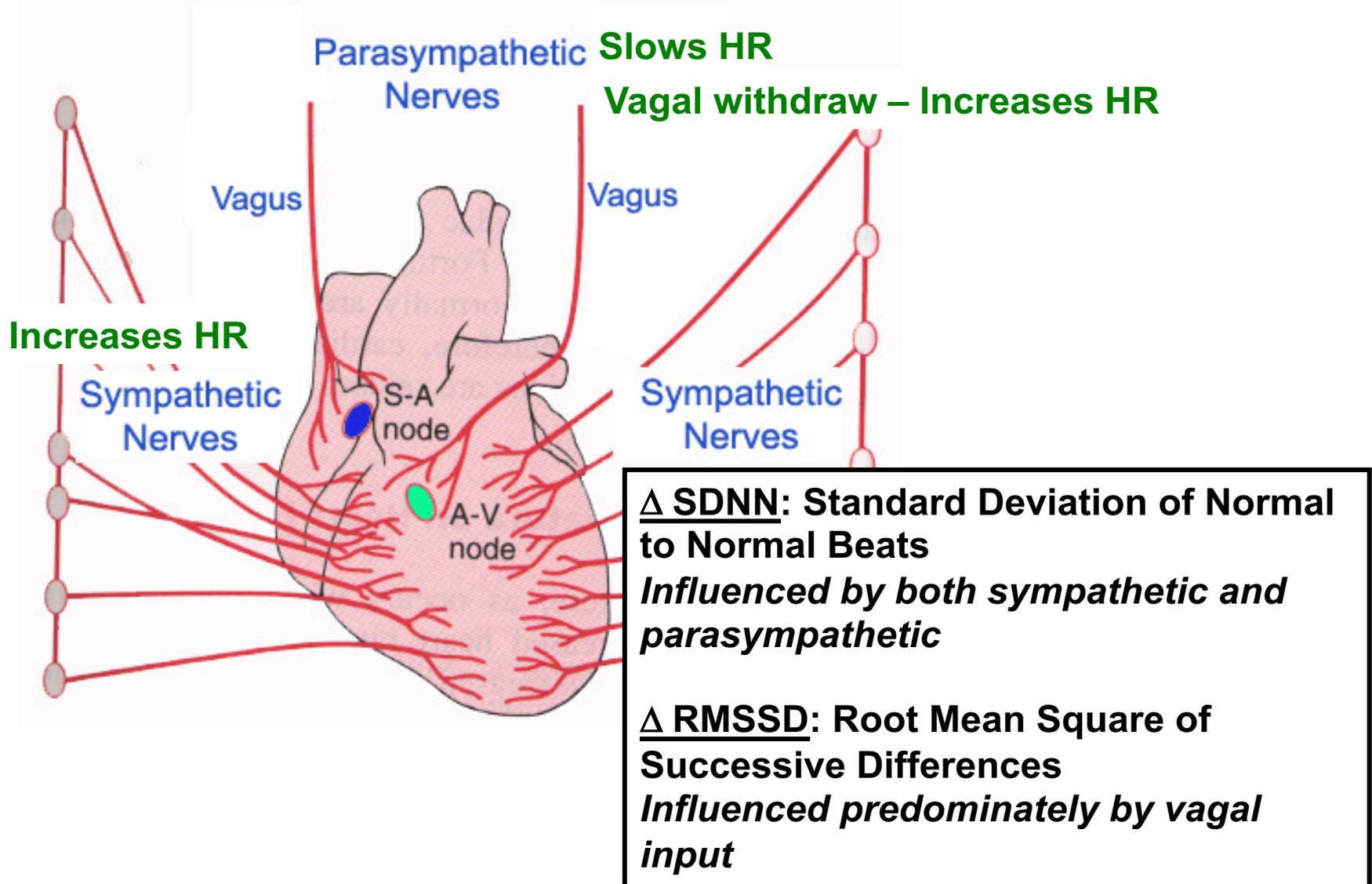
Hazari MS et al. Environ Health Perspect, 2011, 119:951



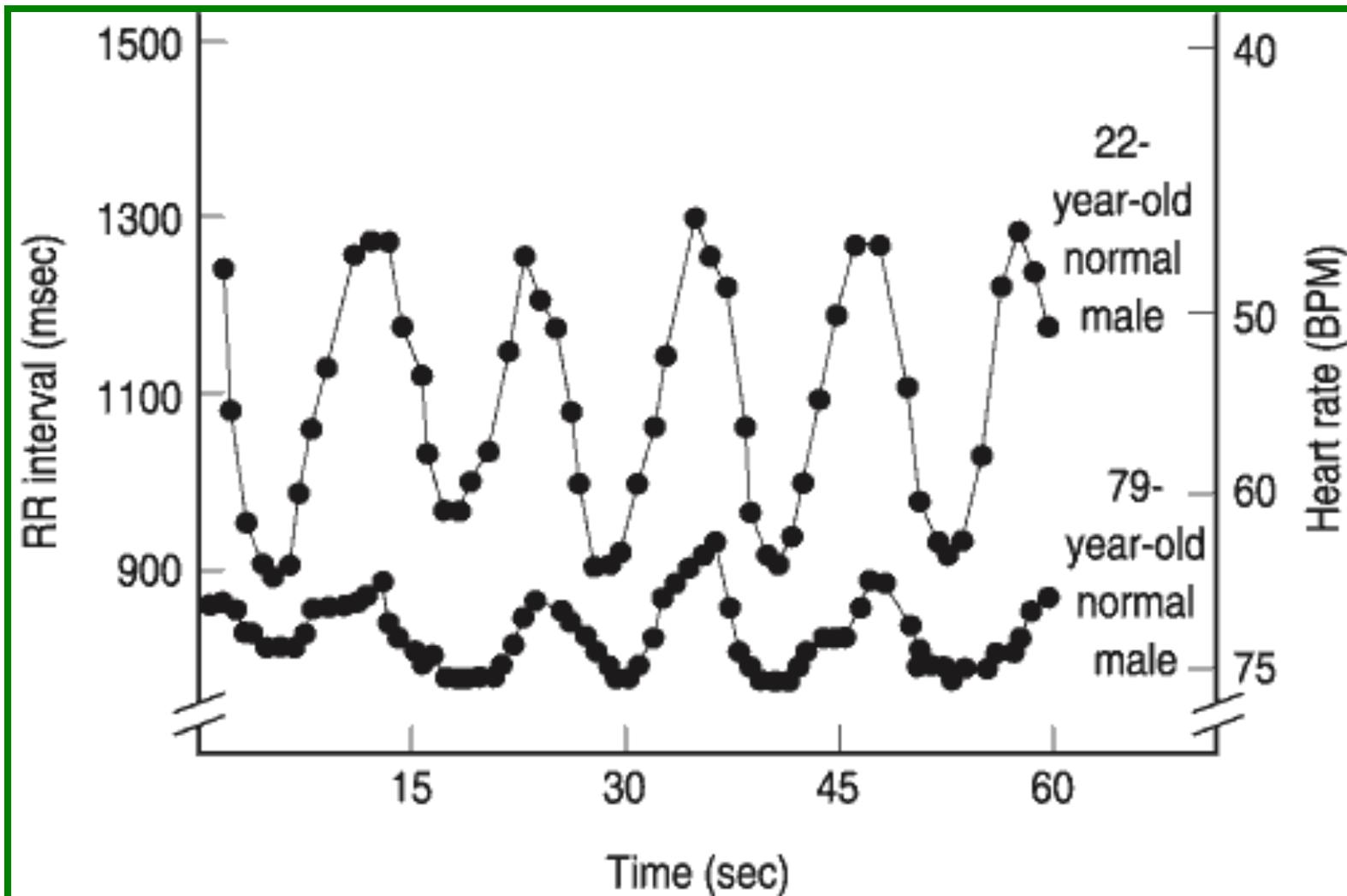
Exposure-induced nasal airway Inflammation and epithelial remodeling



