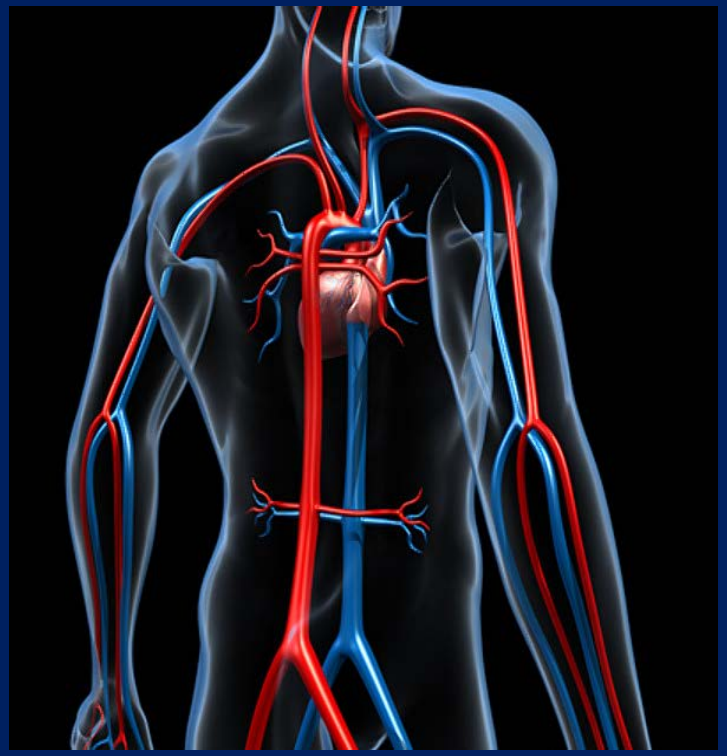
GLACIER
GREAT LAKES AIR CENTER
FOR INTEGRATED ENVIRONMENTAL RESEARCH

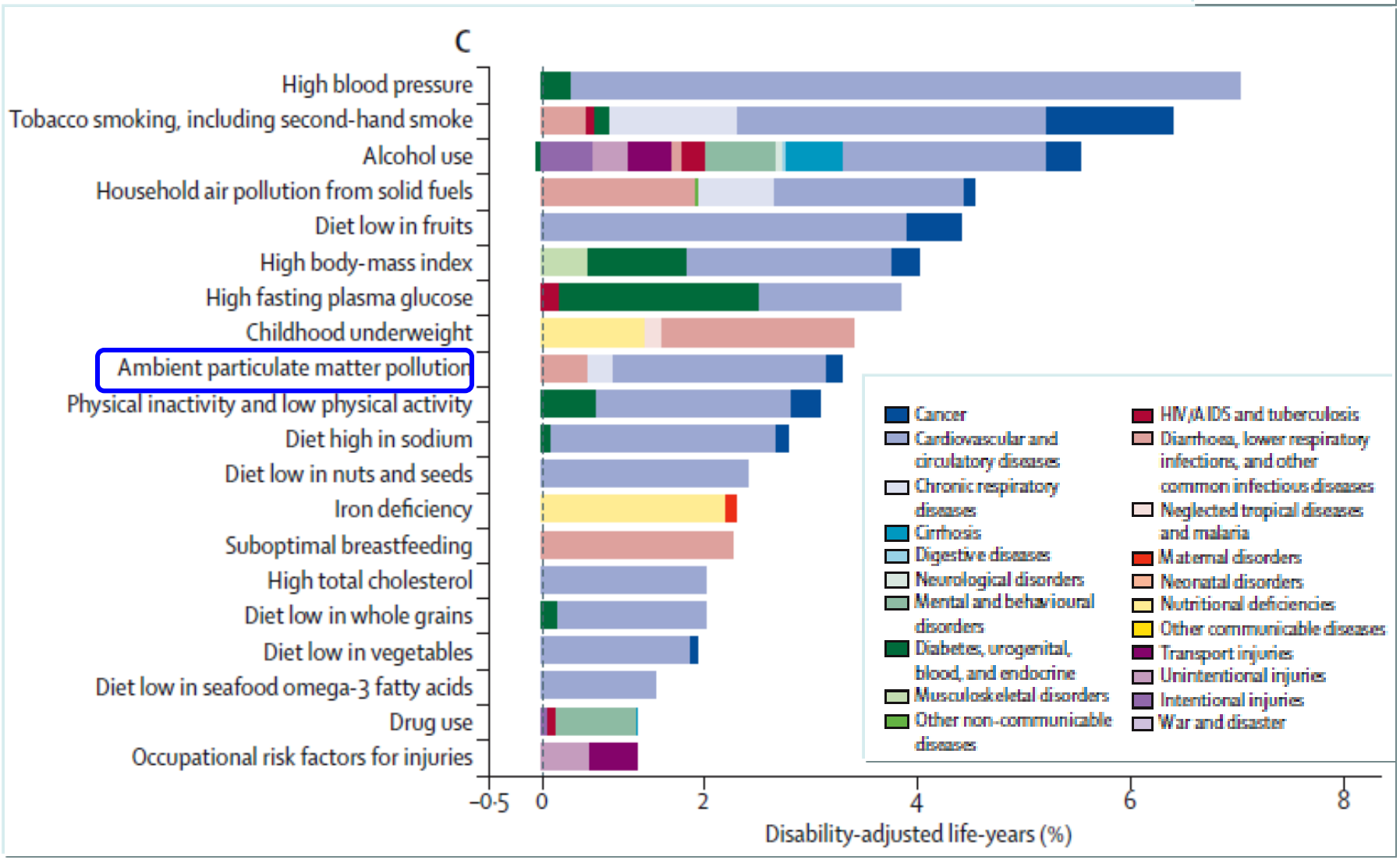
# Cardio-metabolic Effects of Exposure to Concentrated Coarse Ambient Particles



Robert D. Brook, MD
Associate Professor of Medicine
Cardiovascular Medicine, University of Michigan

# Global Burden of Disease: WHO Dec 2012

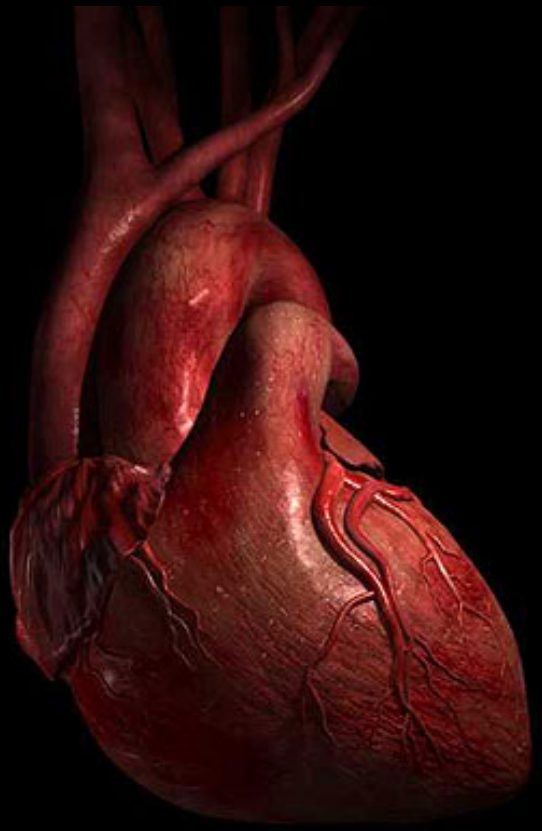
Lancet 2012; 380: 2224–60

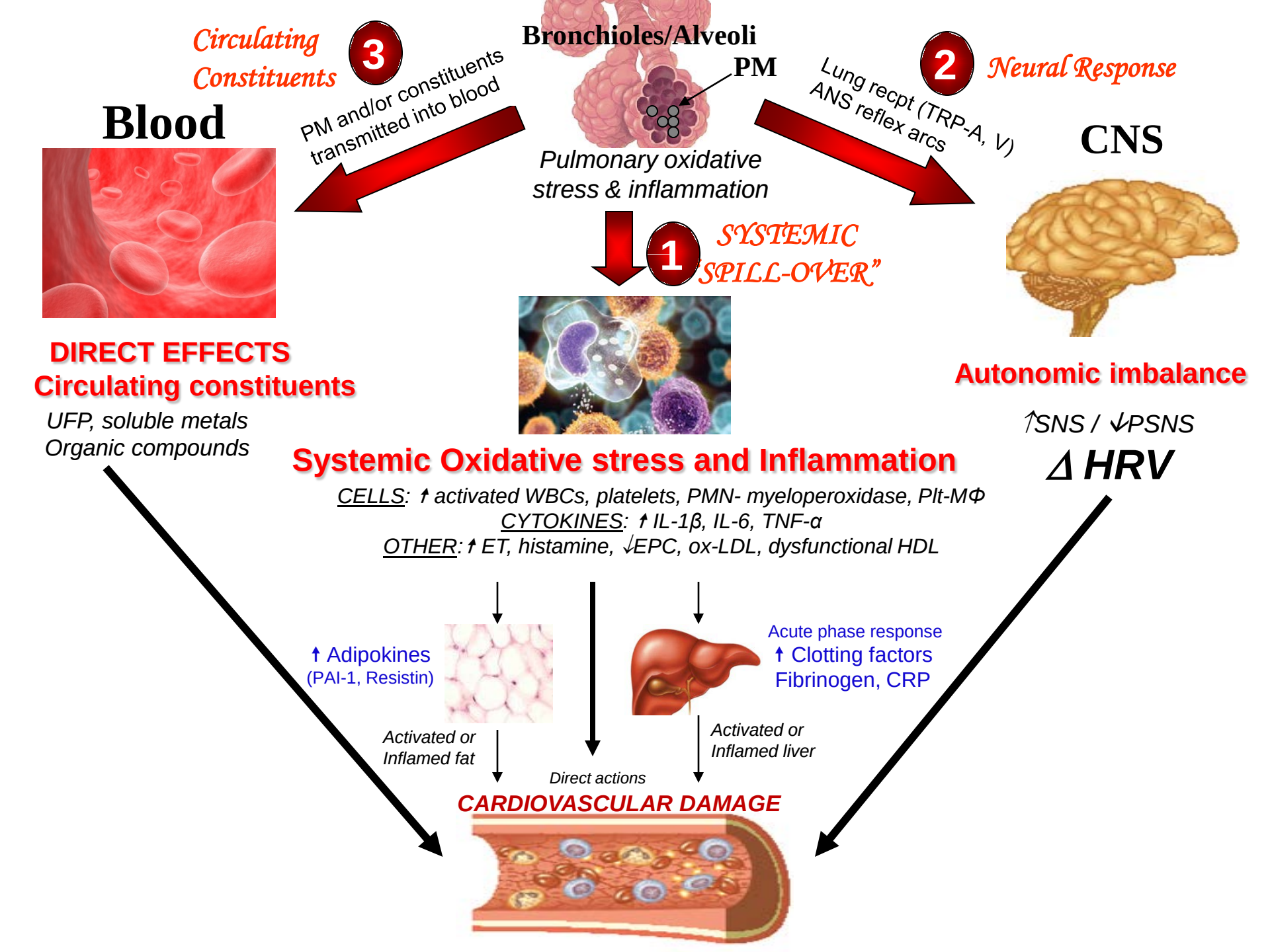



| | |
|---|---|
| **Annual PM-related deaths:** | **3.2 million** |
| **Annual world % of all DALY:** | **3.1%** |
| **CV population attributable factor:** | **22%** |

# What are the mechanisms whereby PM instigates CVD?

?




