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THE OVERALL (MOSTLY CARDIOVASCULAR) HEALTH BURDEN OF INDOOR PM2.5 EXPOSURE

Howard M. Kipen, MD, MPH
Professor & Director
Clinical Research & Occupational Medicine Division
Environmental & Occupational Health Sciences Institute
Rutgers- School of Public Health

Indoor Exposure to Fine PM Workshop
NAS
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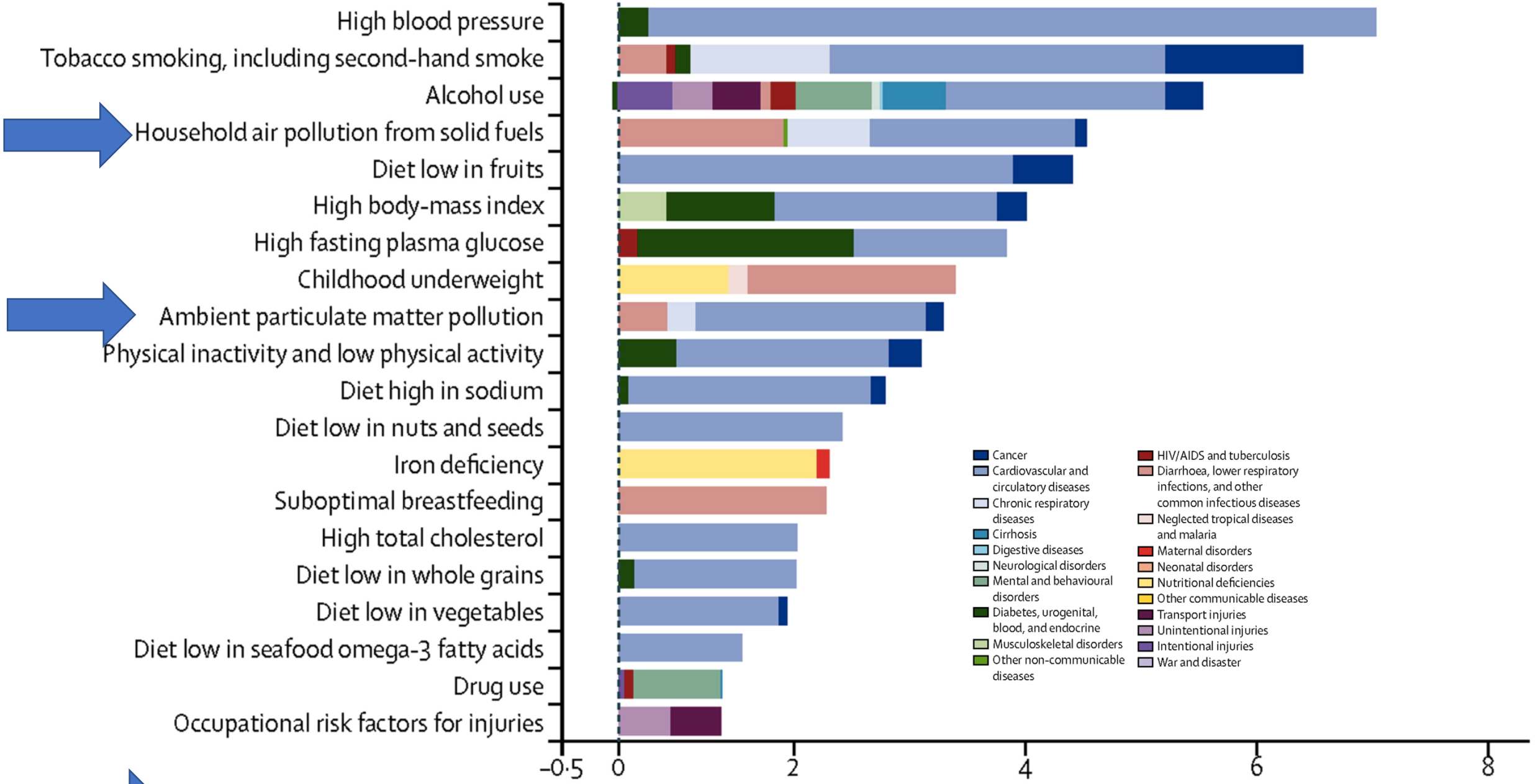
Nothing to Disclose

Outline

- Outdoor (Indoor) Air Pollution Epidemiology
- Pathophysiology, Mechanisms, and Biomarkers
- A Natural Experiment
- Indoor (Outdoor) Air Pollution Epidemiology
- Cleaning the Air
- Benefits and CO_2STS
- What if there is a New Variant?

Global Burden of Disease



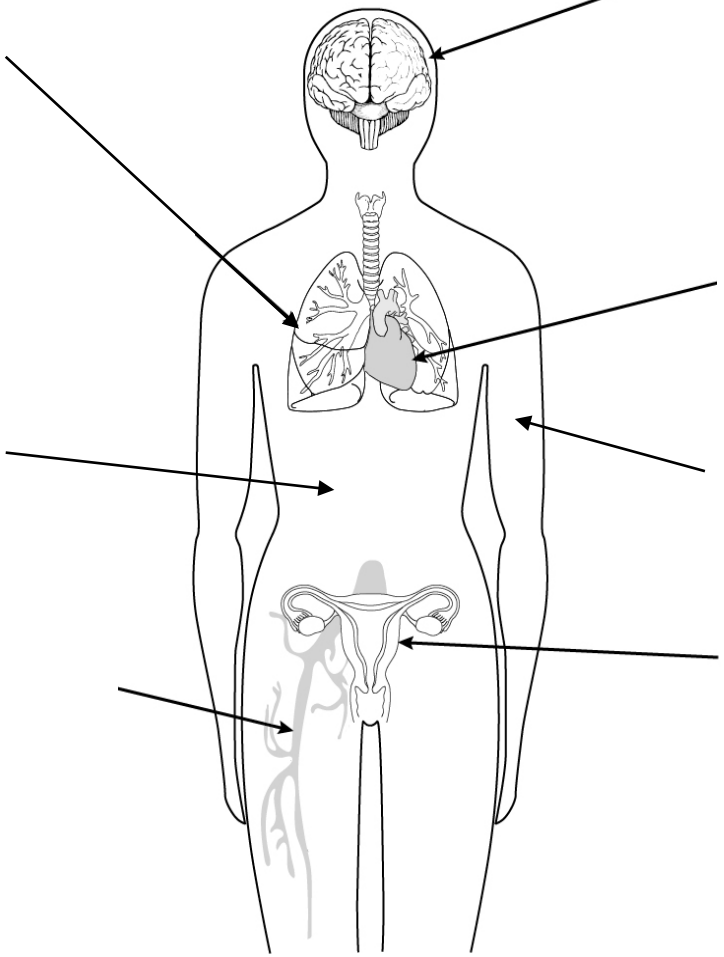
As of 2017 GBD does not specify IAQ

Lim et al. Lancet 2012

EMERGING TARGETS FOR AIR POLLUTION

- **Respiratory Disease Mortality**
- **Respiratory Disease Morbidity**
- **Lung Cancer**
- **Pneumonia**
- Rhinitis
- Airway inflammation
- Decreased lung function
- Decreased lung growth

- **Stroke**
- Neurological development
- Mental Health
- **Neurodegenerative diseases**



- **Cardiovascular Disease Mortality**
- **Cardiovascular Disease Morbidity**
- Changes in Heart Rate Variability
- ST-Segment Depression

- Insulin Resistance
- **Type 2 diabetes**
- **Type 1 diabetes**
- Bone metabolism