Heart Rate Variability in Health and Disease



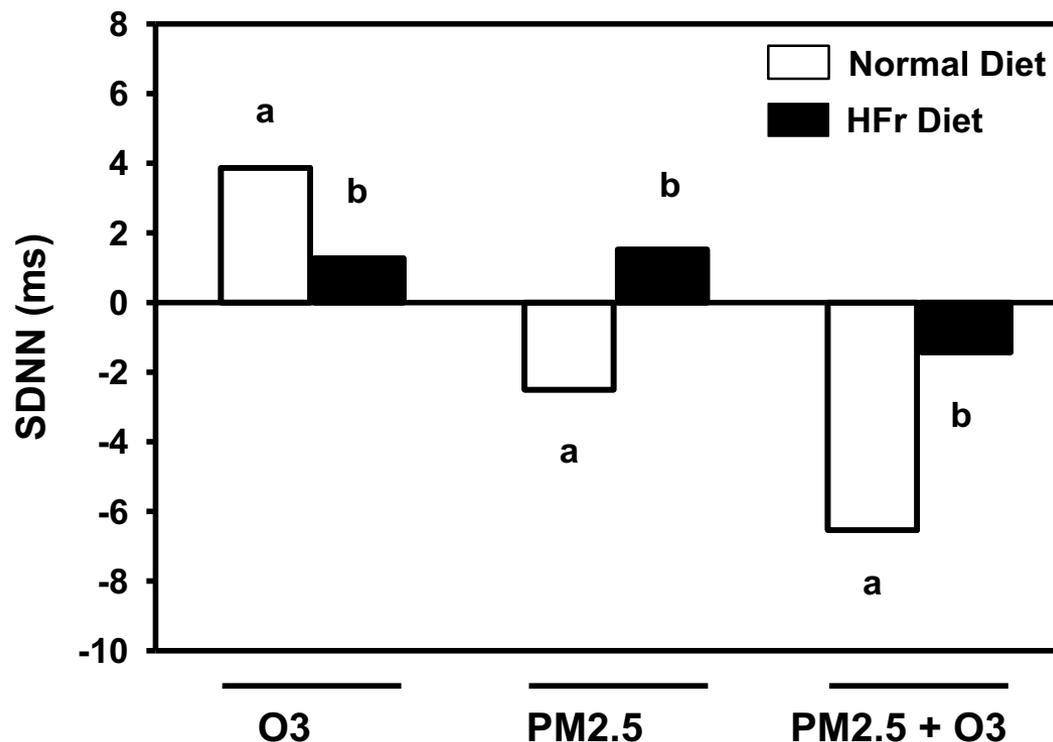
Heart Rate Variability in Health and Disease



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Results: Heart Rate Variability