Circulating Constituents
3
Bronchioles/Alveoli
PM
2
Neural Response
Blood
PM and/or constituents transmitted into blood
Lung recpt (TRP-A, V)
ANS reflex arcs
CNS
Pulmonary oxidative stress & inflammation
1
SYSTEMIC "SPILL-OVER"
DIRECT EFFECTS
Circulating constituents
UFP, soluble metals
Organic compounds
Autonomic imbalance
↑SNS / ↓PSNS
Δ HRV
Systemic Oxidative stress and Inflammation
CELLS: ↑ activated WBCs, platelets, PMN- myeloperoxidase, Plt-MΦ
CYTOKINES: ↑ IL-1β, IL-6, TNF-α
OTHER: ↑ ET, histamine, ↓EPC, ox-LDL, dysfunctional HDL
↑ Adipokines
(PAI-1, Resistin)
Acute phase response
↑ Clotting factors
Fibrinogen, CRP
Activated or Inflamed fat
Direct actions
Activated or Inflamed liver
CARDIOVASCULAR DAMAGE

Tobacco smoke

⇧ LDL

⇩ HDL

Hypertension

Risk factors

Diabetes

Age

Obesity

Estrogen status (gender)

**AIR POLLUTION**

Lipoprotein size

Lp(a)

Postprandial lipemia

Insulin resistance

Novel factors

Homocysteine

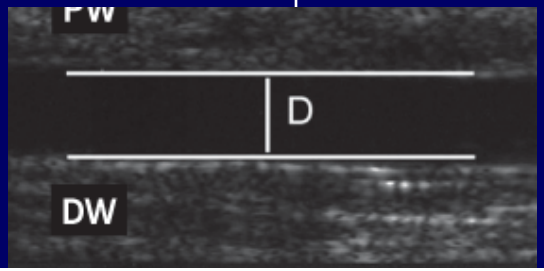
Genetics

Inflammation (cytokines, CRP)
Oxidative stress

**Oxidative stress**
**Inflammation**

# ENDOTHELIAL DYSFUNCTION
## Barometer of Cardiovascular Risk

| ⇩ NO ⇧ ET | ⇧ Oxidative stress (⇧ ROS) | Platelet activation / ⇩ Fibrinolysis |
|---|---|---|
| Vasoconstriction | Mitogenesis / Inflammation | ⇧coagulation / Thrombosis |