- Skin Aging

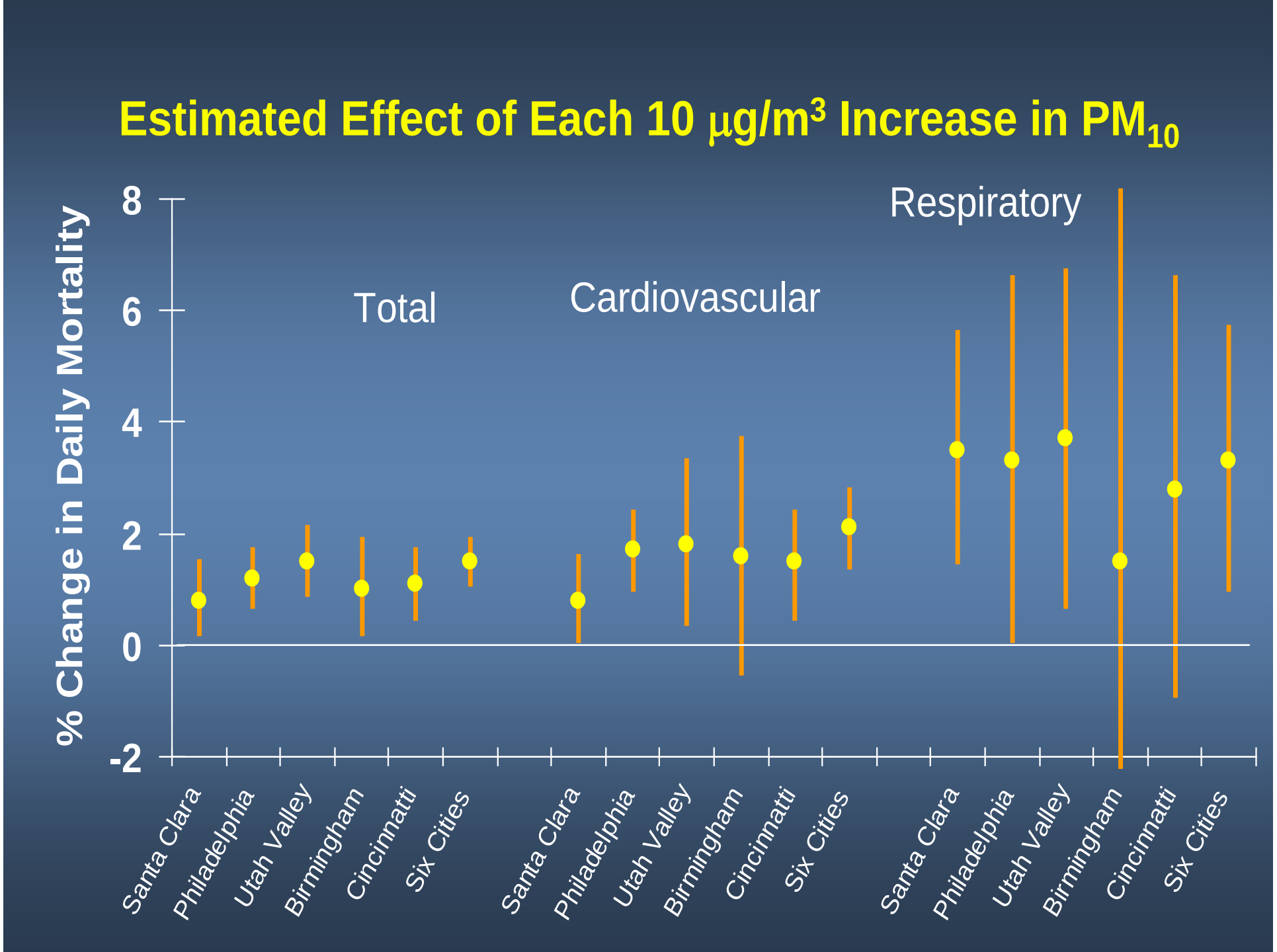
- Changes in blood pressure
- Endothelial dysfunction
- Increased blood coagulation
- Systemic inflammation
- **Deep Venous Thrombosis**

- **Premature Birth**
- **Decreased Birth Weight**
- Decreased foetal growth
- In uterine growth retardation
- Decreased sperm quality
- Preclampsia

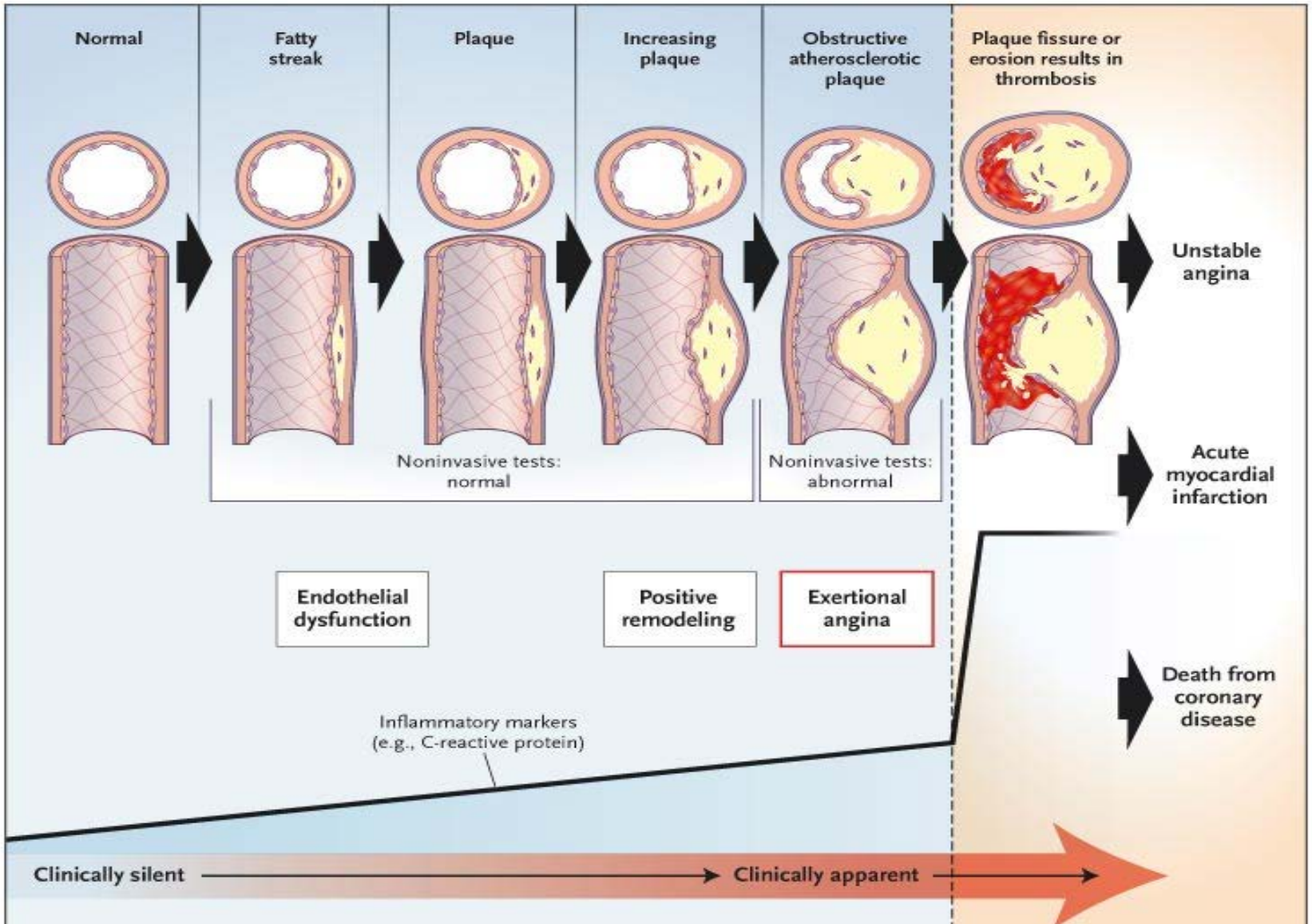
Thurston, Kipen et al.,
European Resp J, 2017

Outcomes Linked to Outdoor Air Pollution (ACUTE / CHRONIC EPIDEMIOLOGY)

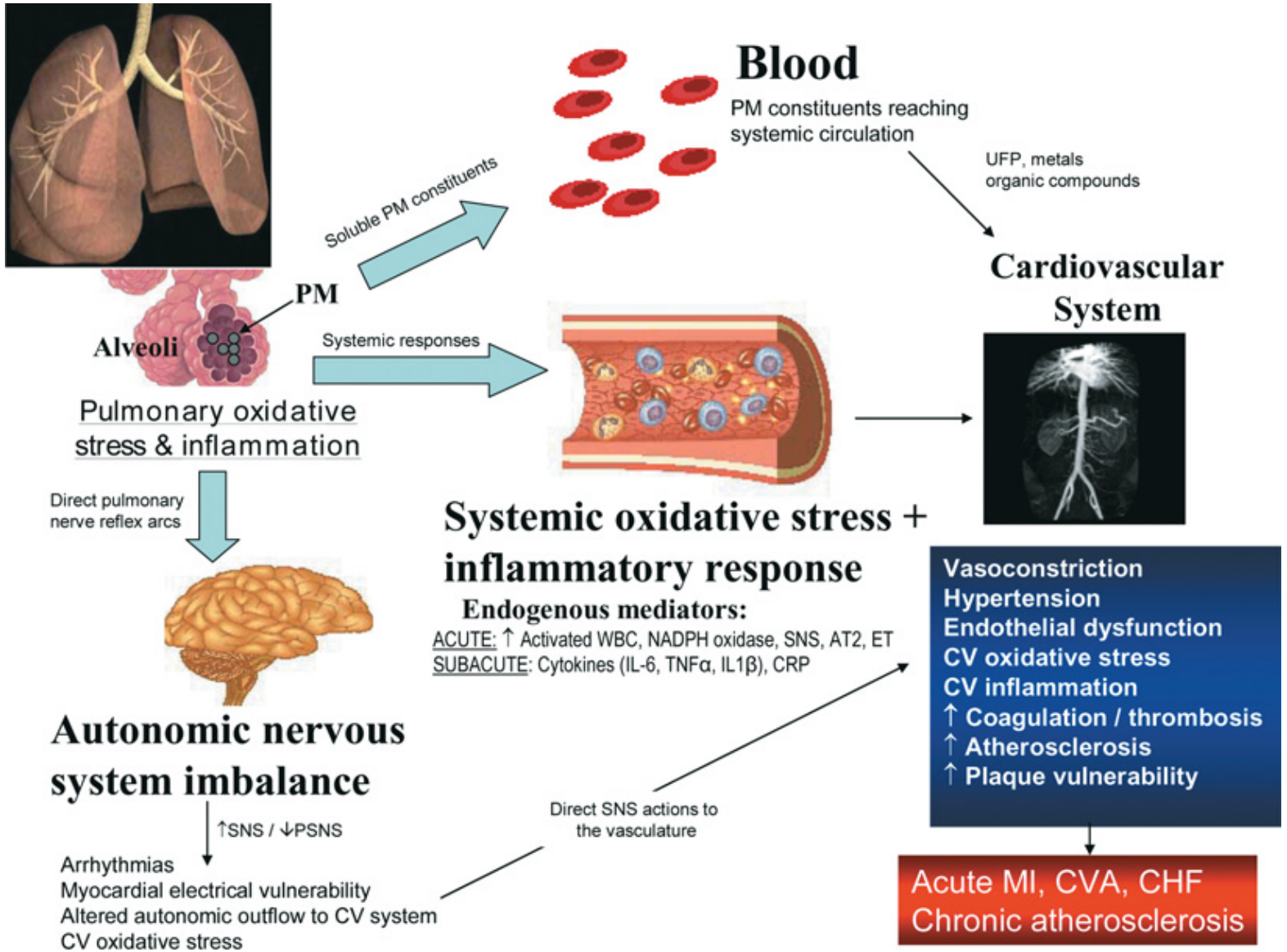
- **MORTALITY**
- **Heart Attack (Acute Myocardial Infarction)** (HOURS)
- **Heart Failure (Congestive Failure Decompensation)**
- Stroke
- Heart Rhythm Disturbances
- **Atherosclerosis (Cholesterol Plaques)** (DECADES)
- Asthma Incidence & **Exacerbation**
- **COPD Exacerbation**
- Lung Cancer
- Reproductive, Metabolic, & Psychiatric
- RESPIRATORY, ASCVD, DIABETES, OBESITY HYPOTHESIZED TO BE SUSCEPTIBLE
- **BIOMARKERS are PROXIES FOR CLINICAL EVENTS (or EXPOSURES)**