Effects of O3 and PM2.5 Exposures on SDNN

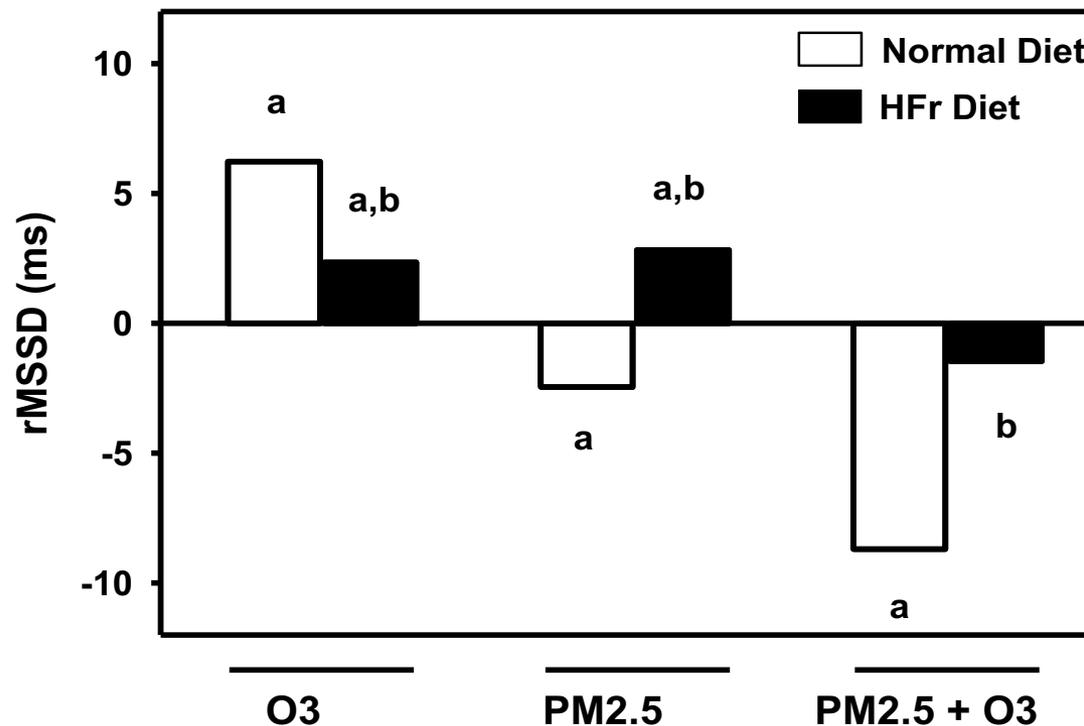


a= significantly different from respective group exposed to AIR

b = significantly different from respective group fed a Normal Diet

Results: Heart Rate Variability

Effects of O3 and PM2.5 Exposures on RMSSD



a = significantly different from respective group exposed to AIR

b = significantly different from respective group fed a Normal Diet

Results – Daily HRV

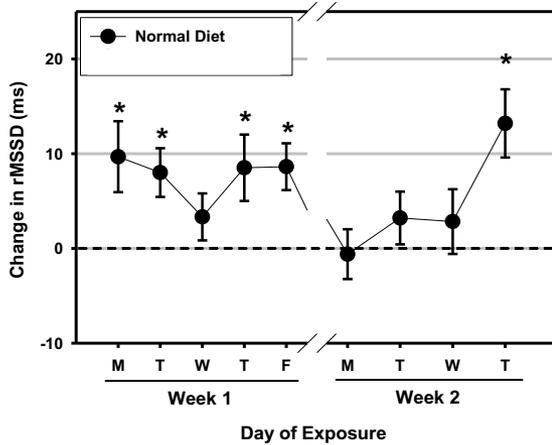
Ozone

PM2.5

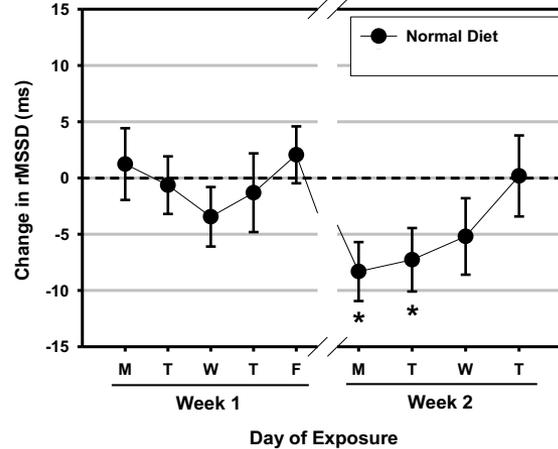
Ozone + PM2.5

Daily Effect of Ozone Exposure on rMSSD
In Rats Fed Normal or High Fructose Diets

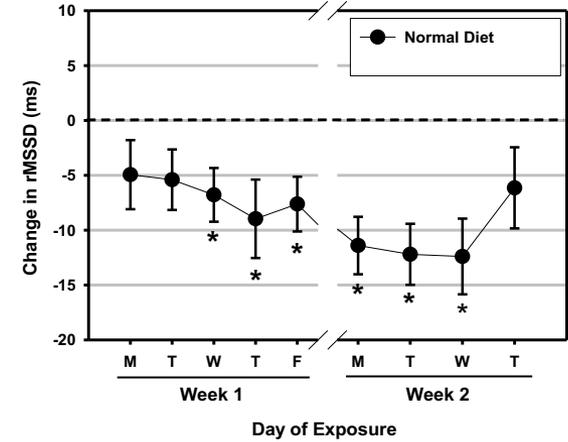
rMSSD



Daily Effect of CAP Exposure on rMSSD
In Rats Fed Normal or High Fructose Diets

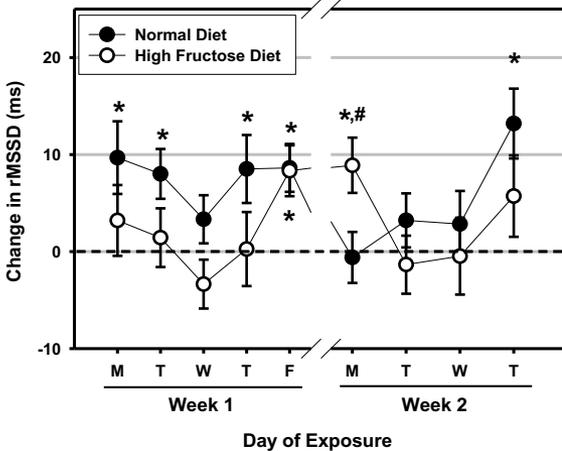


Daily Effect of CAP+Ozone Exposure on rMSSD
In Rats Fed Normal or High Fructose Diets

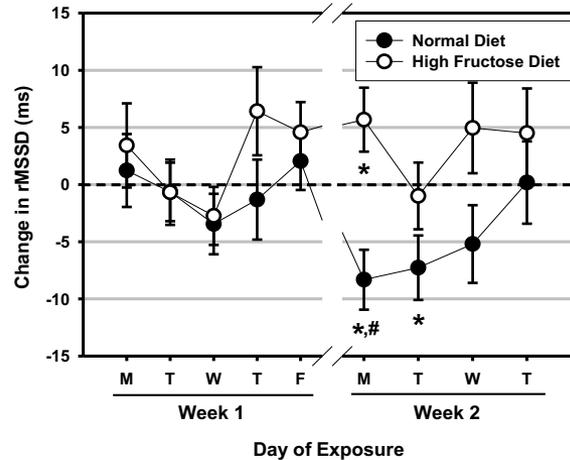


Daily Effect of Ozone Exposure on rMSSD
In Rats Fed Normal or High Fructose Diets