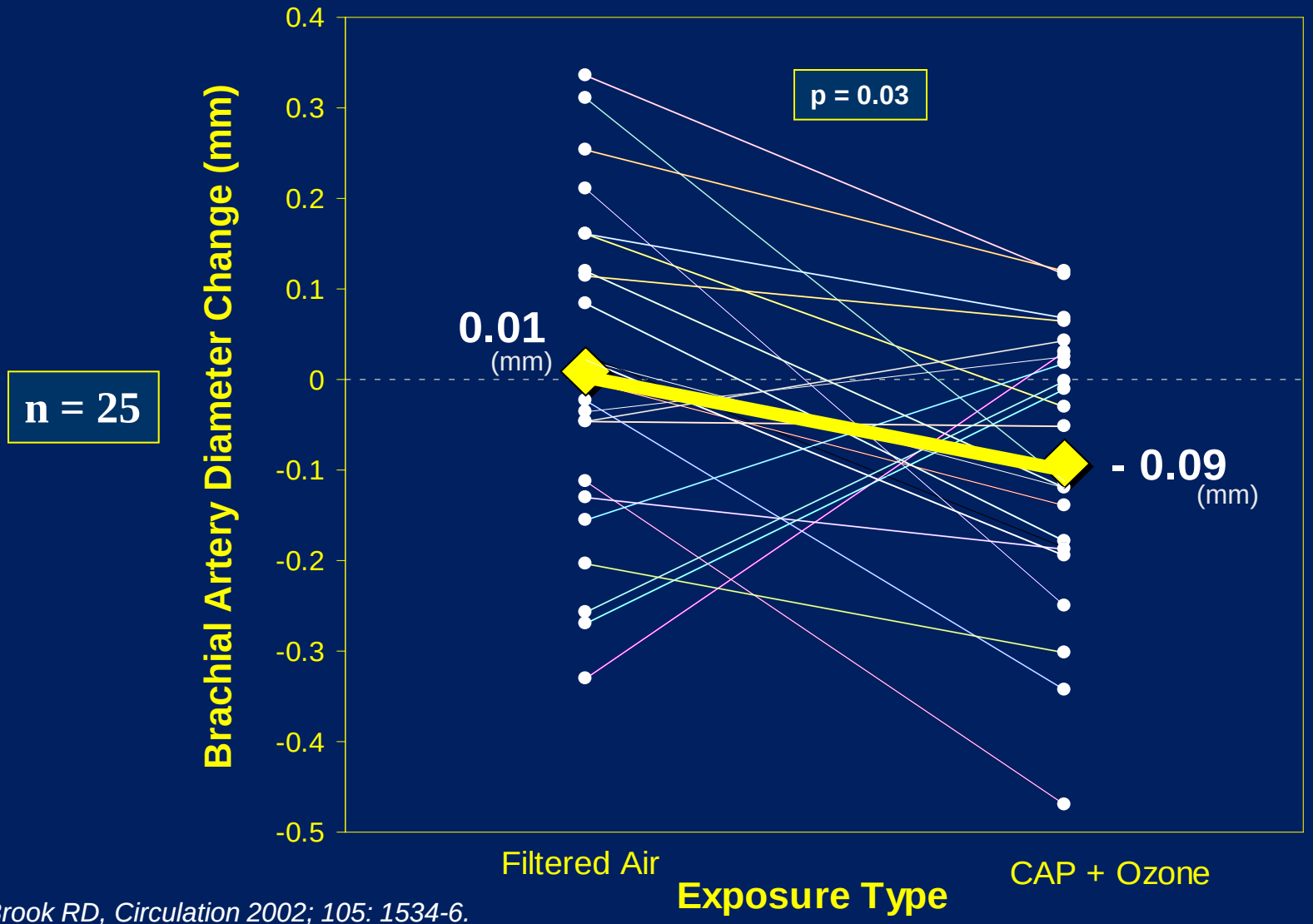



FLOW MEDIATED DILATATION

Progression/Instability

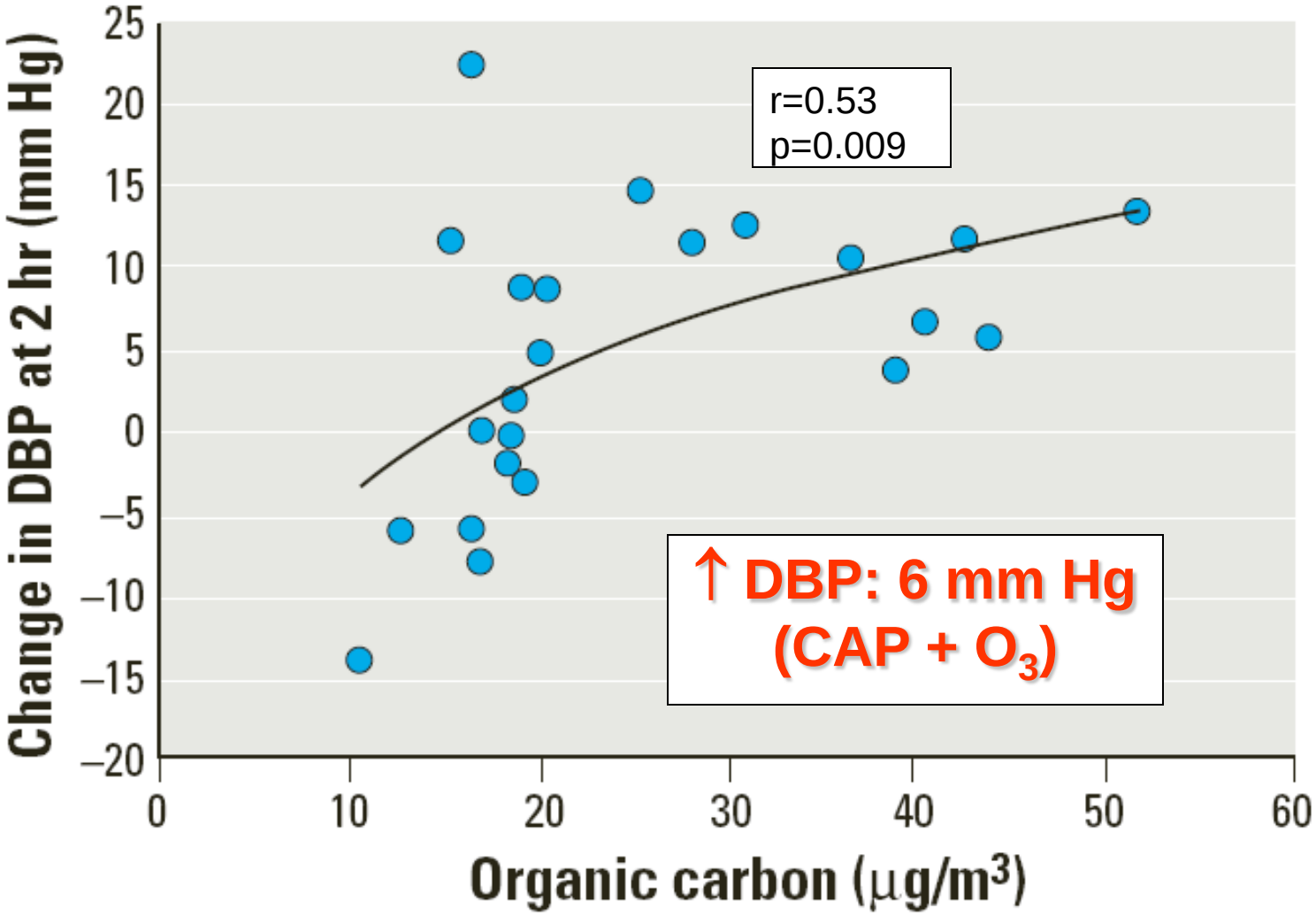
Acute coronary events

# EXPOSURE TO CONCENTRTED AMBIENT $PM_{2.5}$ (CAP) + OZONE FOR 2 HRS CAUSES BRACHIAL ARTERY VASOCONSTRICTION




*Brook RD, Circulation 2002; 105: 1534-6.*

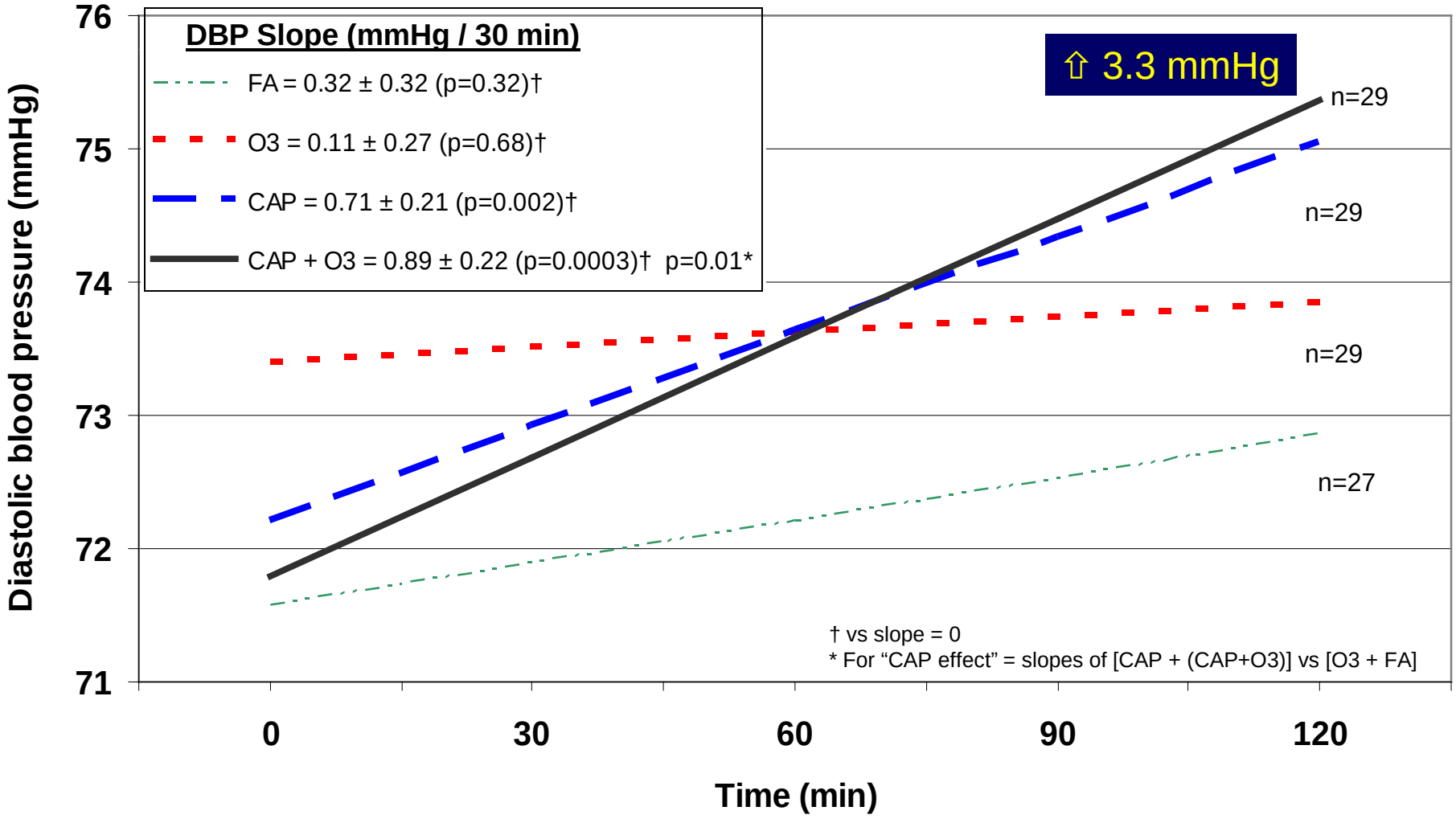
# Blood Pressure Responses to Concentrated Ambient $PM_{2.5}$ (CAP) versus Filtered Air




Urch B, Environ Health Perspectives 2005; 113: 1052-55.

# Diastolic Blood Pressure Changes during Exposures in Toronto

FA (filter air); O3 (ozone); CAP (concentrated ambient fine particulate matter); DBP (diastolic blood pressure)




DBP correlates: (1) ⇧ CAP mass* (2) ⇩heart rate variability (SDNN)

*Brook RD, et al. Hypertension 2009; 54: 659-667*

*β =1.6 mmHg per 100 μg/m$^3$

# Endothelial Function (FMD) Changes in Toronto Exposures

24 post – pre-exposure FMD changes N=31

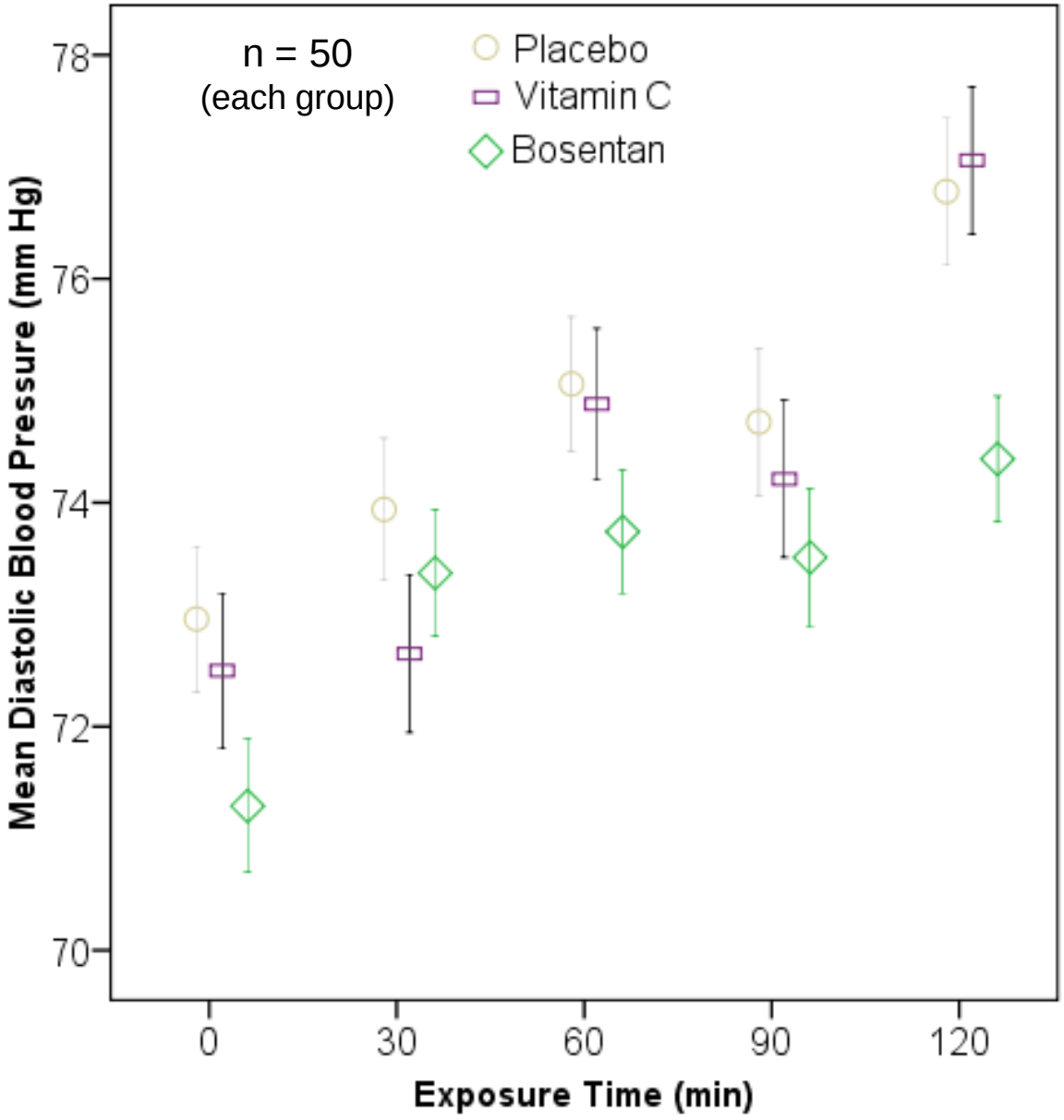
- FA: 2.7 ± 9.0% (n=30) p=0.11
- O3: -0.9 ± 7.5% (n=29) p=0.50
- CAP: -2.9 ± 6.2% (n=28) p=0.02
- CAP+O3: -2.3 ± 6.4% (n=28) p=0.07

No change in NMD at any time point, or FMD immediately post exposures

⇩ FMD correlates: ⇧ CAP mass*, ⇧ TNFα**

*β =-2.3% per 100 μg/$m^3$
**r =-0.26, p=0.023

# Diastolic Blood Pressure Changes during CAP + $O_3$ Exposure (Ann Arbor)




**Diastolic Blood Pressure**

(slope: mmHg / 30 min SE )