Estimated Effect of Each 10 μg/m3 Increase in PM10
% Change in Daily Mortality
8
6
4
2
0
-2
Total
Cardiovascular
Respiratory
Santa Clara
Philadelphia
Utah Valley
Birmingham
Cincinnati
Six Cities
Santa Clara
Philadelphia
Utah Valley
Birmingham
Cincinnati
Six Cities
Santa Clara
Philadelphia
Utah Valley
Birmingham
Cincinnati
Six Cities

ATHEROSCLEROSIS LEADS TO CORONARY ARTERYDISEASE (CAD) AND MI AND HF



Chronic Leads to Acute



Brook, Clinical Science, 115, 2008

Hypotheses of The HEART Study

In Healthy Young Students **Biomarkers** of

-systemic inflammation

-vascular endothelial dysfunction

-blood coagulation including platelet function

-autonomic dysfunction

-oxidative stress

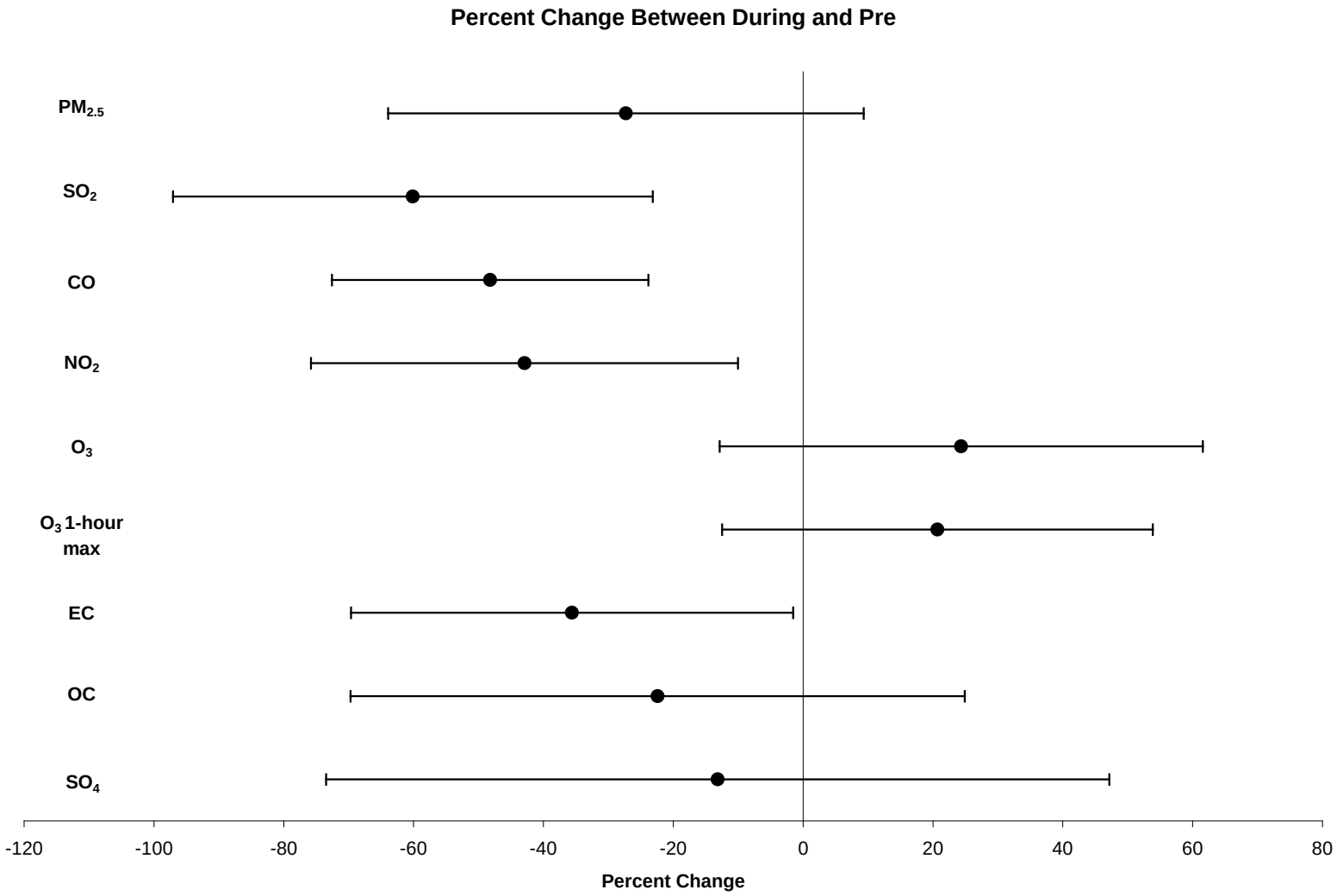
- **improve** significantly during the 2008 Olympic air pollution reduction period (summer)

- **return** in the post-Olympic period (fall).