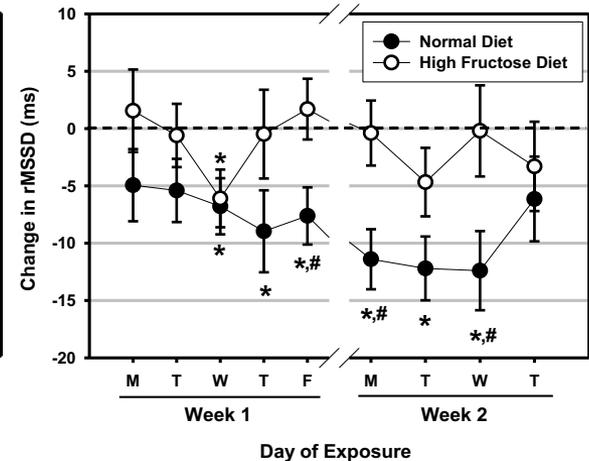
rMSSD



Daily Effect of CAP Exposure on rMSSD
In Rats Fed Normal or High Fructose Diets



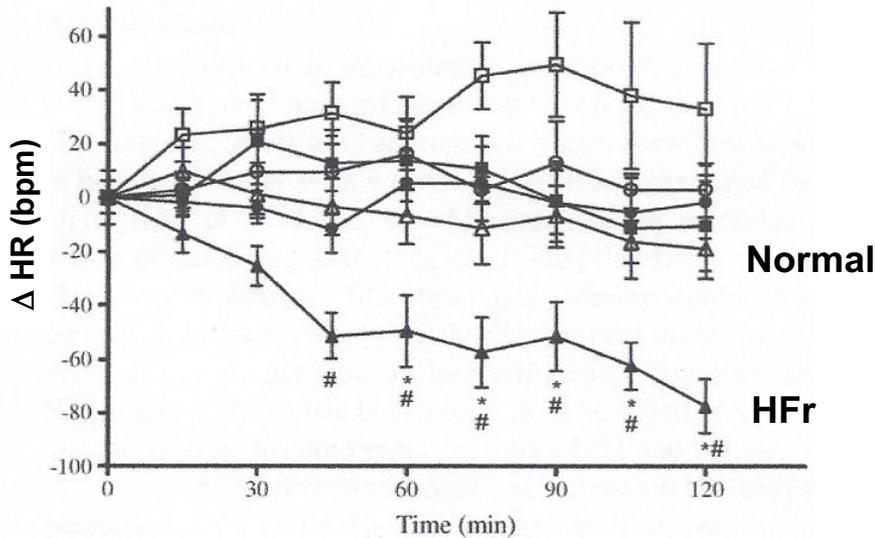
Daily Effect of CAP+Ozone Exposure on rMSSD
In Rats Fed Normal or High Fructose Diets



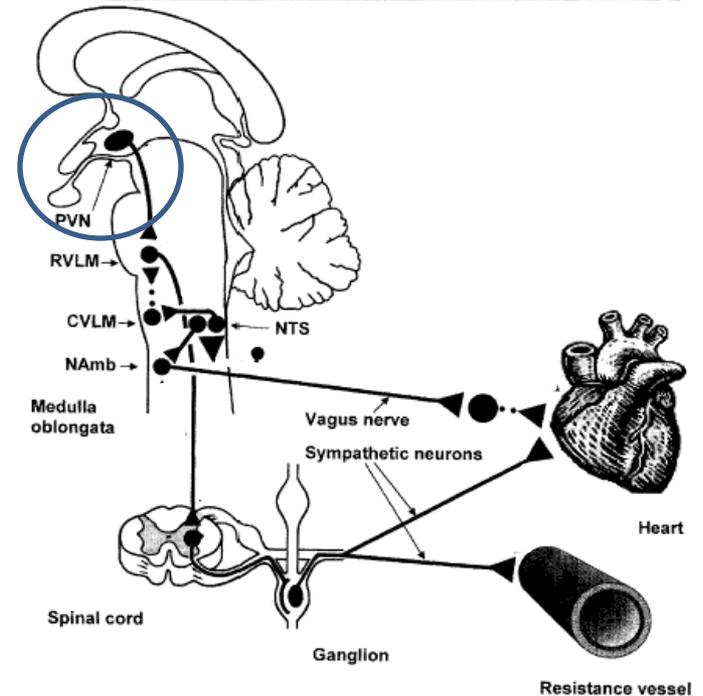
Central Control of Heart Rate: Hypothalamus

Paraventricular Nucleus: α_2 -adrenoceptors Activation decreases HR and BP

High Fructose Rats: Supersensitivity of α_2 -adrenoceptors

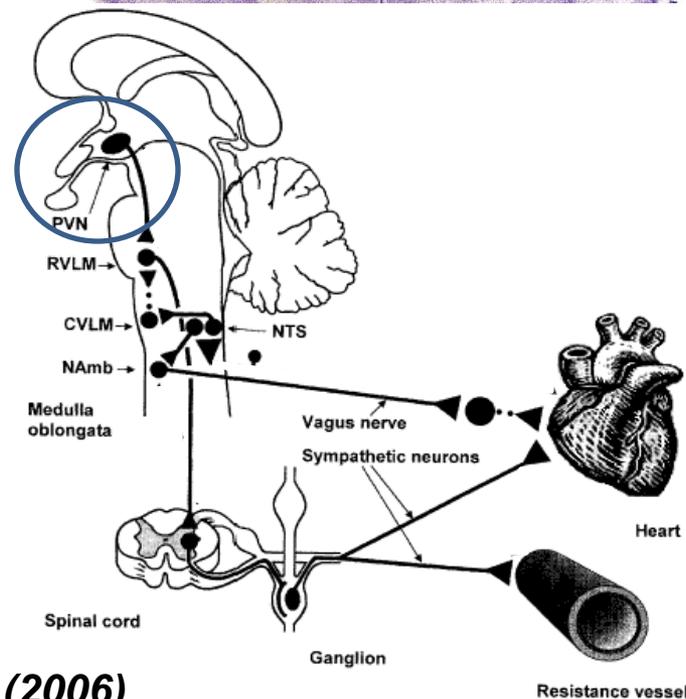
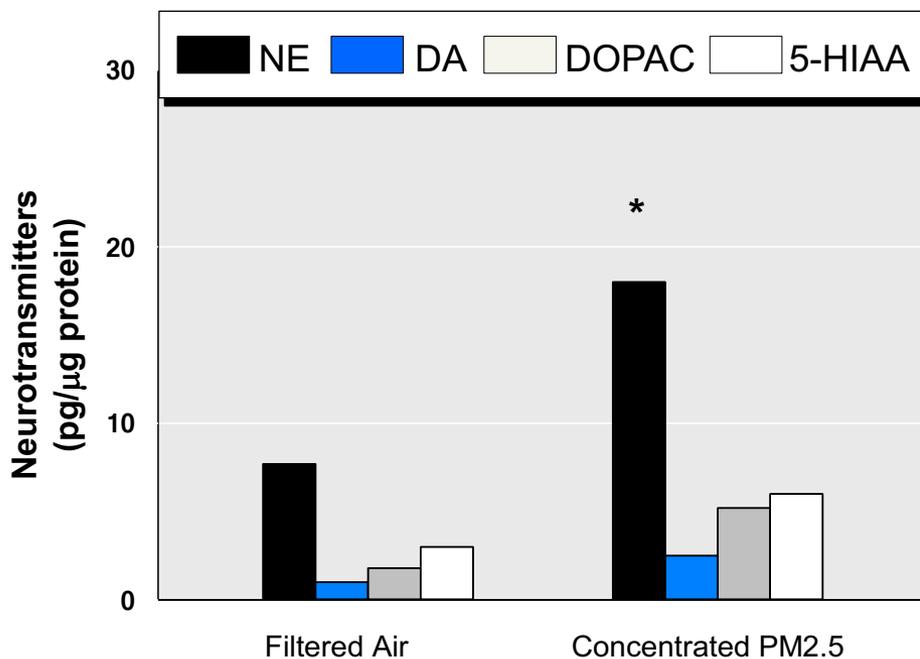