Pretreatment

Placebo = 0.84 0.29
p=0.002†

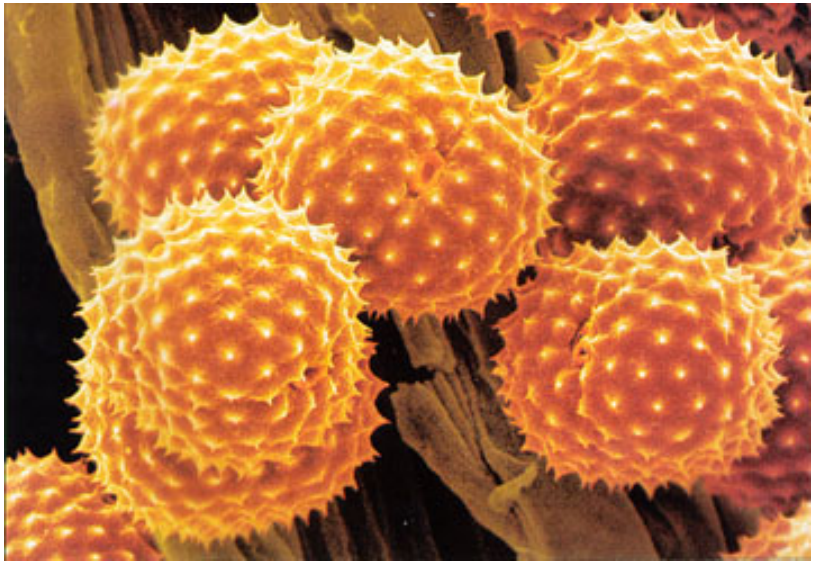
Bosentan = 0.63 0.21
p=0.003†
p=0.60*

Vitamin C = 0.99 0.33
p=0.003†
p=0.67*

†vs slope = 0
*vs placebo pre-treatment slope

⇧ 3-4 mm Hg

# Coarse PM



# The Effect of Fine and Coarse Particulate Air Pollution on Mortality: A National Analysis

*Environ Health Perspect* 117:898–903 (2009).

**Table 3.** Percent increase (95% CI) in mortality for 10-μg/m$^3$ increase in PM coarse and $PM_{2.5}$ for the mean01 across the 47 cities; two-pollutant model and single-pollutant model results for $PM_{2.5}$ in 47 cities.

| | $PM_{2.5}$ | PM coarse |
|---|---|---|
| All-cause mortality | 0.77 (0.43 to 1.12) | 0.47 (0.21 to 0.73) |
| | 0.94 (0.65 to 1.22) | |
| CVD | 0.61 (0.05 to 1.17) | 0.29 (–0.04 to 0.61) |
| | 0.97 (0.51 to 1.43) | |
| MI | 0.75 (–0.12 to 1.63) | 0.04 (–0.72 to 0.81) |
| | 1.18 (0.43 to 1.93) | |
| Stroke | 0.82 (–0.21 to 1.86) | 0.71 (0.02 to 1.41) |
| | 1.96 (0.88 to 3.07) | |
| Respiratory | 1.63 (0.69 to 2.59) | 1.14 (0.43 to 1.85) |
| | 1.92 (1.08 to 2.78) | |

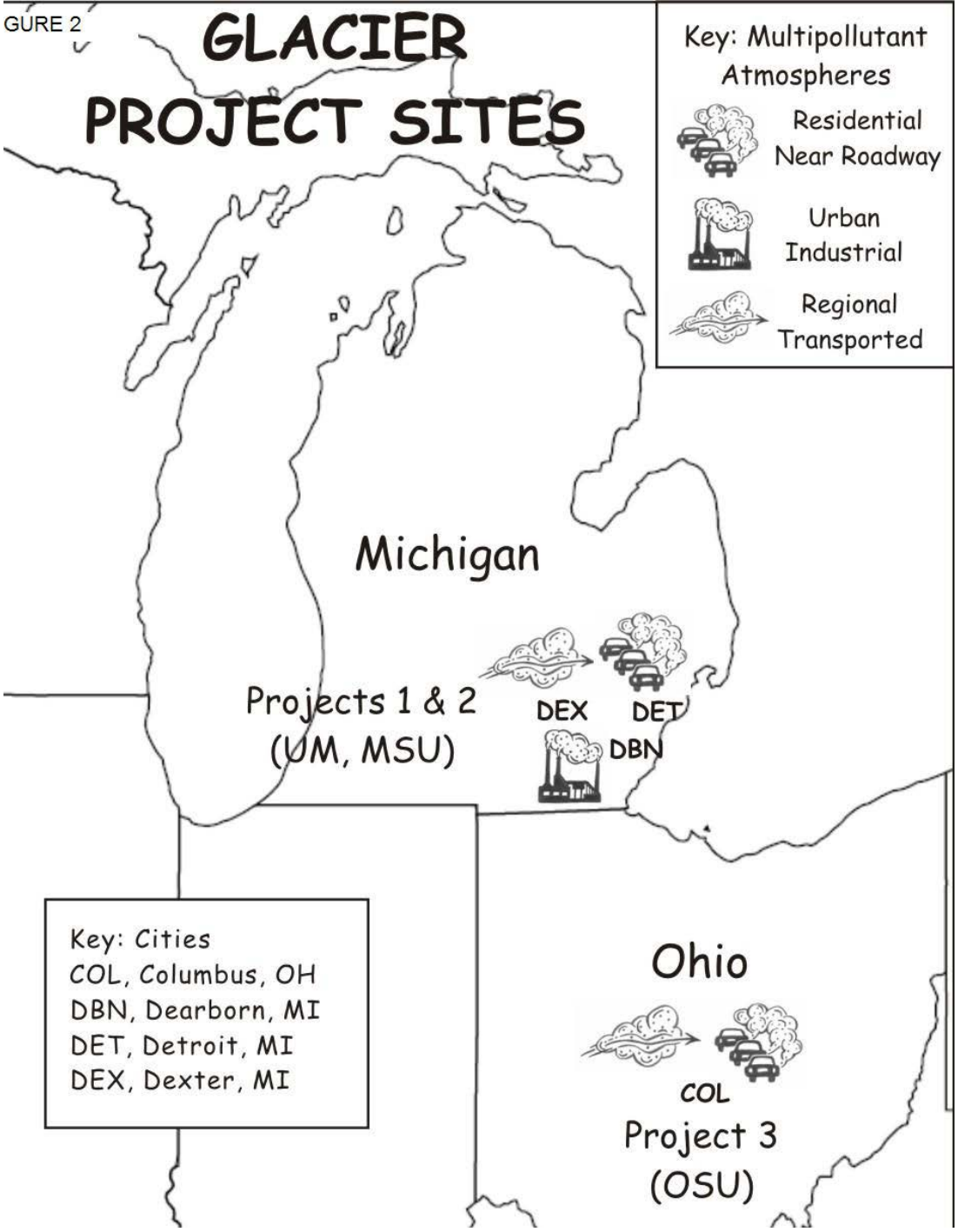
Two-pollutant models are shaded. Mean01 is the mean of lags 0 and 1.

## US Medicare Cohort

**(JAMA 2008; 299: 2172)**

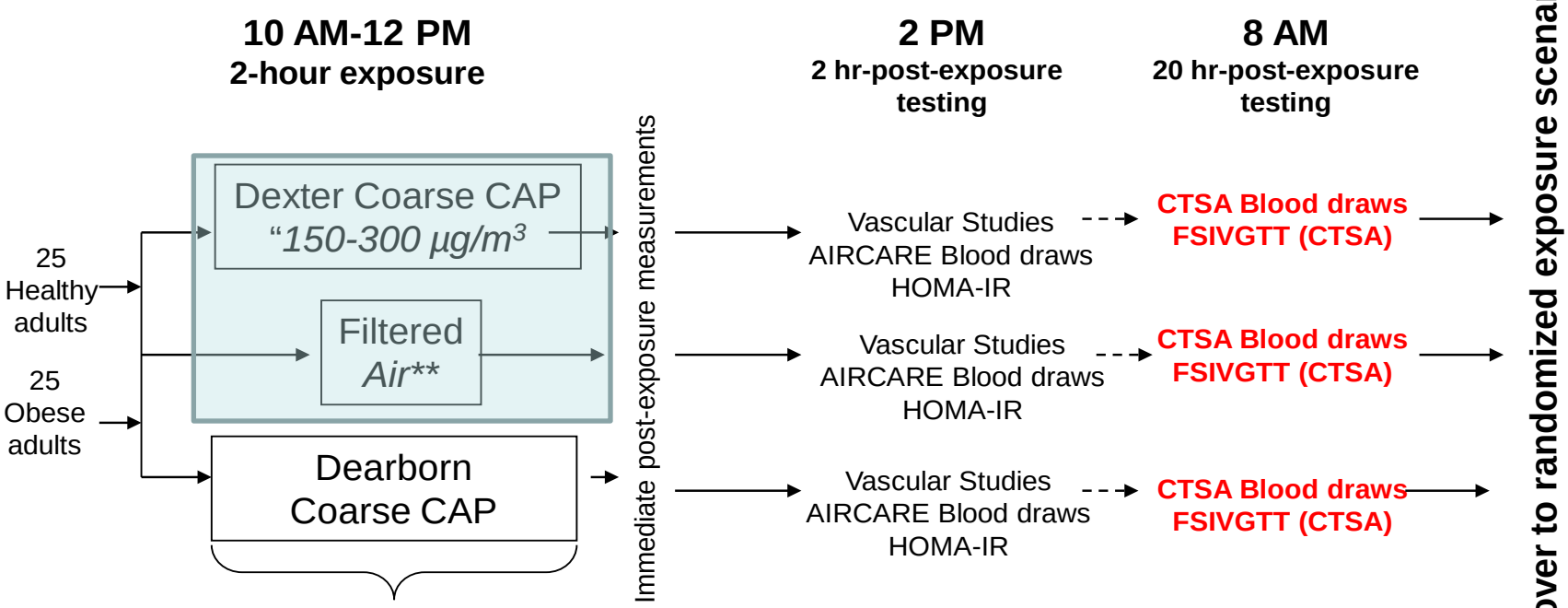
**No association for CVD hospital admissions controlling for $PM_{2.5}$**