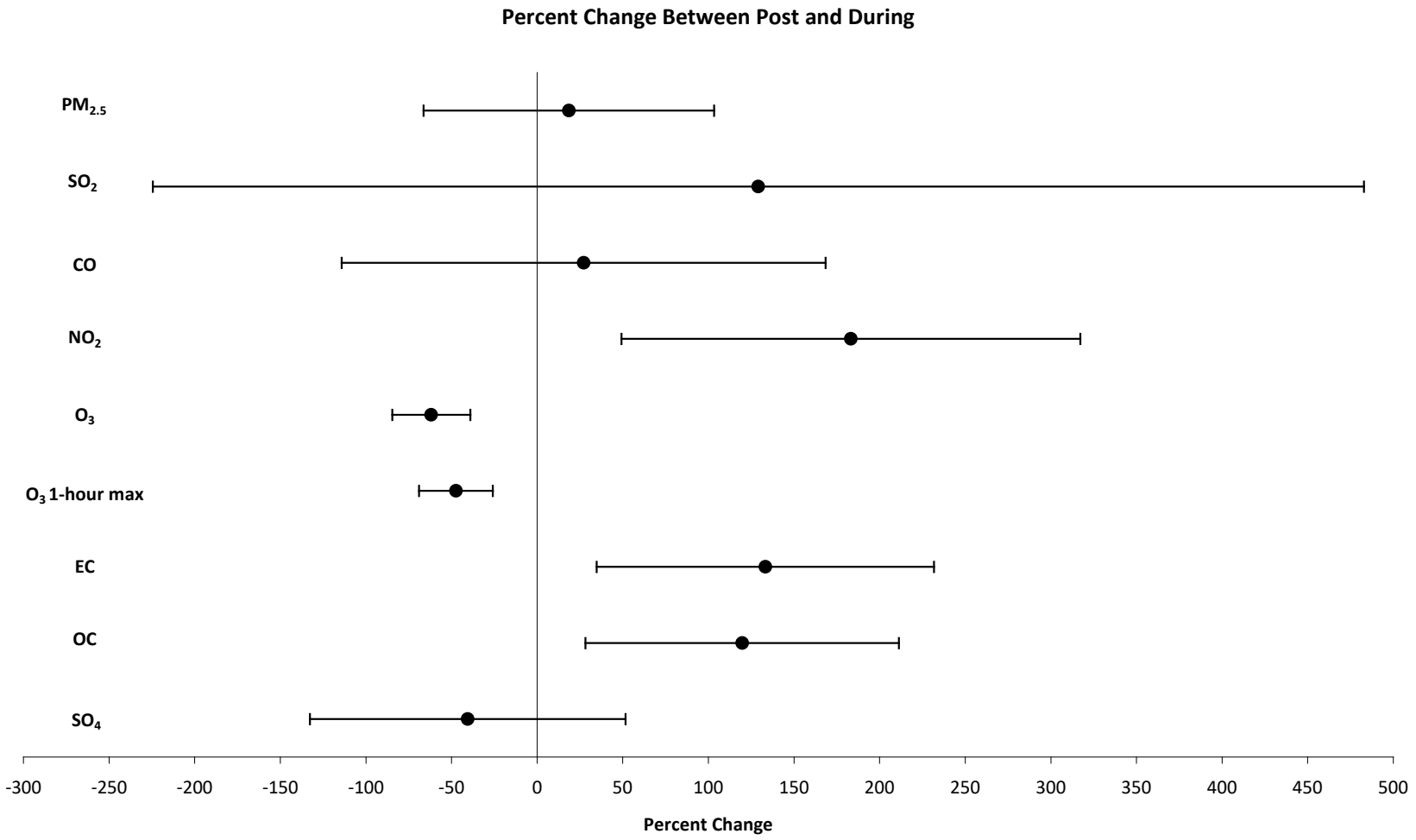
Pre-Olympics: June 6, 2008

During Olympics: August 16, 2008

Mean conc change (%) from the pre- to the during-Olympic Period



Mean conc change (%) from the during- to the post-Olympic Period



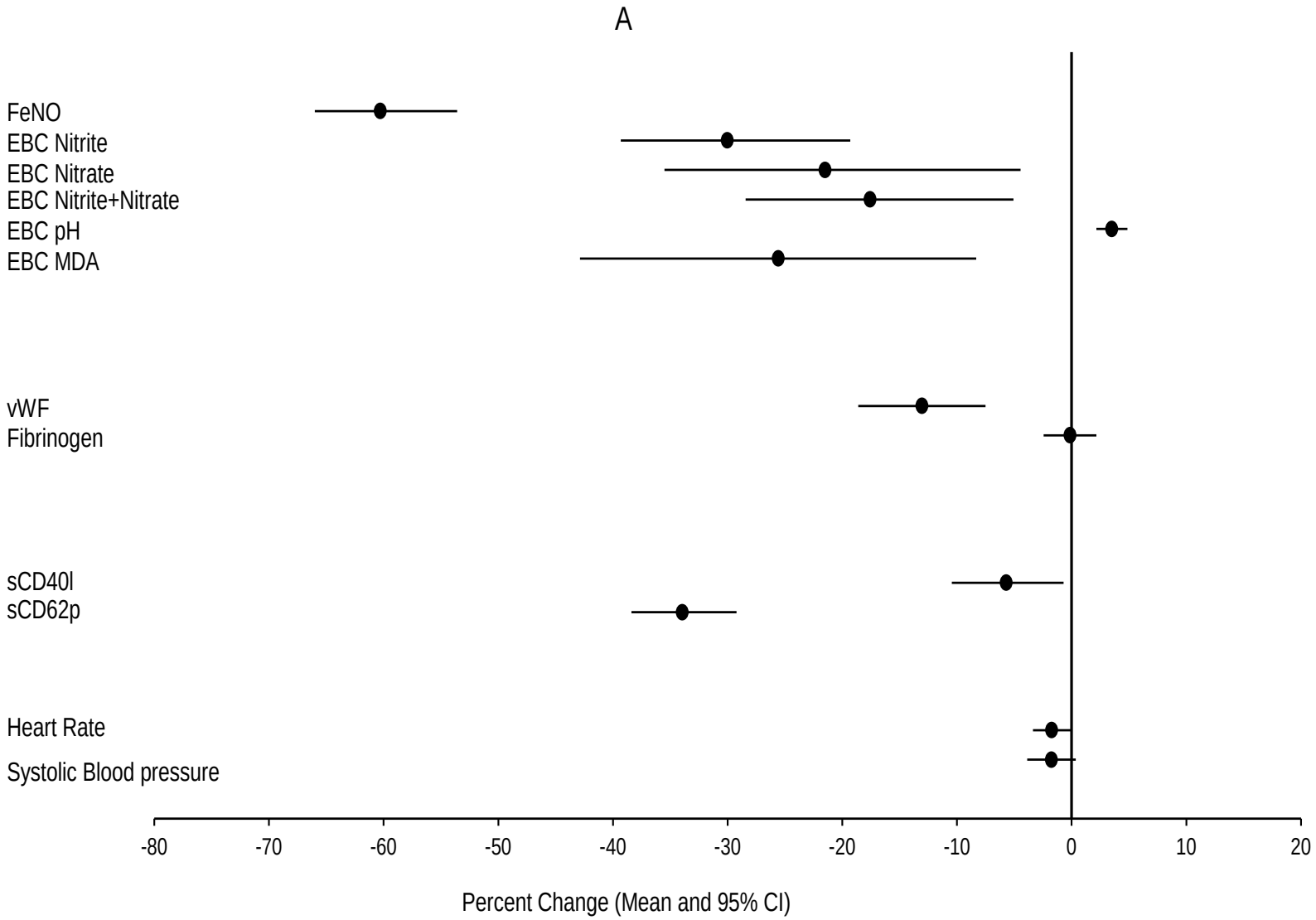
Rich, Kipen et al., JAMA, 2012

Huang et al., Am J Resp Crit Care Med, 2012

Summary of physiological endpoints and biomarkers measured in the HEART Study

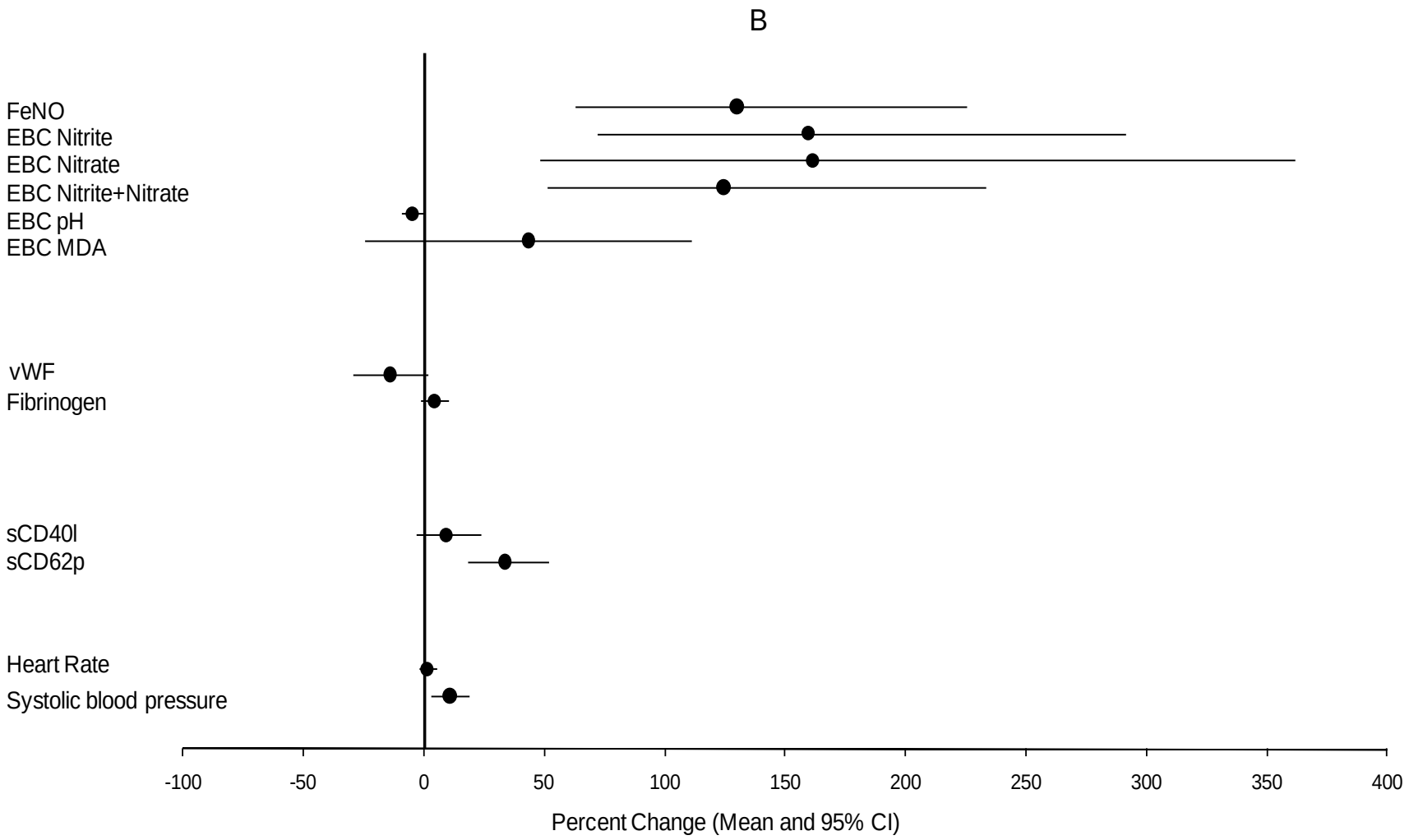
Physiological function	Specimen type	Biomarkers/endpoint	Principle/equipment of measurement
Pulmonary inflammation and oxidative stress	Exhaled breath condensate	pH	pH meter
		8-Isoprostane	ELISA based assay
		Nitrite + nitrate	HPLC-UV
	Exhaled breath	Fractional exhaled nitric oxide (FeNO)	NO_x chemiluminescence analyzer
Autonomic tone	N/A	Heart rate variability (HRV) Heart Rate	ECG Analysis Systems
		Blood Pressure	Sphygmomanometer
Endothelial derived procoagulation	Blood	von Willebrand Factor (vWF)	ELISA assay
Platelet function	Blood	Platelet aggregation	Photometric aggregometer
		Platelet activation (sCD40L & sCD62P)	ELISA assay
Systemic inflammation	Blood	White blood cell (WBC)	Standard automated clinical methods
		Plasma C-reactive protein (CRP)	ELISA based assay
		Plasma fibrinogen	Immunological based chemistry assay
Systemic oxidative stress	Urine	8-Hydroxy-2'-deoxyguanosine	HPLC-ECD