Mayer et al., *Neurosci Lett* 423:129-132 (2007)



Central Control of Heart Rate: Hypothalamus

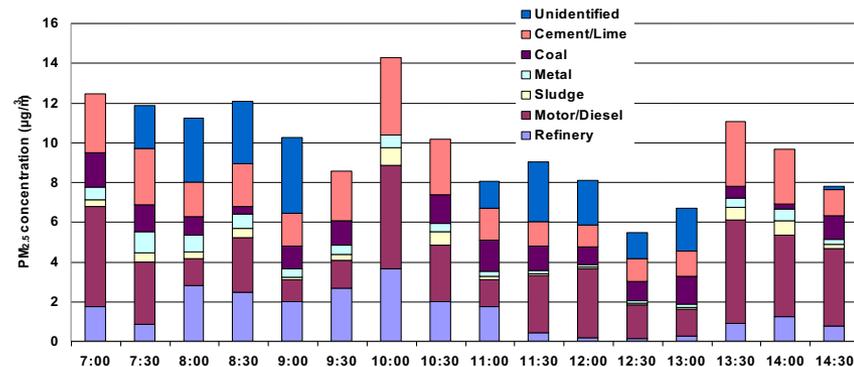
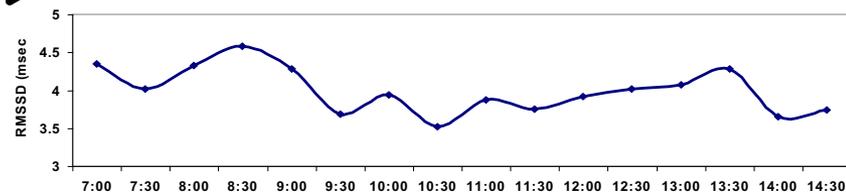
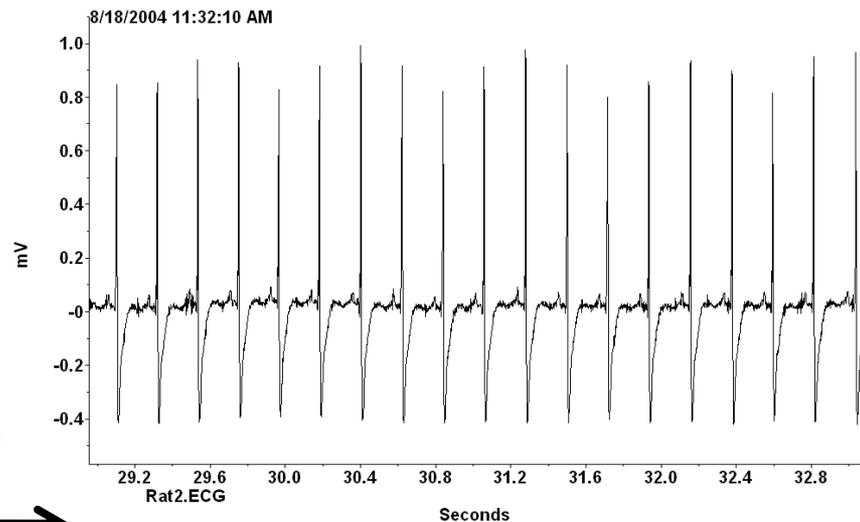
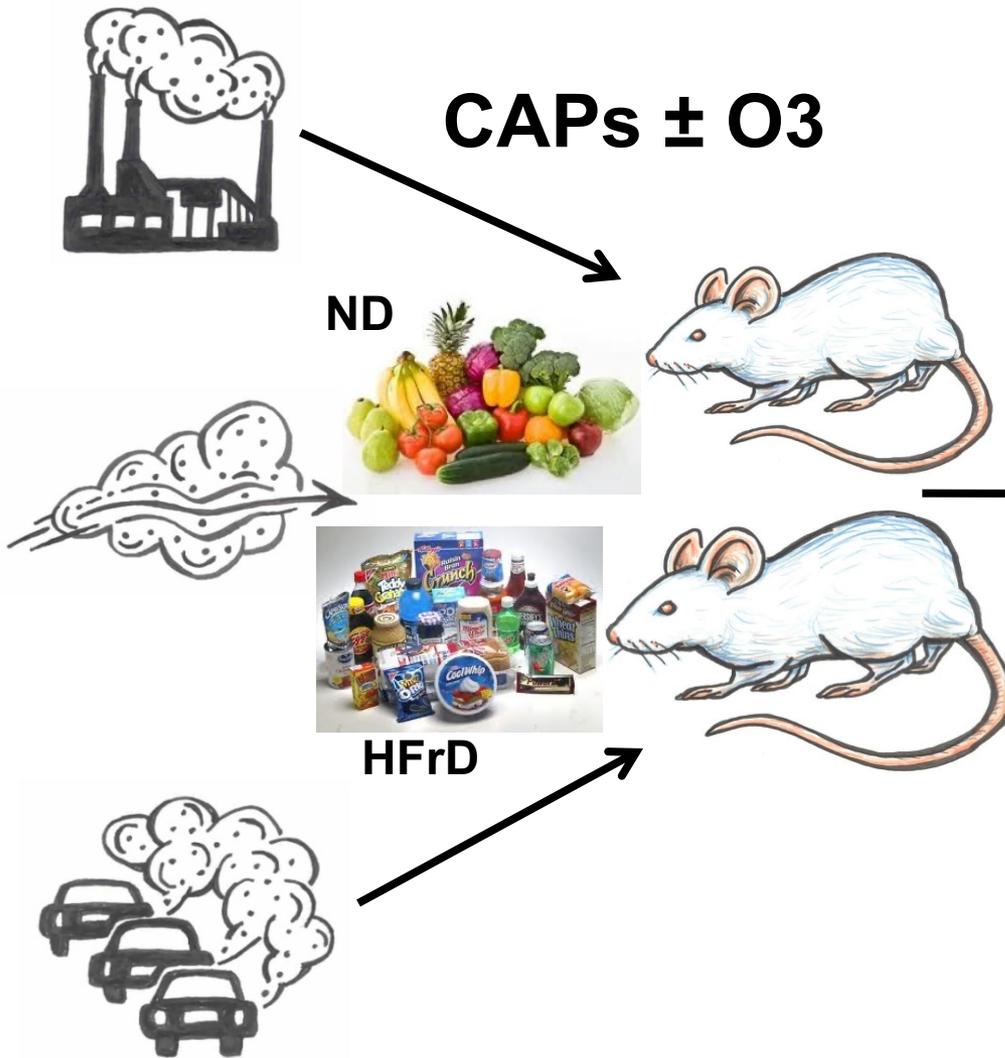
Exposure to concentrated PM_{2.5} increases production of norepinephrine in the paraventricular nucleus