GURE 2


GLACIER
PROJECT SITES
Key: Multipollutant Atmospheres
Residential Near Roadway
Urban Industrial
Regional Transported
Michigan
Projects 1 & 2
(UM, MSU)
DEX
DET
DBN
Key: Cities
COL, Columbus, OH
DBN, Dearborn, MI
DET, Detroit, MI
DEX, Dexter, MI
Ohio
COL
Project 3
(OSU)

# Dexter, Michigan

# Human Study #1
# STUDY DESIGN




INTRA-EXPOSURE TESTING
BOTH EXPOSURES
Ambulatory BP monitoring
HRV monitoring

CAP, concentrated ambient PM2.5; HRV, heart rate variability
Vascular studies (SphygmoCor, EndoPAT, brachial BAD, FMD, NMD)
FMD, flow-mediated dilatation; NMD, nitroglycerin-mediated dilatation
BAD, brachial artery diameter; Blood tests (blood biomarkers- see text)
HOMA-IR, homeostasis model assessment of insulin resistance
FSIVGTT, frequently sampled intravenous glucose tolerance test

**FA will be done only once per subject. This will be done in all patients in Dexter. If subjects do not follow-up and get a 3rd Dearborn exposure in year 2, they will then receive 2 exposures (FA and coarse CAP) in Dearborn. If they got a FA in Dexter and are participating in Dearborn in year 2, they will get only 1 coarse exposure and they will not get a second FA exposure

Bold and red endpoints at 20 hour post are performed in the CTSA

# The Hemodynamic, Autonomic, and Vascular Effects of Exposure to Coarse Particulate Matter Air Pollution in a Rural Location

Robert D Brook MD[1]; Robert L Bard MS[1]; Masako Morishita PhD[2]; J Timothy Dvonch PhD[2]; Lu Wang PhD[2]; Hui-yu Yang MS[2]; Catherine Spino ScD[2]; Bhramar Mukherjee PhD[2]; Mariana J. Kaplan MD[1]; Srilakshmi Yalavarthi MS[1]; Elif A Oral MD[1]; Nevin Ajluni MD[1]; Quingua Sun MD[3]; Jeffrey R. Brook PhD[5], Jack Harkema DVM PhD[4]; Sanjay Rajagopalan MD[3]

[1]Department of Internal Medicine, University of Michigan, Ann Arbor, MI; [2]School of Public Health, University of Michigan, Ann Arbor, MI; [3]Davis Heart Lung Research Institute, College of Medicine, Ohio State University, Columbus, OH; [4]College of Veterinary Medicine, Michigan State University, East Lansing, MI; [5]Environment Canada and University of Toronto, ON

# Subject Characteristics (n=32)

| Variable | Mean | SD | Minimum | Maximum |
|---|---|---|---|---|
| **Age** (years) | 25.9 | 6.6 | 18.0 | 46.0 |
| **Weight** (kg) | 78.4 | 16.3 | 55.9 | 111.4 |
| **Height** (m) | 1.7 | 0.1 | 1.6 | 2.0 |
| **Body mass index** ($kg \cdot m^{-2}$) | 26.3 | 5.7 | 18.3 | 43.5 |
| **Fasting glucose** ($mg \cdot dL^{-1}$)* | 86.9 | 6.9 | 70.0 | 103.0 |
| **Total cholesterol** ($mg \cdot dL^{-1}$) | 163.9 | 31.4 | 104.0 | 244.0 |
| **HDL-C** ($mg \cdot dL^{-1}$) | 55.4 | 15.9 | 25.0 | 91.0 |
| **LDL-C** ($mg \cdot dL^{-1}$) | 88.8 | 26.1 | 49.0 | 135.0 |
| **Triglycerides** ($mg \cdot dL^{-1}$) | 106.0 | 80.9 | 40.0 | 401.0 |

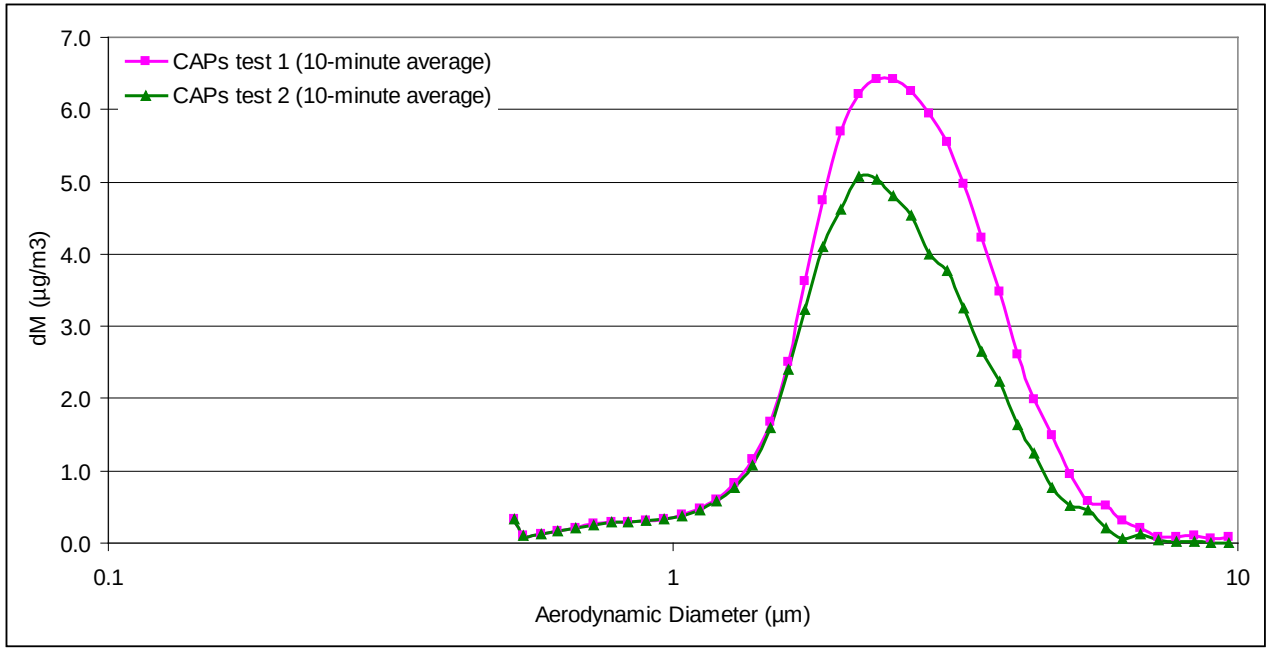
# $PM_{10-2.5}$ concentrations during exposures

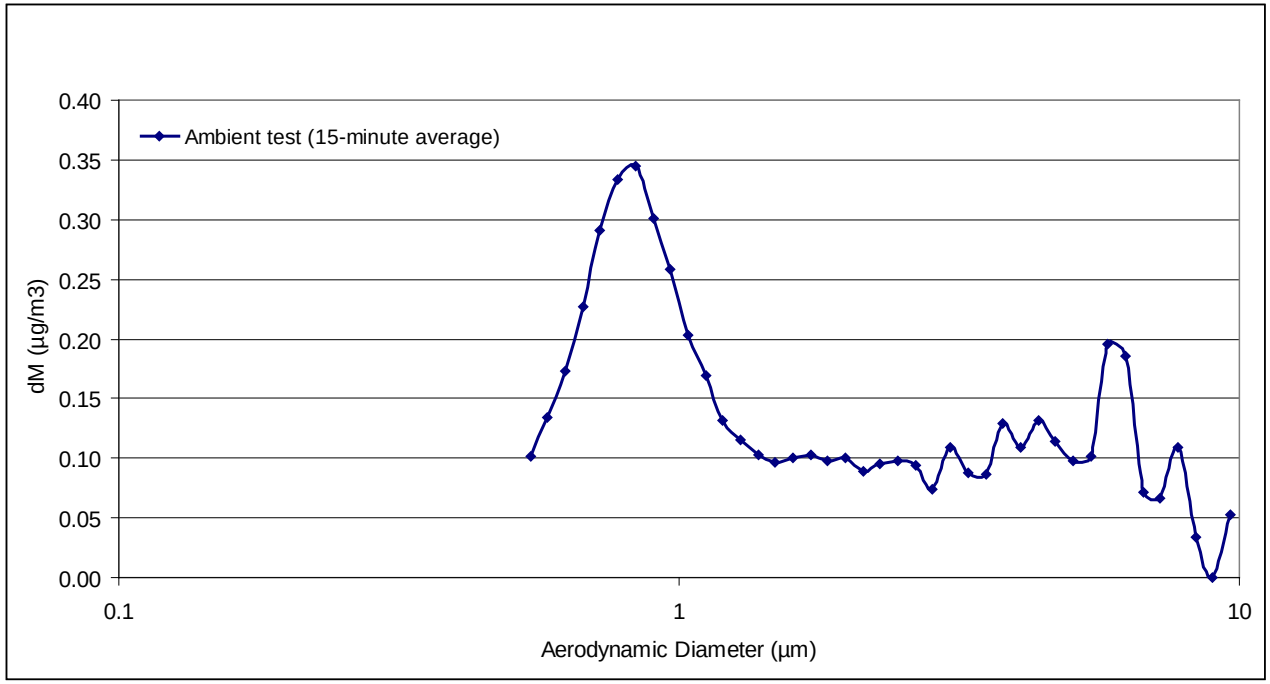
| Exposure | Mean | SD | Minimum | Maximum |
|---|---|---|---|---|
| **Filtered air** | 10.1 | 7.1 | 2.6 | 27.4 |
| **Coarse CAP** | 76.2* | 51.5 | 10.3 | 246.5 |

CAP, concentrated ambient particles

$PM_{10-2.5}$ concentrations are in $\mu g \cdot m^{-3}$ and determined by Teflon filter-based gravimetric mass measurements for the 2-hour period of exposures. Mass levels below the detection limit (6.8 $\mu g \cdot m^{3}$) were recorded at this value for analyses (n=15, filtered air exposures only)