Estimated Means and 95% Confidence Intervals for Percent Changes in Biomarker Levels (A) from Pre-Olympic to During-Olympic Period



Care

Estimated Means and 95% Confidence Intervals for Percent Changes in Biomarker Levels (B) from During-Olympic to Post-Olympic Period



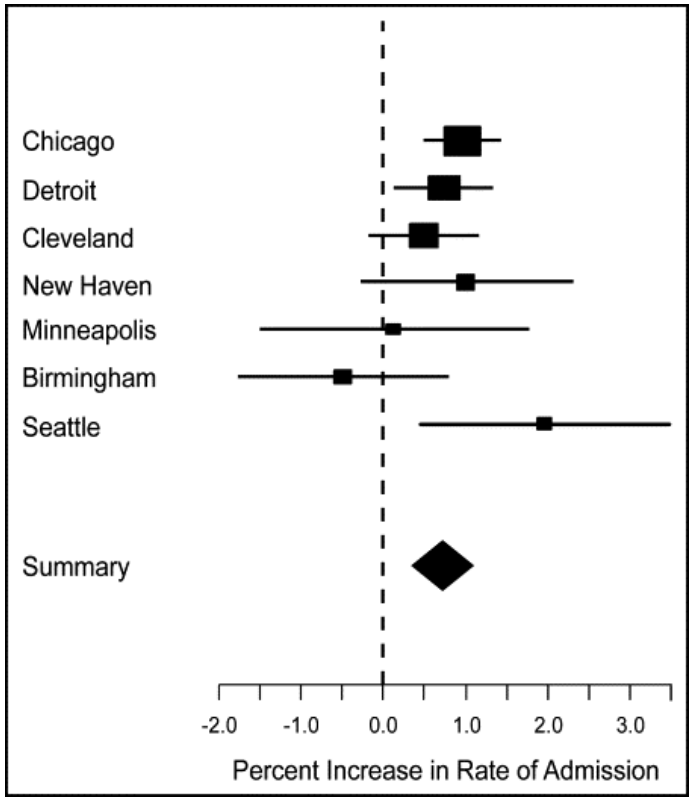
Conclusions and Significance

- **Healthy and young** adults.
- REVERSIBLE

PM_{10} and Congestive Heart Failure

- Medicare beneficiaries in 7 US cities (n=292,918)
- Primary discharge of CHF
- Time-stratified case-crossover design
- Controlled for meteorology

Percentage change in the rate of hospital admission for CHF associated with a 10 μg/m^3



Wellenius et al., The American Journal of Cardiology,, 2006, 404 - 408

Wellenius *et al* (2006)

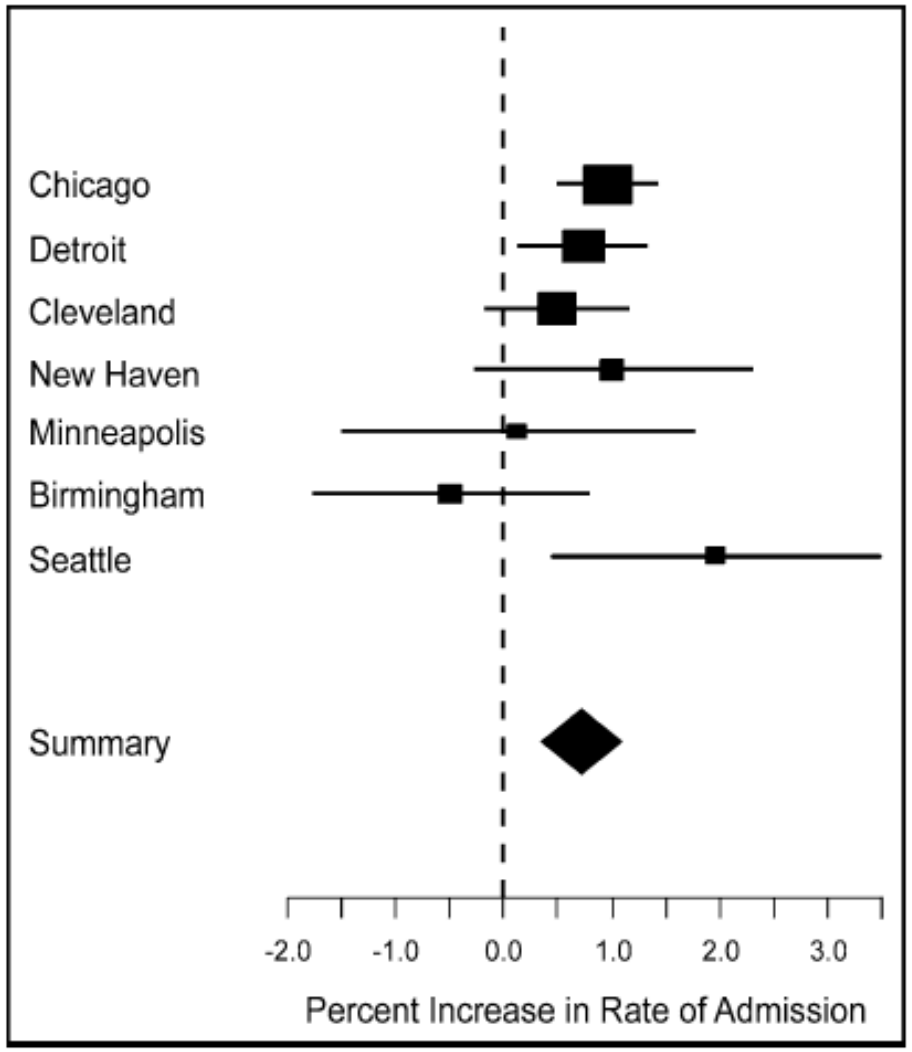


Figure 1. City-specific (*squares*; height inversely proportional to variance of estimate) and summary (*diamonds*; horizontal limits indicate 95% CIs) estimates of the percentage change in the rate of hospital admission for CHF associated with a 10 $\mu g/m^3$ increase in daily PM_{10} on the same day. The summary effect estimate was obtained from a meta-analysis of the city-specific estimates assuming a random city effect.

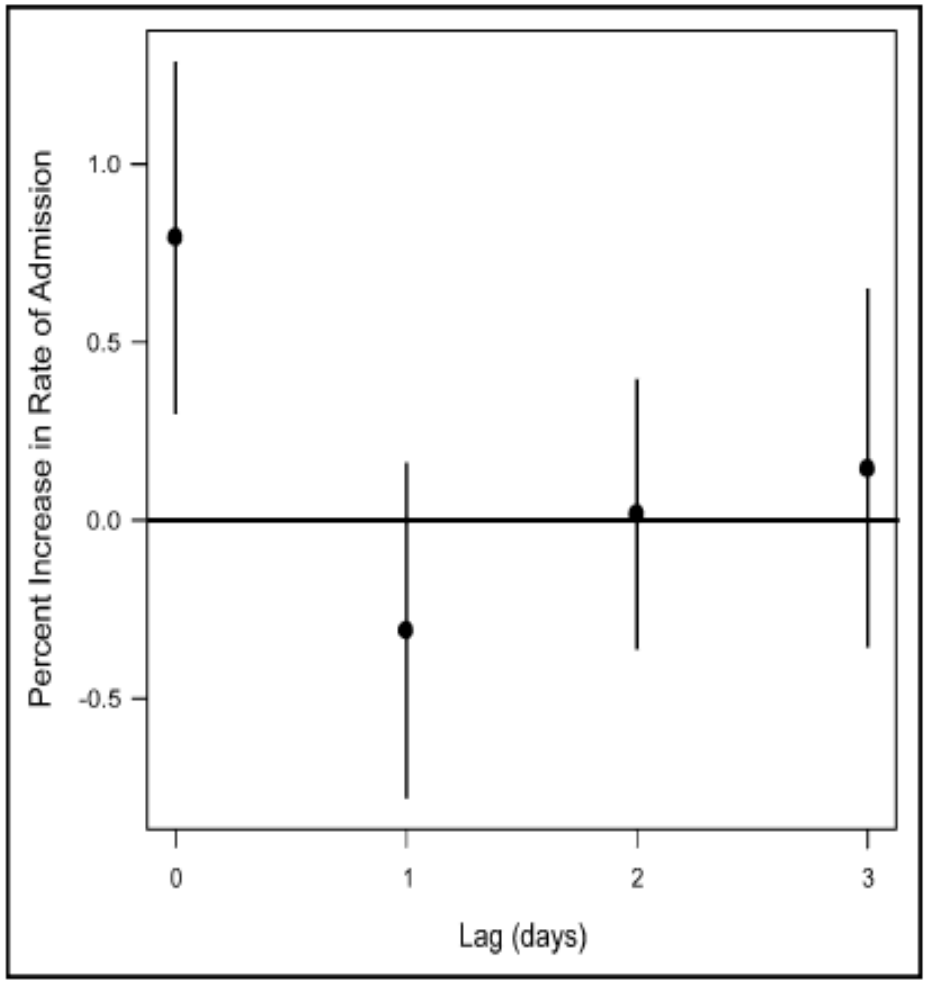


Figure 2. Estimated percentage change in rate (and 95% CIs) of emergency hospitalization for CHF associated with a 10 $\mu g/m^3$ increase in daily PM_{10} 0 to 3 days before the admission date. Each point represents the result of a meta-analysis of the city-specific estimates assuming a random city effect.