Summary of Current Findings

- **High fructose diet produced facets of the CMS in rats (e.g., hypertension, insulin resistance, hyperglycemia, and hepatic steatosis).**
- **On a normal diet, heart rate variability was enhanced with O₃, decreased with CAPS, and markedly decreased with CAPs & O₃.**
- **On a high fructose diet, changes in heart rate variability were blunted to O₃, CAPs, or CAPs+O₃ exposures.**
- **Acute exposures to O₃, CAPs, or CAPs+O₃ caused reductions in BP and HR that were markedly enhanced in HFrD-fed rats.**
- **Enhanced BP and HR responses, and blunting of HRV responses, in HFrD-fed rats suggest a diet-induced dysfunction in the autonomic nervous system.**
- **CAPs+O₃ caused a greater decrease in BP and HR in the first few days of exposure, but a quick adaptive response with repeated exposures.**

Project 2: Future Studies



Project 2: Sources to Health Outcomes

GOAL: Conduct animal CAPs exposures in different sites selected for their unique PM atmospheres: e.g., urban, rural, industrial, traffic.

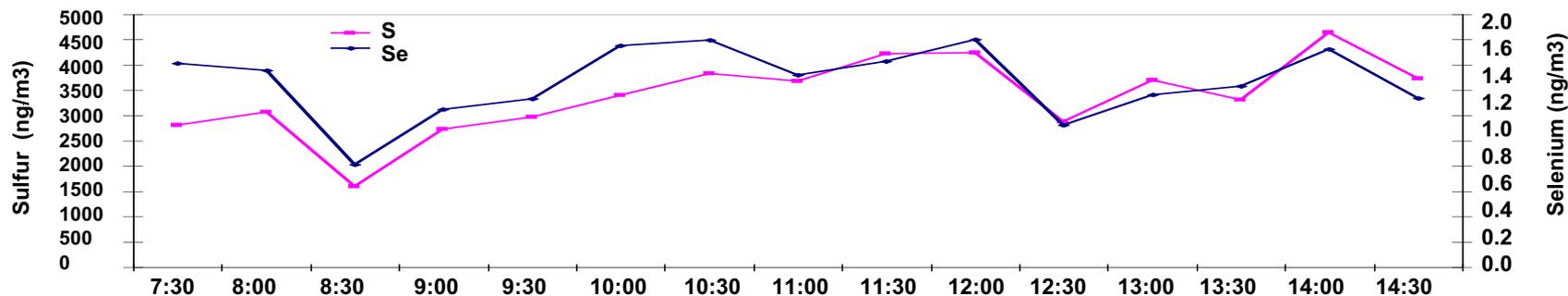
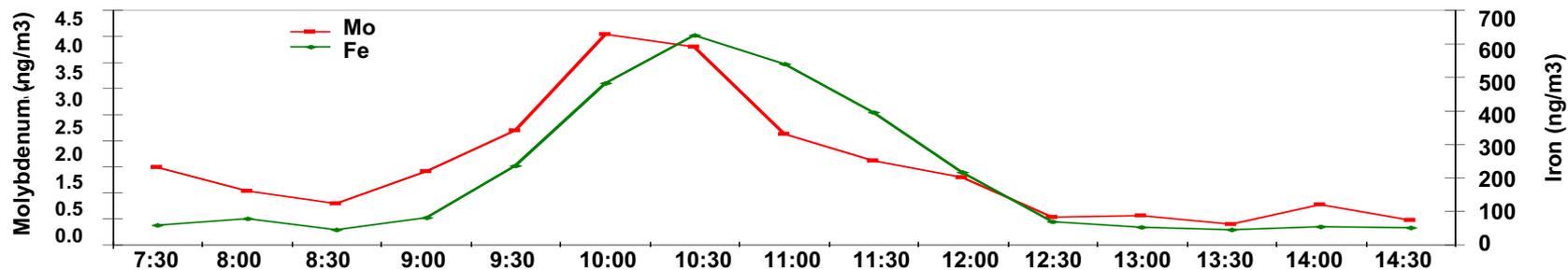
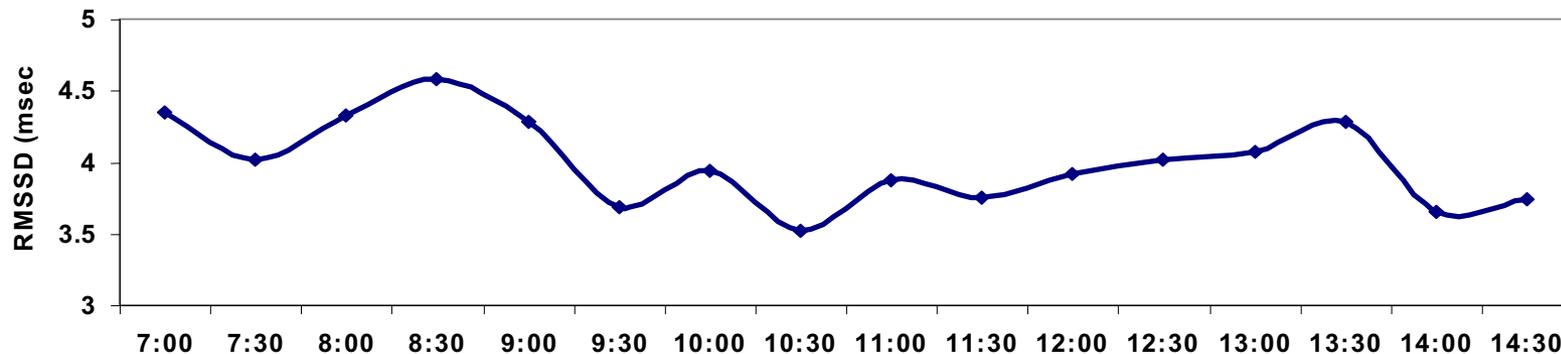
PM Characterization and Air Chemistry:

Measurement	PM Property	Sampling Media	Sample Duration (hr)	Analytical Method
TEOM	Mass	-	Continuous	
APS 3320	Size (0.5-20 μm)	-	Continuous	
Aethelometer	Black carbon	-	Continuous	
SMPS 3936	Size (0.01-.6 μm)	-	Continuous	-
MOI	Size (10 stages)/Mass & Trace elements	Teflon	8	Gravimetric/ICP-MS
Filter (PM _{2.5})	Trace elements	Teflon	8	Gravimetric/ICP-MS
Filter (PM _{2.5})	Soluble trace elements	Teflon	8	Gravimetric/ICP-MS
PM2.5	Trace Elements	aqueous	30 minute	SEAS / ICP-MS
Annular Denuder-Filter Pack System	Acid gases & aerosols and major ions	Teflon/Glass /denuders	8	IC/pH
Filter	Elemental & organic carbon	Quartz	8	TOA

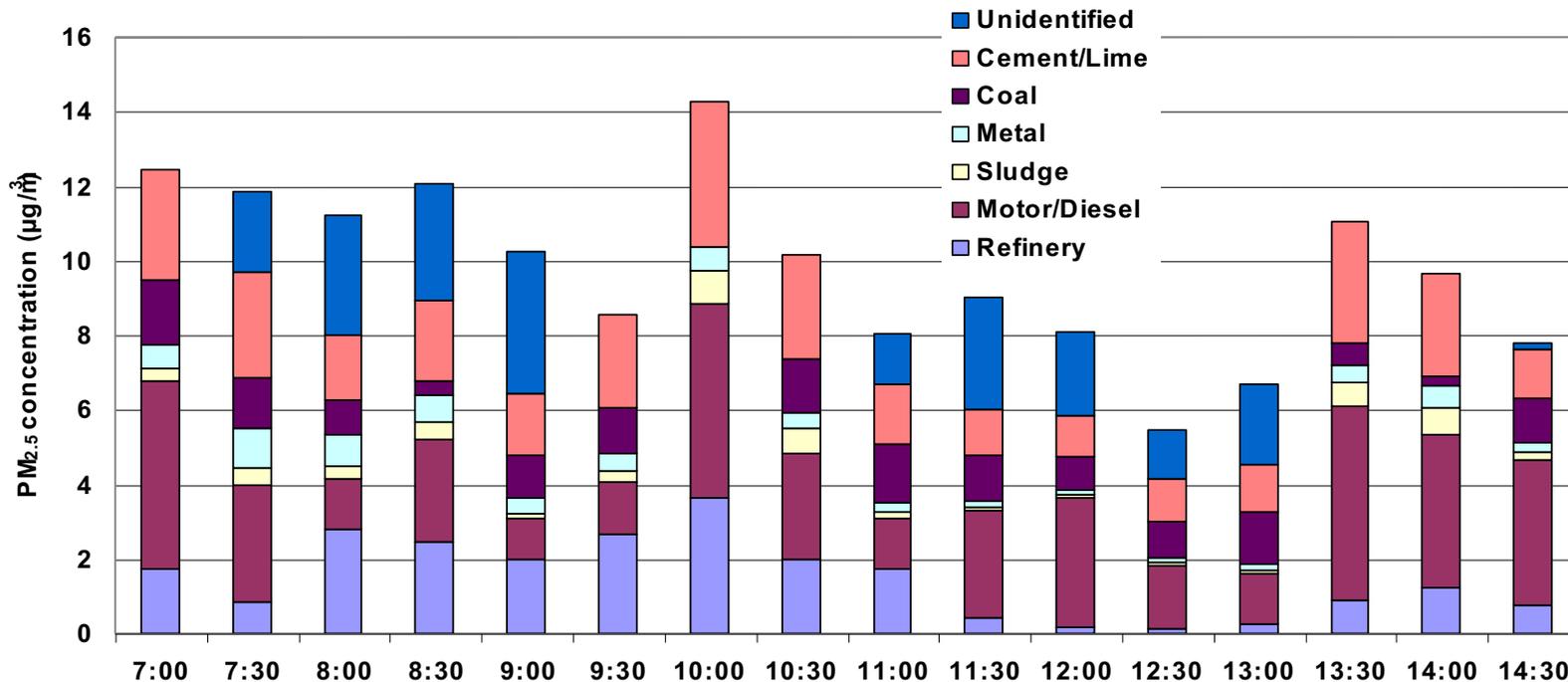
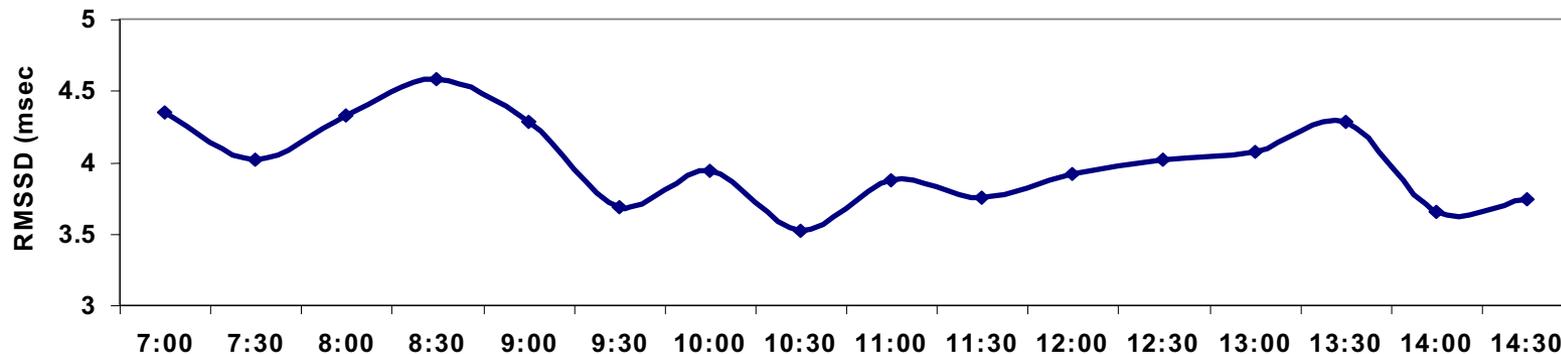