*P values <0.01 for differences of mean or median levels between exposure types



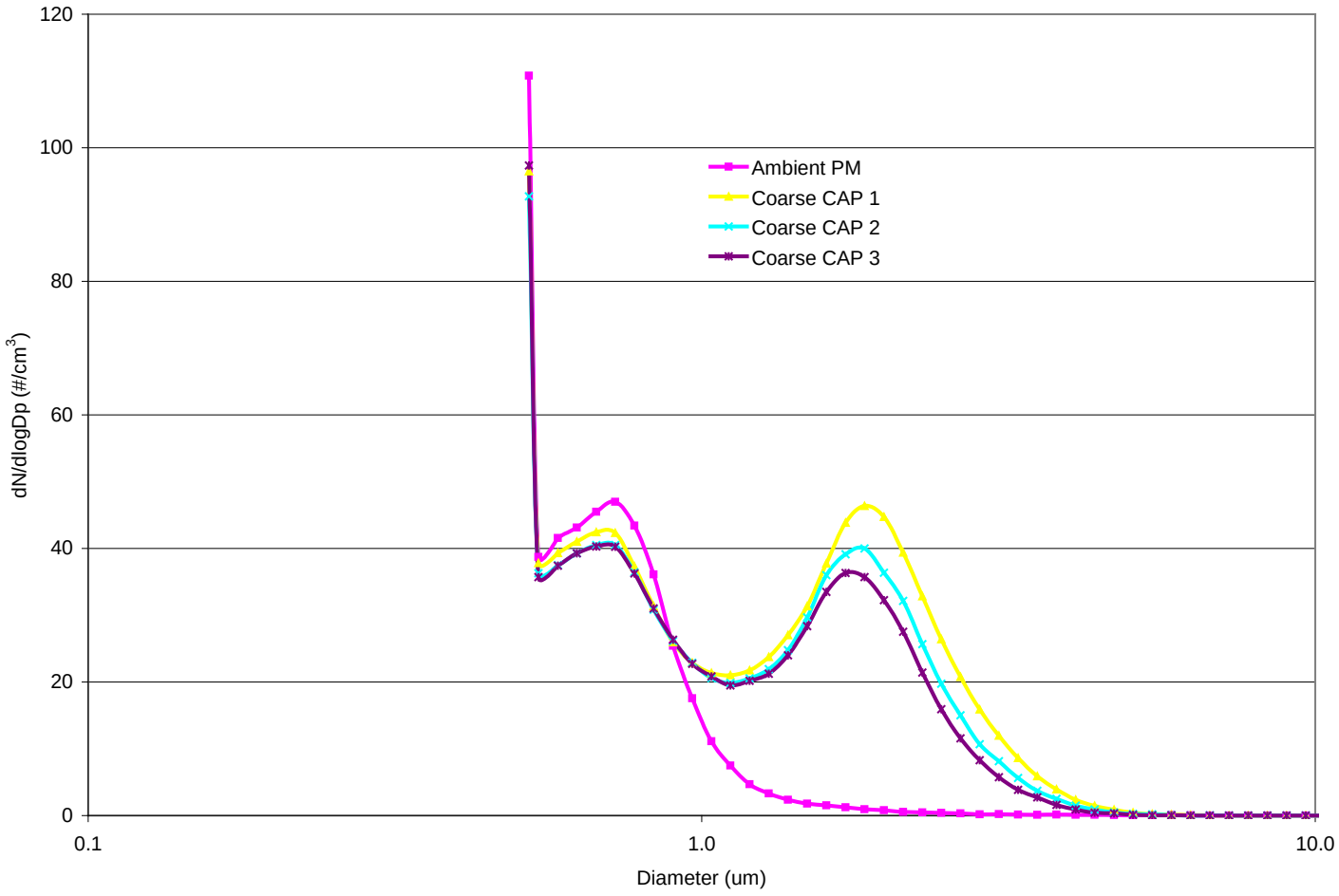




# Comparison of size distributions between ambient $PM_{10-0.54}$ and Coarse CAPs by APS

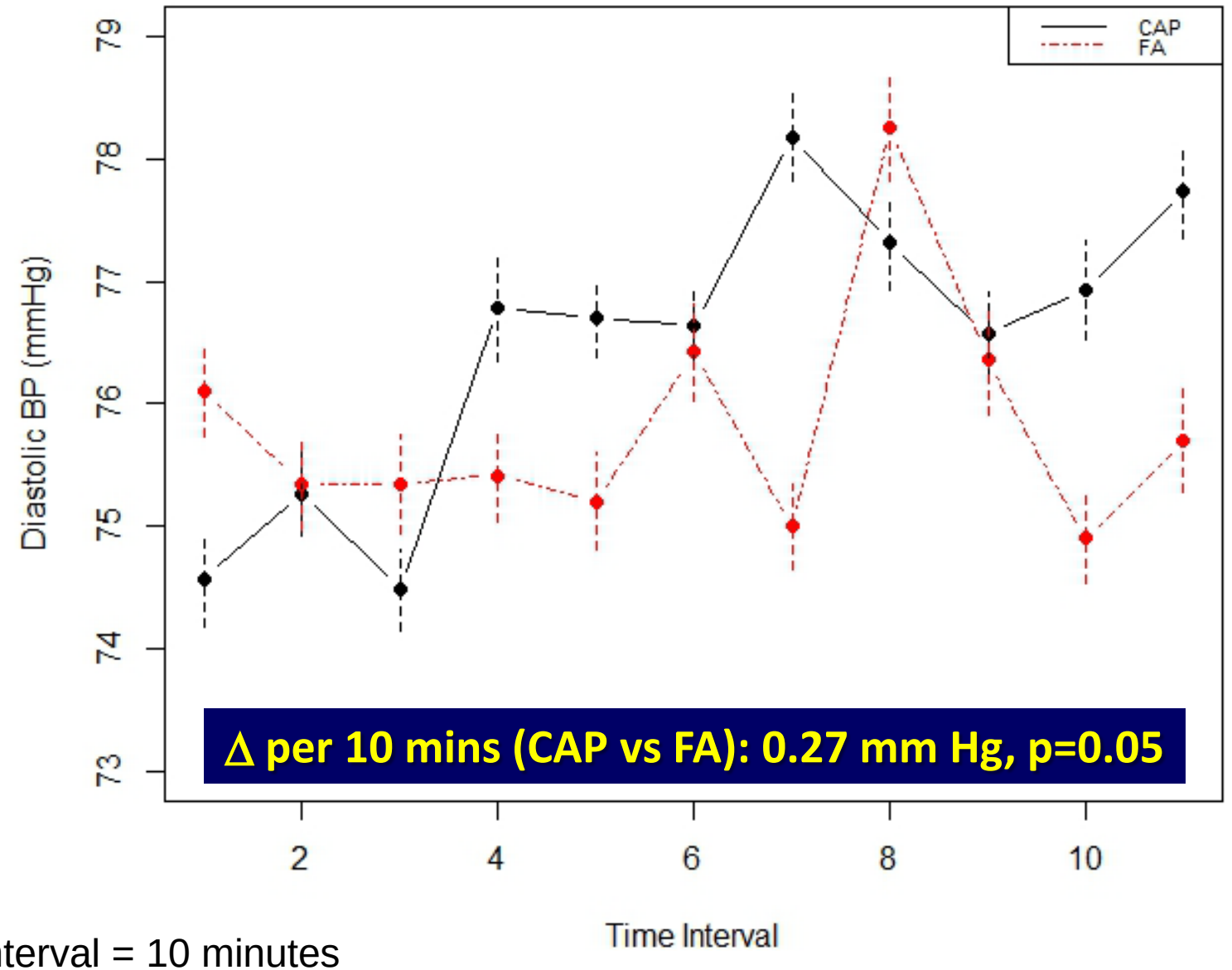
| | Mass ($\mu g/m^3$) | CEF |
|---|---|---|
| Ambient PM2.5 | 4.1 | |
| CAPs (<2.5µm) | 43 | 11 |
| Ambient PM10-2.5 | 1.9 | |
| CAPs (2.5<10µm) | 40 | 21 |

| | Median (µm) |
|---|---|
| Ambient PM10-0.54 | 1.3 |
| Ambient PM10-2.5 | 4.7 |
| CAPs (2.5<10µm) | 3.1 |