(Am J Cardiol 2006;97:404–408)

Chronicle – Implantable Hemodynamic Monitor
®Medtronic Inc.- Minneapolis, MN

RV pressure sensor measures:

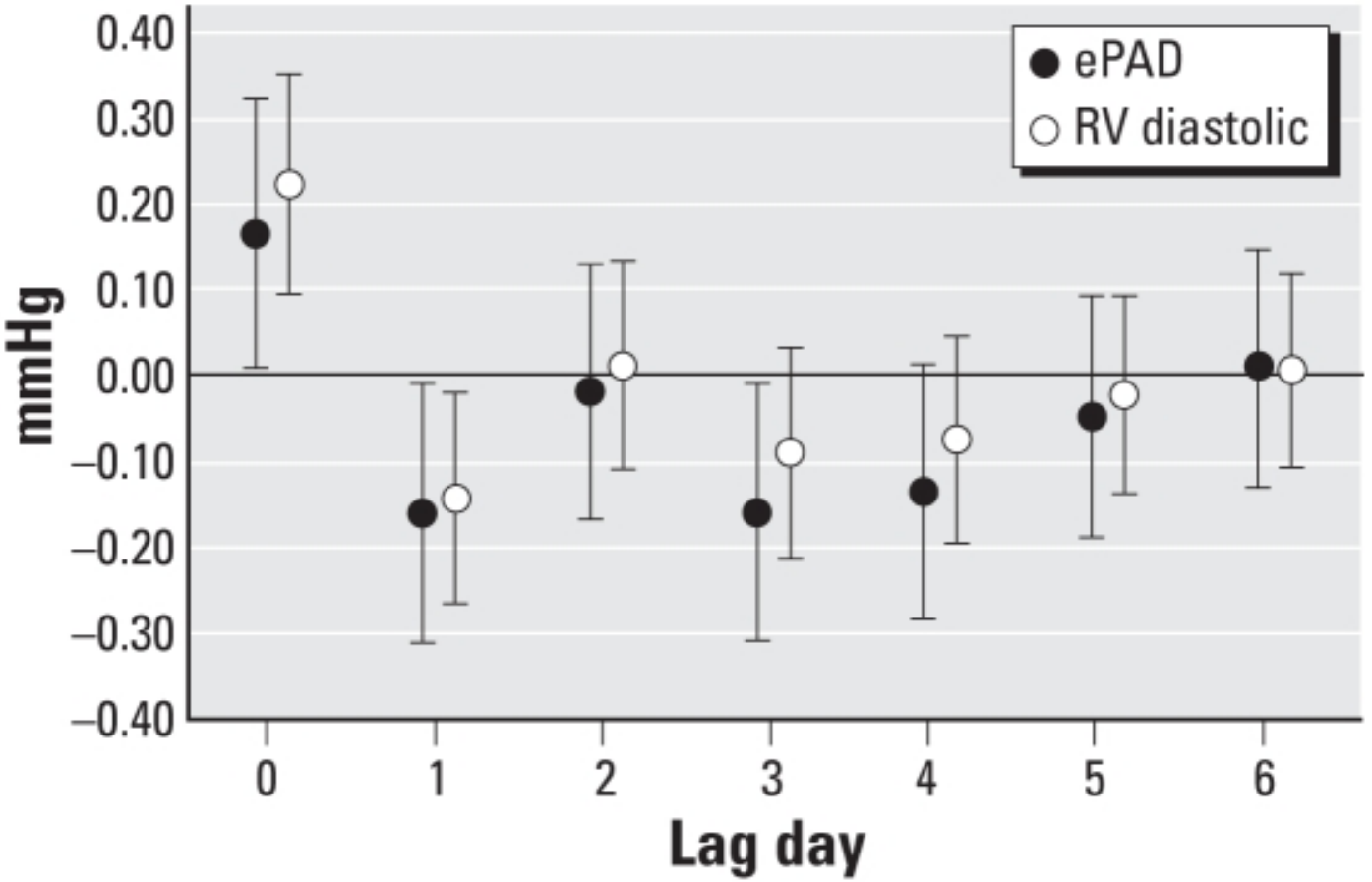
- Systolic and Diastolic pressure
- Estimated pulmonary artery diastolic pressure
- RV dp/dt
- Heart rate

Mean pulmonary arterial pressure

Pulse pressure

Rich et. al. EHP, .2008.

Association of Right Heart Pressures in 11 Heart Failure Patients with IQR Increases in $PM_{2.5}$



Rich et al., EHP 2008

The epidemiology of indoor exposures to air pollutants has been done BUT WE DON'T ACKNOWLEDGE IT

- ACUTE AND CHRONIC EPIDEMIOLOGY / CLINICAL STUDIES ATTRIBUTING HEALTH EFFECTS TO AMBIENT PM2.5 ARE ACTUALLY PEDOMINANTLY STUDIES OF INDOOR EXPOSURES RATHER THAN OUTDOOR.
- **No epidemiology of indoor exposures distinct from outdoor: But indirectly the epidemiology of indoor is already done (just called outdoor)**

- US mortality burden associated with PM2.5 ranges from ~230,000 to ~300,000 deaths per year in 2012.
- Indoor exposure to PM2.5 of outdoor origin accounts for largest proportion of exposure, ~40%-60% of total mortality.

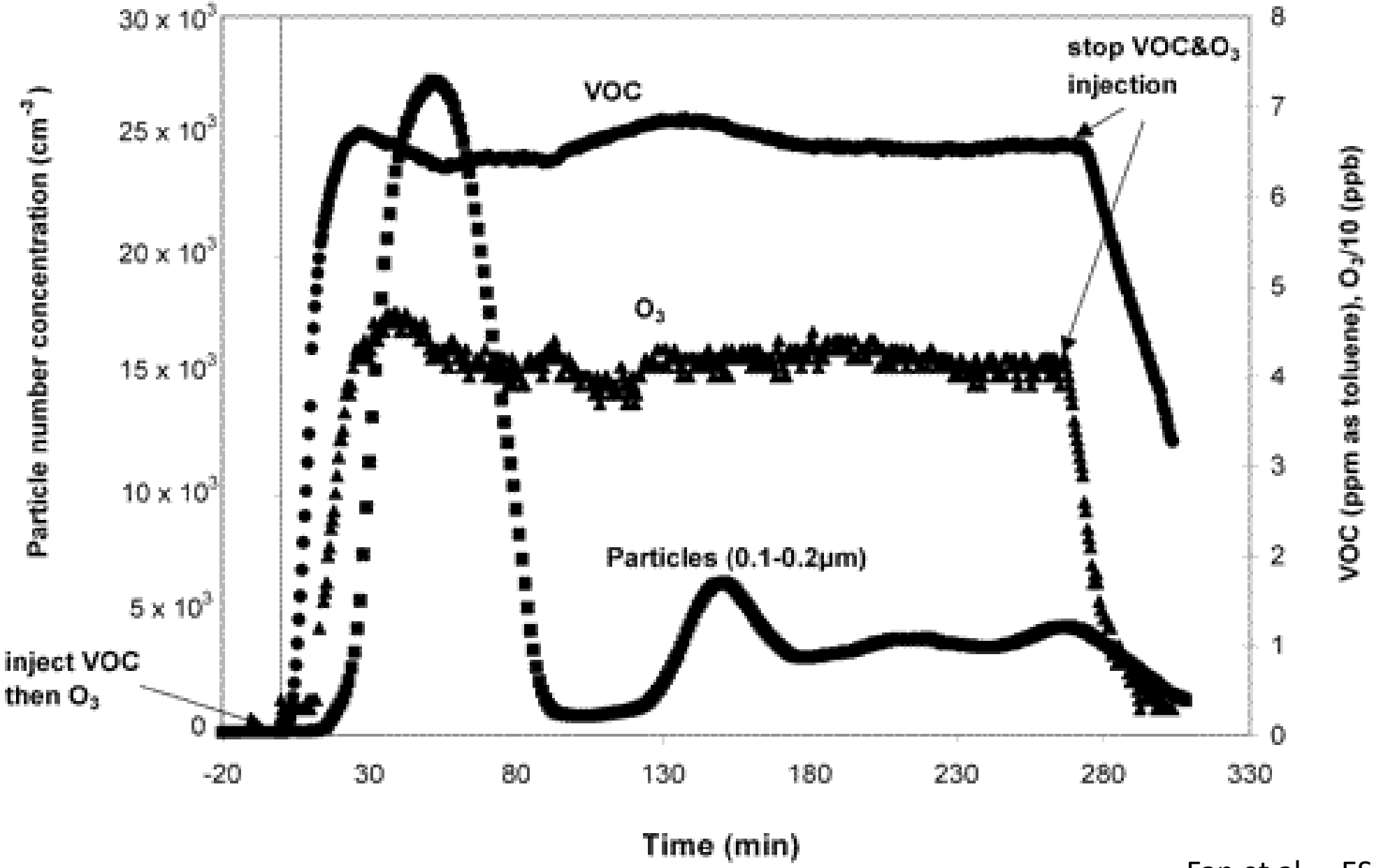
Every Breath You Take

1. Calculations for an adult:
   - **a. <u>At rest indoors</u>**: Assume tidal volume of 500 ml and 12 breaths/min = 6 liters per minute
   - b. 6 liters/min x 60 min / h x 24 h / day x 90% = **6998** l/day (ventilation rate)
   - **c. <u>Outdoors</u>**: 500 ml and 20 breaths/min = 10 liters per minute
   - d. 10 liters/min x 60 min / h x 24 h/day x 10% time outdoors = **1440 l/day**
   - **e. ~ 5 - fold difference in daily ventilation**
   - **f. Assume national average 9 mcg/m3 outdoor PM2.5 (EPA, 2012)**
   - **g. Assume 50% infiltration factor so indoor concentration of outdoor origin is 4.5 mcg/m3**
   - **h. Indoor Dose of outdoor origin = 31,491 mcg (71%)**
   - **i. Outdoor dose of outdoor origin = 12,960 mcg (29%)**

Figure 1. Medify Air MA-40 Air Purifier

Indoor Air Filtration Efficacy

- **16 studies in review**:
- Significant reductions in $PM_{2.5}$ ranging from 40% to 82%
- Reduced Systolic BP
- Increased PEFR
- Non-significant improvements in:
- MVF (e.g., Endothelial Function (EndoPAT, 3/5);
- CRP 3/8;
- IL-6 (0/4); SBP 4/6.