**SEAS:
Semi-continuous
Elements in
Aerosol Sampler**

Component- and Source-associated Health Effects in Animal Studies with CAPs



Component- and Source-associated Health Effects in Animal Studies with CAPs



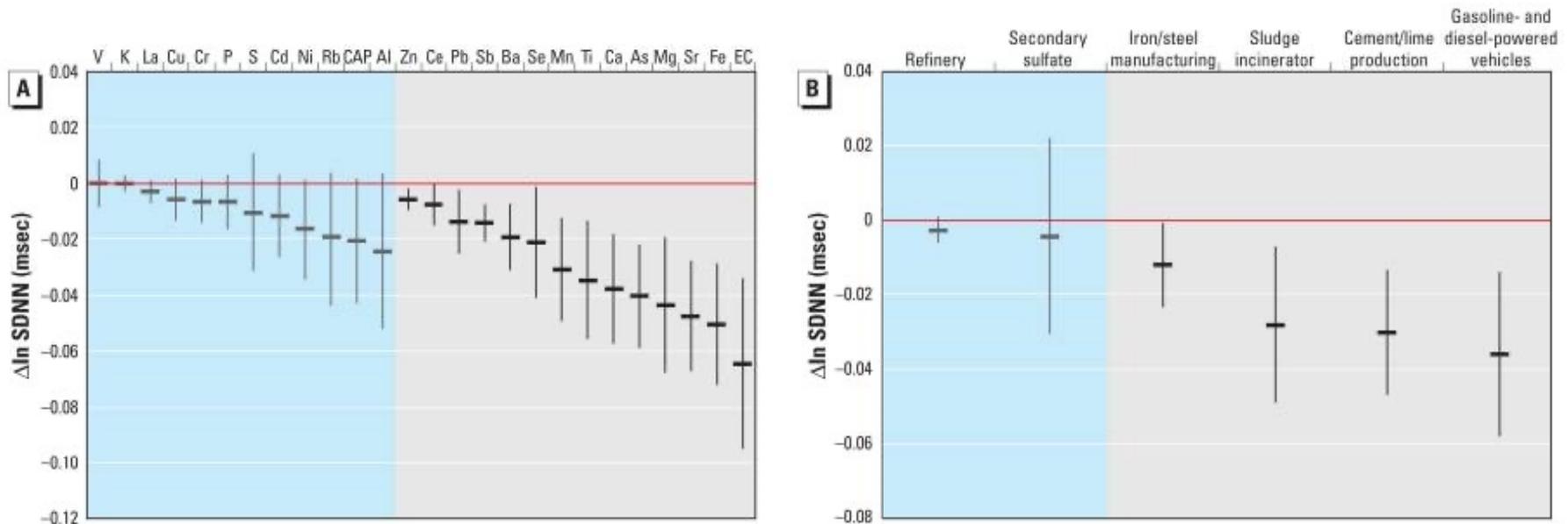
Component- and Source-associated Health Effects in Animal Studies with Detroit CAPs

OBJECTIVE:

We used a rat model to investigate linkages between cardiac effects of concentrated ambient particle (CAP) constituents and source factors using a unique, highly time-resolved data set.

METHODS:

Spontaneously hypertensive rats inhaled Detroit Michigan, CAPs during summer or winter (2005-2006) for 13 consecutive days. Electrocardiogram data were recorded continuously, and heart rate (HR) and heart rate variability (HRV) metrics were derived. Extensive CAP characterization, including use of a Semicontinuous Elements in Aerosol Sampler (SEAS), was performed, and positive matrix factorization was applied to investigate source factors.



Acknowledgments

- **MSU:** Drs. Katy Allen, Jim Wagner, and Greg Fink
- **UM:** Drs. Robert Brook, Tim Dvonch, Masako Morishita, Bin Nan, Cathie Spino and Bhramar Mukherjee
- **OSU:** Drs. Qinghua Sun and Sanjay Rajagopalan
- **MSU Lab:** Ryan Lewandowski, Lori Bramble, Christina Brandenberger, Ian Hotchkiss, Vanessa Hoang, Dennis Shubitowski, Daven Jackson-Humbles, Hannah Garver



Questions?