# Comparison of size distributions between ambient PM and CAPs by number concentration

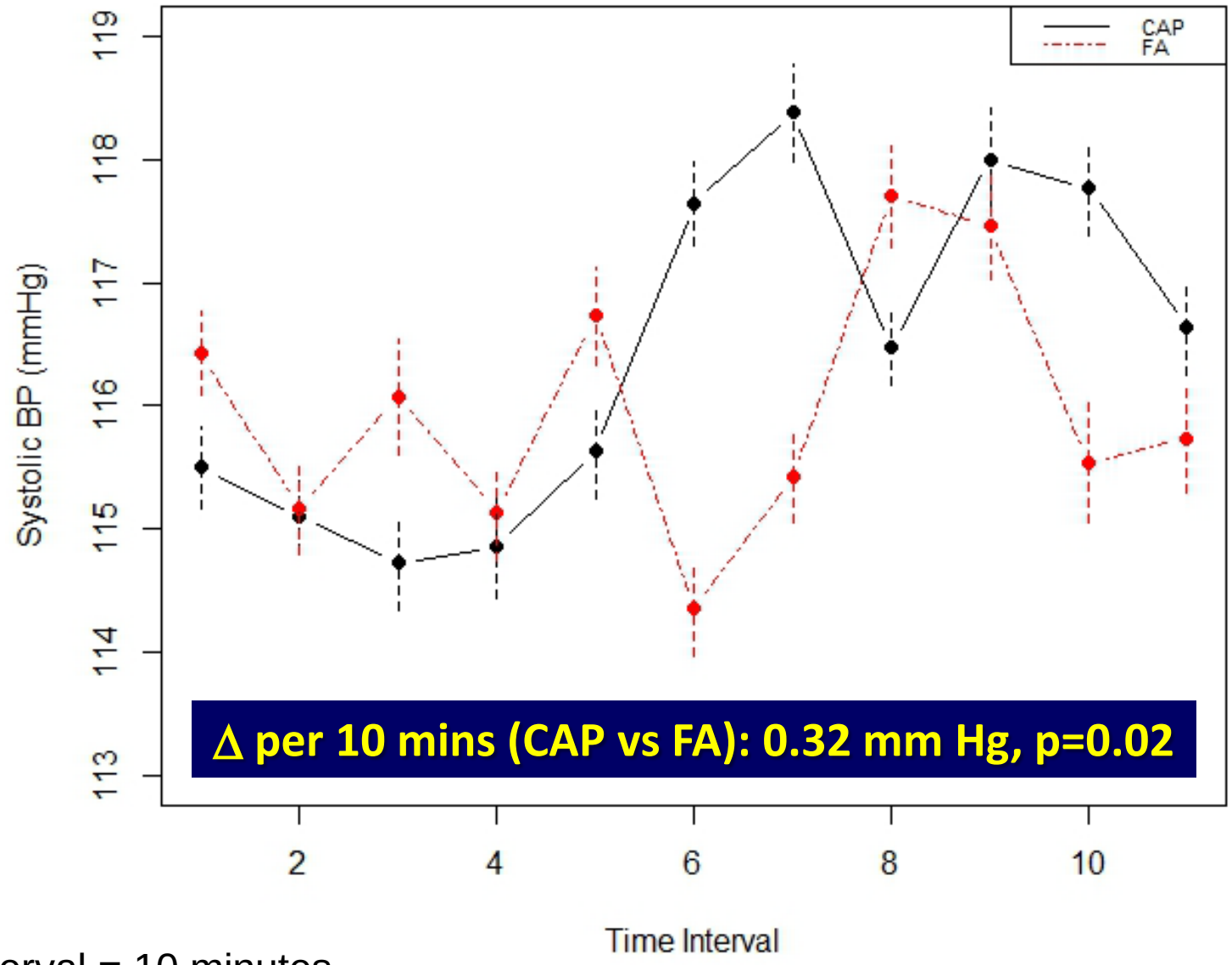


# Diastolic BP Responses During Exposures



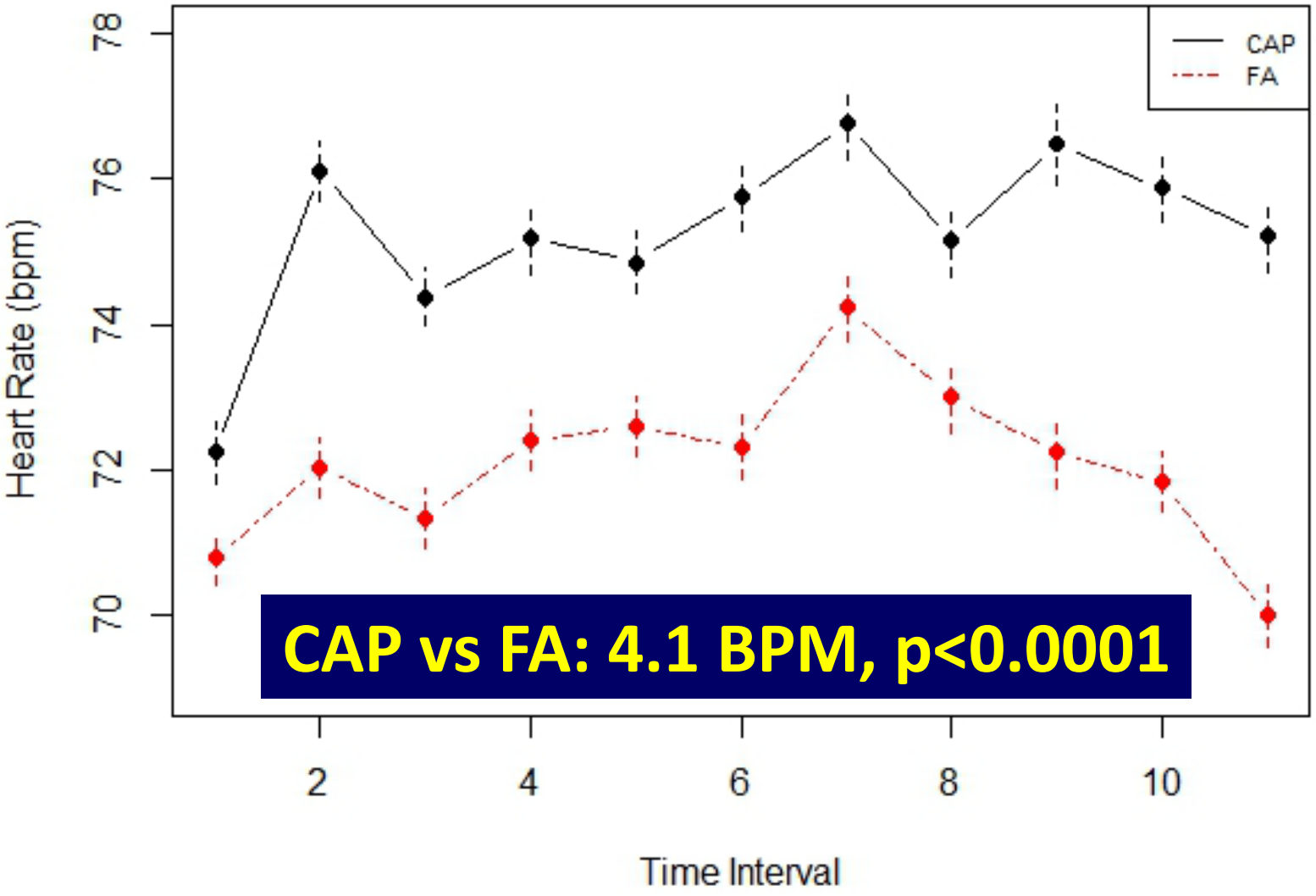

Time interval = 10 minutes

# Systolic BP Responses During Exposures

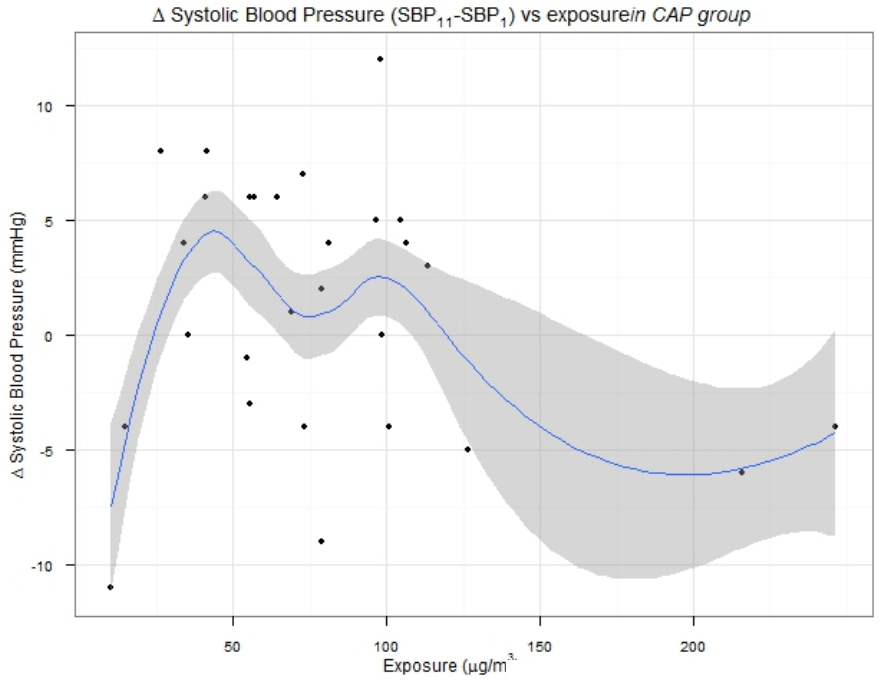


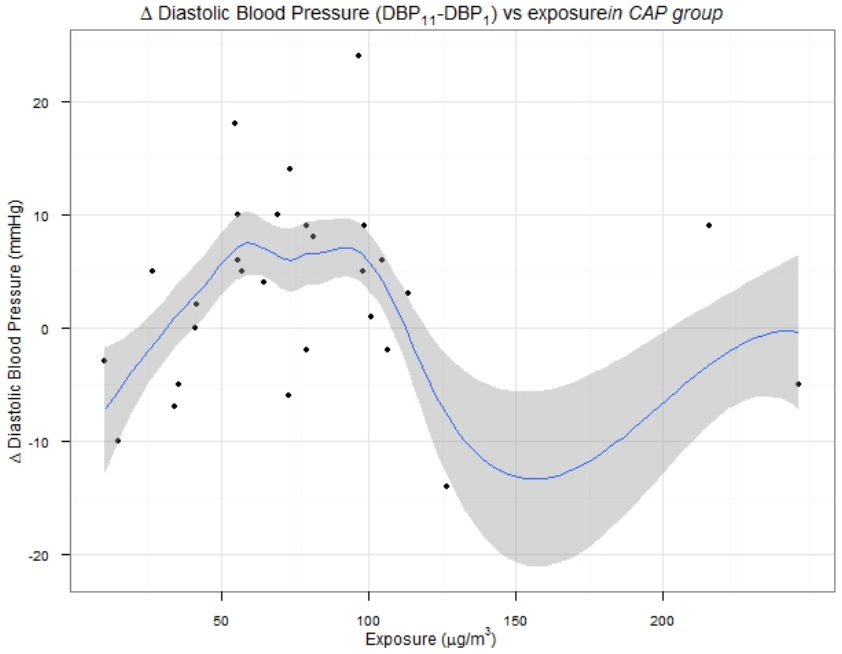

Time interval = 10 minutes

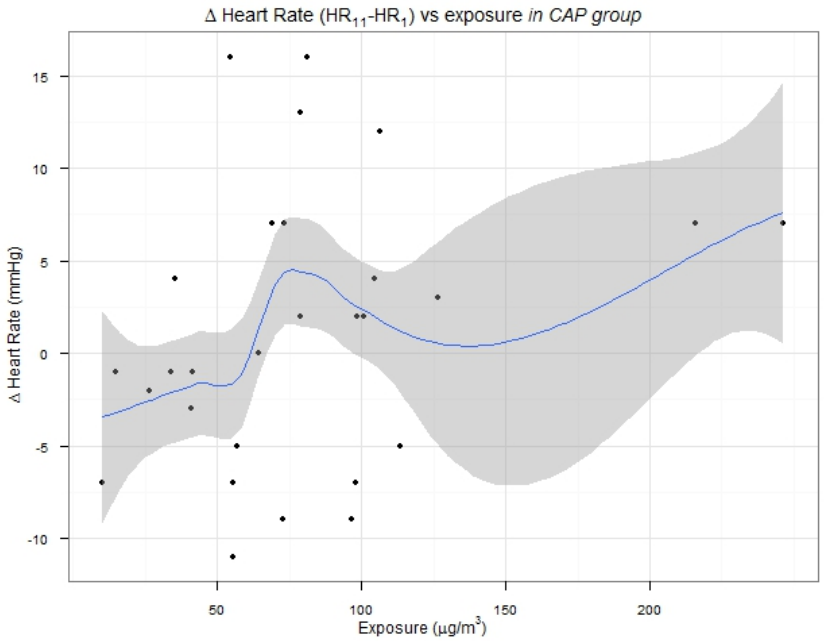
# Heart Rate Responses During Exposures




N=32 subjects




The nonparametric regression curve was estimated using local regression (loess) models, with shading representing the 95% confidence intervals