Fan et al ., ES&T, 2003

Nasal Effects of a Mixture of Volatile Organic Compounds and Their Ozone Oxidation Products

- Laumbach RJ, Fiedler N, Gardner CR, Laskin DL, Fan ZH, Zhang J, Weschler CJ, Lioy PJ, Devlin RB, Ohman-Strickland P, Kelly-McNeil K, Kipen HM. J Occup Environ Med. 2005

- 130 healthy women
- 25 mg/m ^{3} VOC + 40 ppb O^3
-
- **Symptoms:** no significant differences except odor
- **Nasal lavage:** no significant differences

  PMN;

  IL-6, IL-8

  Total protein

TABLE 2

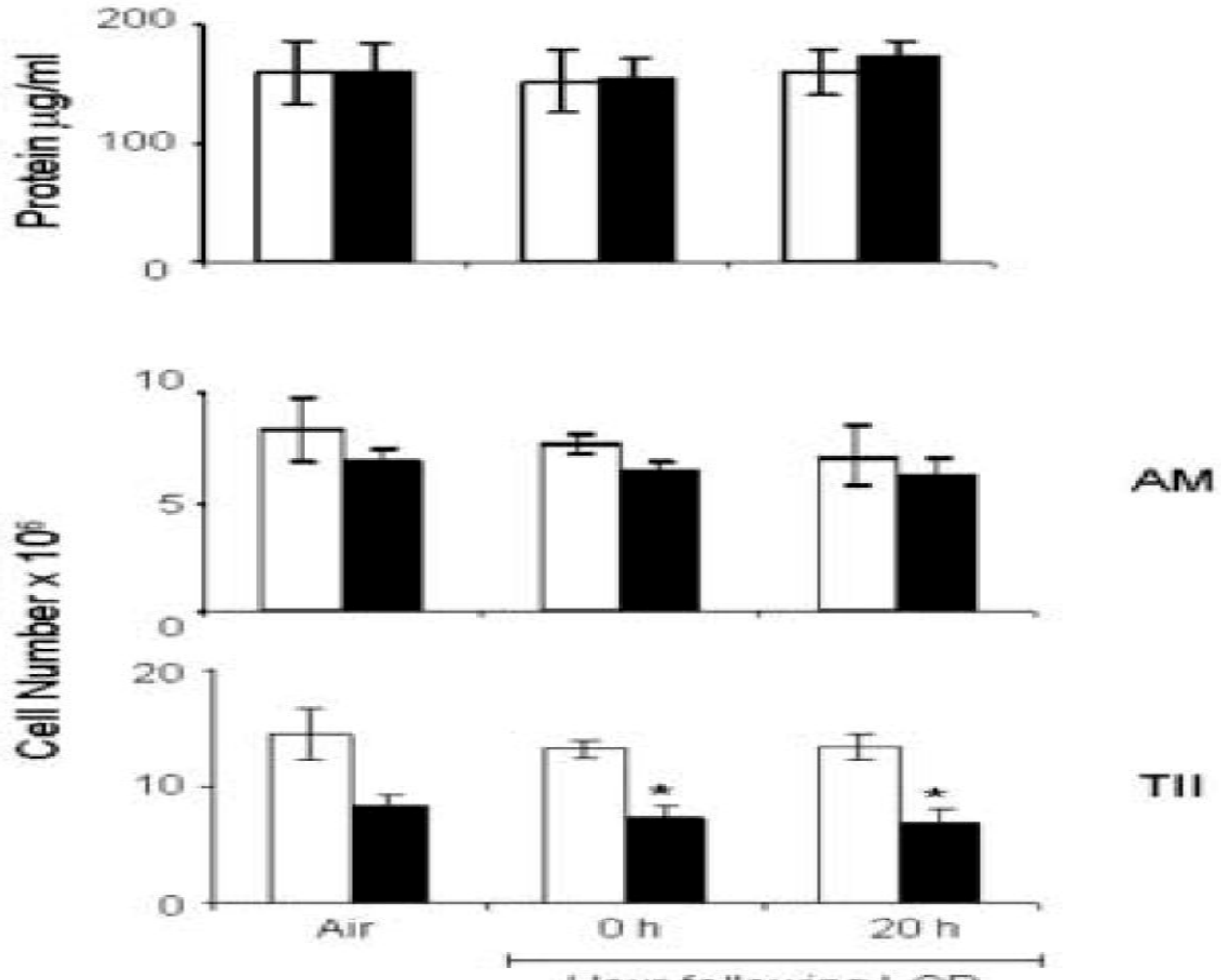
Point and Interval Estimates for the Odds of Increasing in Polymorphonuclear Cell Response Category by Exposure

	Odds Ratio	95% Confidence Interval
All (n = 130)		
MA	1.11	(0.65–1.90)
VOC	1.43	(0.80–2.57)
VOCs + O_3	1.41	(0.80–2.49)
Atopic (n = 51)		
MA	0.71	(0.37–2.02)
VOC	4.60	(0.60–6.30)
VOCs + O_3	1.55	(0.49–3.00)
Symptomatic "responders" (n = 49)		
MA	0.53	(0.48–1.20)
VOC	1.40	(0.73–1.83)
VOCs + O_3	0.73	(0.53–1.43)

MA indicates masked air; VOC, volatile organic compound; O_3, ozone.

Laumbach et al., JOEM, 2005

Absence of inflammatory response to Limonene ozone reaction products in young and old rats



Sunil et al., TAP,2007)

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The impact of household air cleaners on the oxidative potential of $PM_{2.5}$ and the role of metals and sources associated with indoor and outdoor exposure

Collin Brehmer[a], Christina Norris[b], Karoline K. Barkjohn[b], Mike H. Bergin[b], Junfeng Zhang[c,d], Xiaoxing Cui[c], Yanbo Teng[d], Yinping Zhang[e], Marilyn Black[f], Zhen Li[g], Martin M. Shafer[h], James J. Schauer[a,h,*]

[a] Environmental Chemistry and Technology Program, University of Wisconsin-Madison, Madison, WI, 53706, USA
[b] Duke University, Civil and Environmental Engineering, 121 Hudson Hall, Durham, NC, 27708, USA
[c] Duke University, Nicholas School of the Environment, 9 Circuit Dr, Durham, NC, 27710, USA
[d] Global Health Research Center, Duke Kunshan University, Kunshan, Jiangsu Province, China
[e] Tsinghua University, School of Architecture, Beijing, 100084, China
[f] [illegible], Chemical Safety, 2227 [illegible], Suite 256, Marietta, GA, 30067, USA
[g] Department of Pediatrics, Shanghai General Hospital, Shanghai, 201620, China
[h] Wisconsin State Laboratory of Hygiene, University of Wisconsin-Madison, Madison, WI, 53706, USA

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Reactive oxygen species
Indoor air quality
Air quality intervention

ABSTRACT

The health effects associated with human exposure to ambient fine particulate matter ($PM_{2.5}$) have been linked to the ability of $PM_{2.5}$ to catalyze the production of excess cellular reactive oxygen species (oxidative potential). Concerns about the adverse human health impacts of $PM_{2.5}$ have led to the increased use of indoor air cleaners to improve indoor air quality, which can be an important environment for $PM_{2.5}$ exposure. However, the degree to which the oxidative potential of indoor and personal $PM_{2.5}$ can be influenced by an indoor air cleaner remains unclear. In this study we enrolled 43 children with physician-diagnosed asthma in suburban Shanghai, China and collected two paired sets of 48-h indoor, outdoor, and personal $PM_{2.5}$ exposure samples. One set of samples was collected under "true filtration" during which a functioning air cleaner was installed in the child's bedroom, and the other ("sham filtration") with an air cleaner without internal filters. The $PM_{2.5}$ samples were characterized by inductively coupled plasma mass spectrometry for elements, and by an alveolar macrophage assay for oxidative potential. The sources of metals contributing to the samples were determined by the EPA Positive Matrix Factorization model. The oxidative potential was lower under true filtration compared to sham for indoor (median true/sham ratio: 0.26) and personal exposure (0.51) samples. Additionally, the sources of elements in $PM_{2.5}$ that were reduced indoors and personal exposure samples by the air cleaner (e.g. regional aerosol and roadway emissions) were found by univariate multiple regression models to be among those contributing to the oxidative potential of the samples. An IQR increase in the regional aerosol and roadway emissions sources was associated with a 107% (95% CI: 50.1–191%) and 34.3% (17.5–53.1%) increase in measured oxidative potential respectively. Our results indicate that indoor air cleaners can reduce the oxidative potential of indoor and personal exposure to $PM_{2.5}$, which may lead to improved human health.

1. Introduction

The diverse and detrimental health impacts of human exposure to fine particulate matter ($PM_{2.5}$) are a global public health concern. Epidemiological studies have linked even moderately elevated levels of $PM_{2.5}$ to cardiovascular disease and have more recently identified associations between $PM_{2.5}$ exposure and chronic diseases such as type 2 diabetes and obesity (Bowe et al., 2018; Mazidi and Speakman, 2017). While the molecular etiology of $PM_{2.5}$-induced disease remains a subject of intense study, toxicological evidence supports cellular oxidative stress as an important mechanism underlying $PM_{2.5}$ toxicity (Deng et al., 2013; Riva et al., 2011; Topinka et al., 2011). Upon inhalation, the redox active chemical components of $PM_{2.5}$ can directly generate reactive oxygen species (ROS) by Fenton chemistry or stimulate the generation of ROS by macrophage cells through respiratory burst (Ray et al., 2012). Excess cellular ROS can induce oxidative stress and

* Corresponding author. Water Science and Engineering Laboratory, 660 N Park St, 113, Madison, WI, 53706, USA.
E-mail address: jjschauer@wisc.edu (J.J. Schauer).

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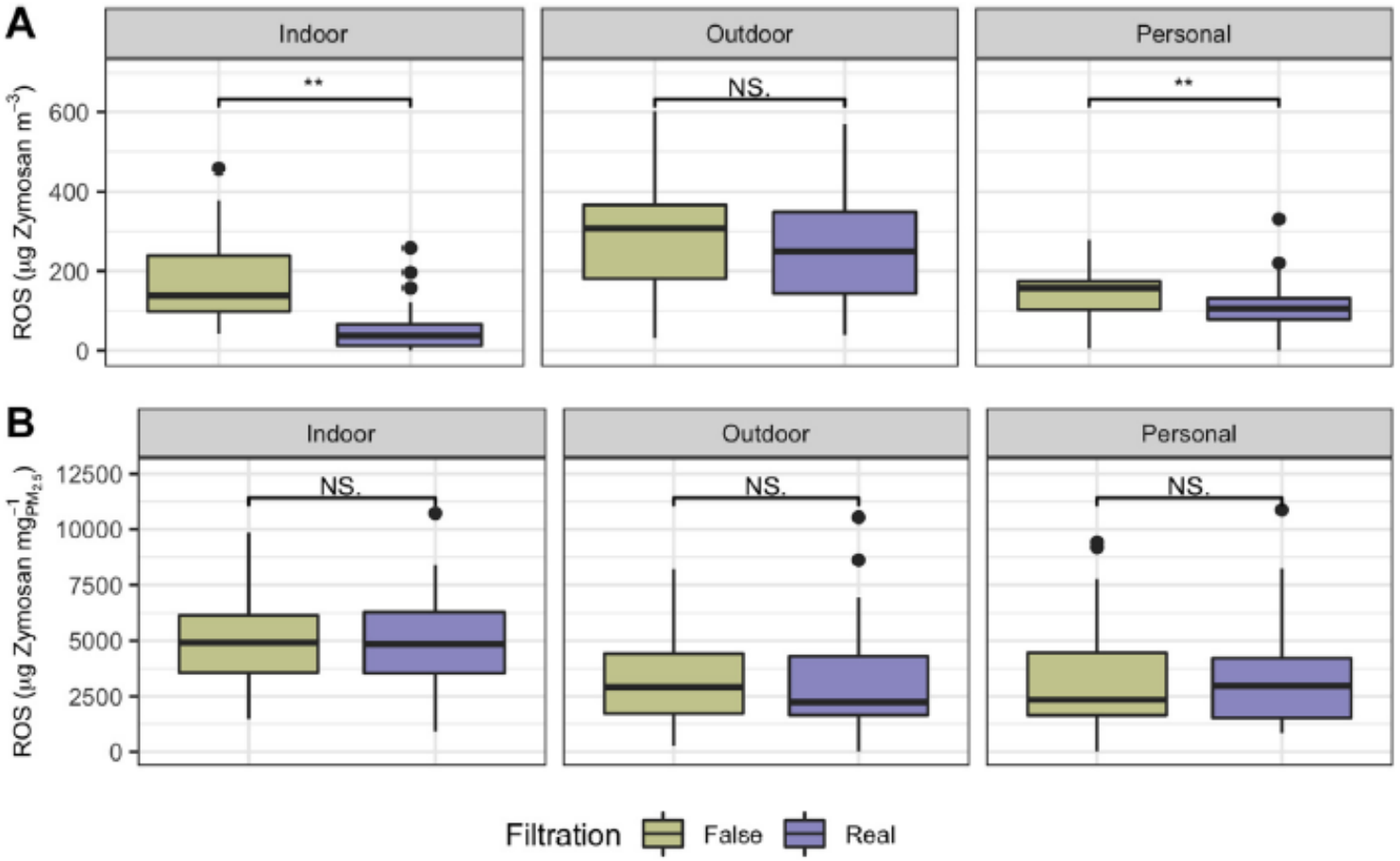
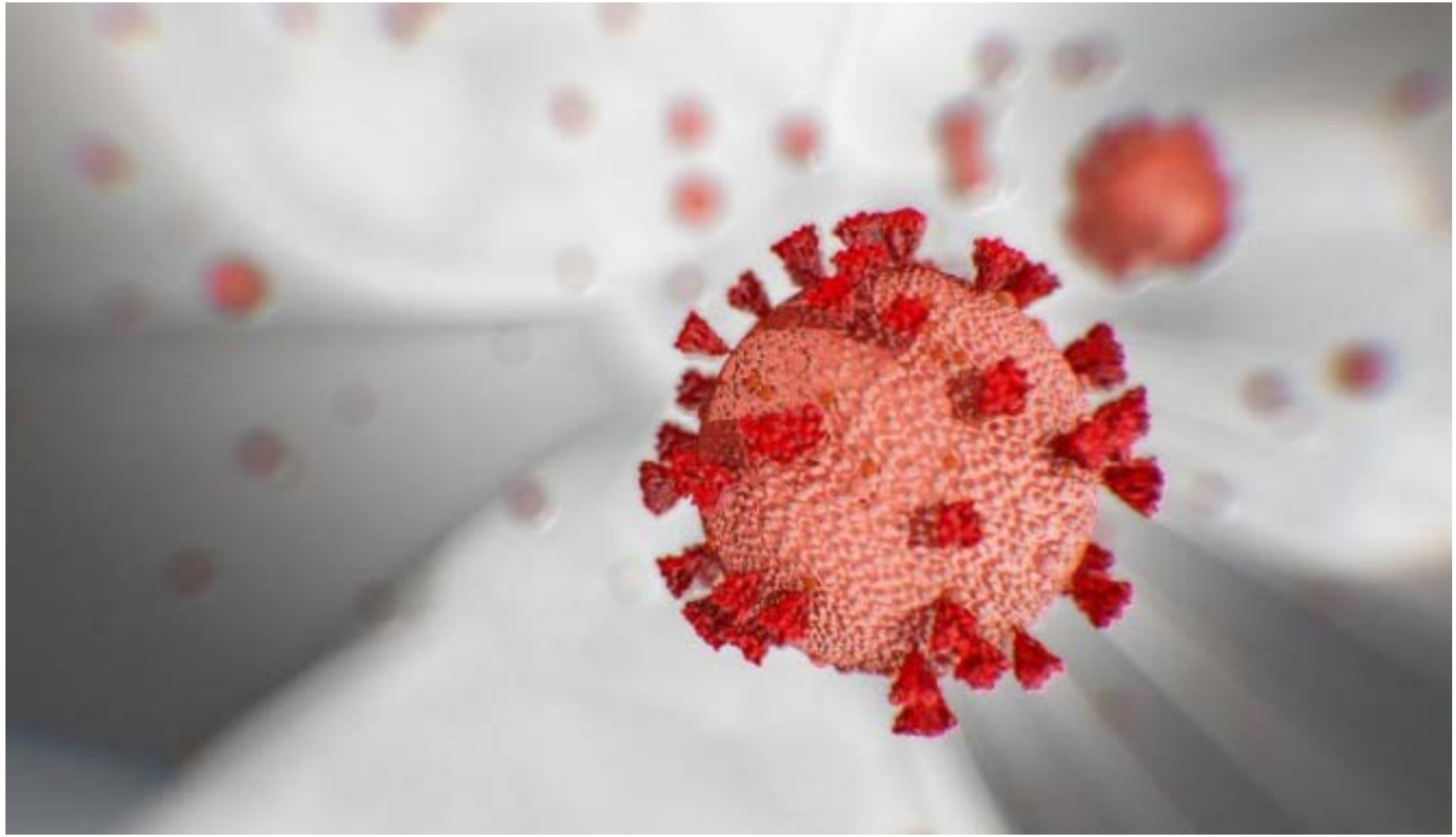


Boxplot of (A) volume-normalize oxidative potential (µg Zymosan m−3) and (B) mass-normalized oxidative potential (µg Zymosan mg−1 PM2.5) for indoor,outdoor, and personal exposure samples collected under real and false filtration.

Brehmer et al., Env Research , 2020.




Wellcome