# Changes in heart rate variability parameters during exposures

| HRV Outcome | Change in Outcome (During CAP exposures versus FA) | P* |
|---|---|---|
| **Log SDNN** (msec) | -0.087 ± 0.30 | 0.107 |
| **Log HF peak** ($msec^2$) | -0.42 ± 0.84 | 0.006 |
| **Log LF peak** ($mec^2$) | -0.068 ± 0.68 | 0.58 |
| **LF/HF ratio** | +0.24 ± 0.49 | 0.007 |

Results are mean  standard deviation

HRV, heart rate variability; CAP, coarse concentrated ambient particles; FA, filtered air; SDNN, standard deviation of the normal-to-normal R-R intervals; HF, high frequency power; LF, low frequency power

*p values are the comparisons of the changes in HRV outcomes during the CAP versus FA exposures. HRV parameters were determined during the first 5 minutes at the start of the exposures (initial HRV results) and compared to those during the final 5 minutes at the end of exposures (final HRV results).

# Differences in study outcomes measured post-exposures

| Outcome | Coarse CAP Exposures | | Filtered Air Exposures | | p* | p† |
|---|---|---|---|---|---|---|
| | Immediate-post | 2 hours-post | Immediate-post | 2 hours-post | | |
| **Brachial SBP** (mm Hg) | 109.2 ± 11.7 | 108.4 ± 11.3 | 108.7 ± 12.3 | 108.8 ± 11.3 | 0.66 | 0.65 |
| **Brachial DBP** (mm Hg) | 72.3 ± 8.4 | 68.1 ± 9.0 | 72.0 ± 9.3 | 68.7 ± 8.4 | 0.72 | 0.61 |
| **Heart Rate** (beats·min$^{-1}$) | 62.9 ± 9.9 | 65.0 ± 9.0 | 60.6 ± 8.9 | 61.1 ± 9.0 | **0.12** | **0.03** |
| **Aortic SBP** (mm Hg) | 97.4 ± 11.2 | 95.0 ± 11.4 | 97.5 ± 12.0 | 95.7 ± 12.2 | 0.94 | 0.49 |
| **AP** (mm Hg) | 3.3 ± 3.3 | 2.2 ± 3.4 | 3.4 ± 3.9 | 2.6 ± 4.9 | 0.63 | 0.26 |
| **AIx@75** (%) | 5.9 ± 12.3 | 2.1 ± 13.0 | 5.0 ± 14.5 | 1.1 ± 16.9 | 0.80 | 0.94 |
| **PWV** (m·sec$^{-1}$) | 6.8 ± 1.6 | 6.6 ± 1.4 | 6.7 ± 1.5 | 6.7 ± 1.6 | 0.96 | 0.19 |
| **BAD** (cm) | 3.62 ± 0.60 | 3.64 ± 0.62 | 3.68 ± 0.66 | 3.70 ± 0.64 | **0.12** | **0.15** |
| **FMD-peak** (%)‡ | | 9.4 (6.3, 12.1) | | 9.0 (6.3, 10.9) | | 0.68 |
| **RHI** | | 2.1 (1.8, 2.2) | | 2.0 (1.7, 2.4) | | 0.57 |

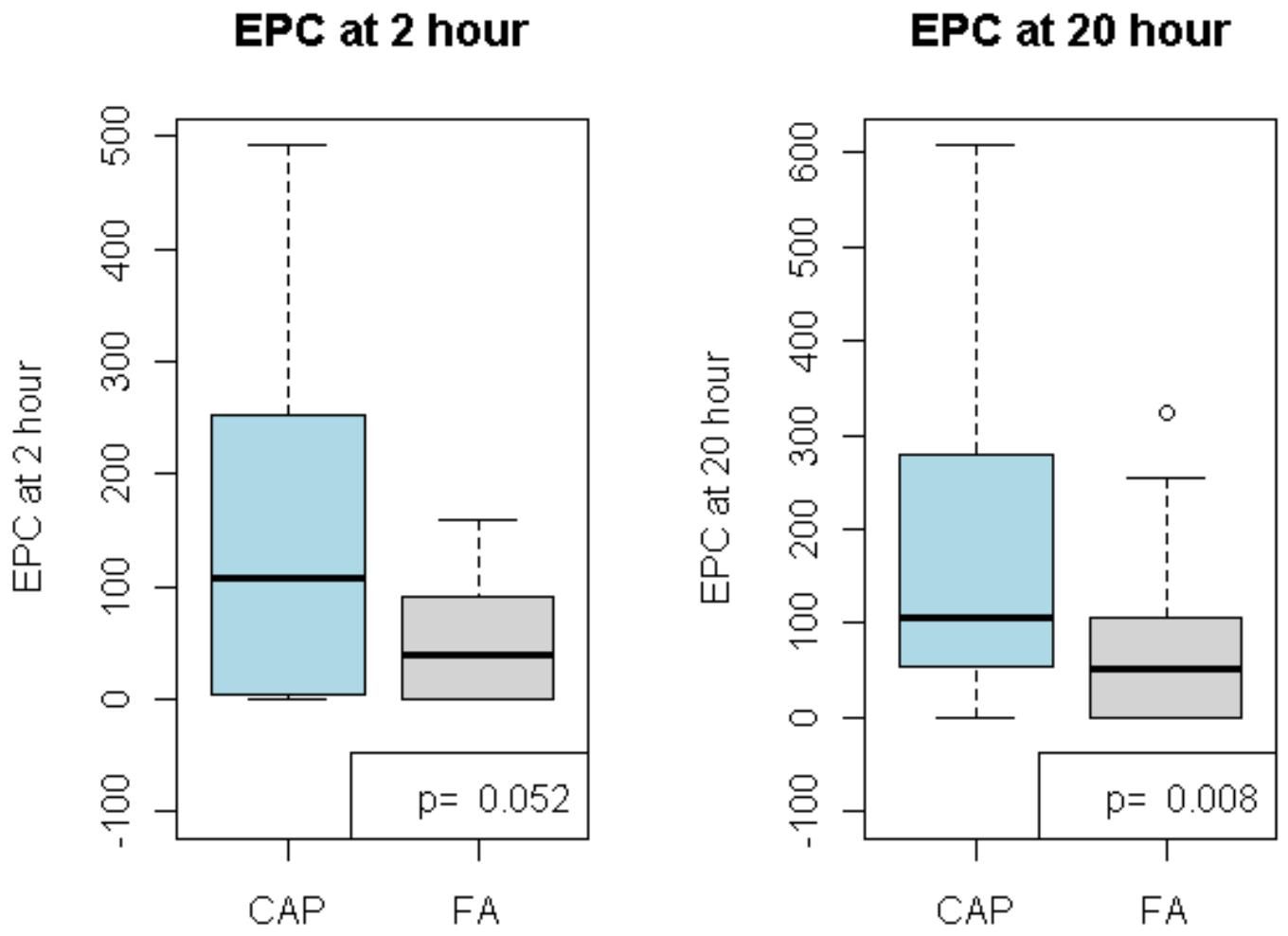
Results are mean standard deviation.
Paired t-tests were used for statistical comparisons

CAP, concentrated ambient particles; SBP, systolic blood pressure; DBP, diastolic blood pressure; AP augmentation pressure; AIx, augmentation index at a heart rate of 75 beats min$^{-1}$; PWV, pulse wave velocity; BAD, brachial artery diameter; FMD-peak, flow-mediated dilatation (peak value); RHI, reactive hyperemia index

FMD and RHI presented as median (1st and 3rd quartile) and Paired Wilcoxon Ranked Sum Tests were used for statistical comparisons

*p values are comparisons of immediate-post (CAP versus FA); †p values are comparisons of 2 hours-post exposures (CAP versus FA).
‡Other FMD metrics (60-sec time point dilatation; 2-min mean dilatation) were also not significantly different between exposures

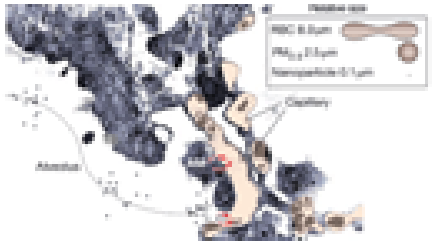
# Endothelial Progenitor Cells

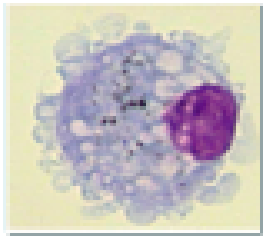



**EPCs were elevated 2 hours (108.29 [6.24, 249.71] EPC·ml$^{-1}$; median [25$^{th}$, 75$^{th}$ percentiles], p=0.052) and 20 hours (106.86 [52.91, 278.35] EPC·ml$^{-1}$, p=0.008) post-CAP exposure compared to the same time points following filtered air (38.47 [0, 84.83] and 50.16 [0.00, 104.79] EPC·ml$^{-1}$).**

PBMCS are isolated by Ficoll gradient, washed and incubated with fluorochrome-conjugated Abs that recognize CD133, CD34, CD3, CD79 and CD56. Cells are analyzed by flow and cells in the lymphocyte gate that are negative for CD3 (t-cell), CD79 (b-cell) and CD56 (NK) and positive for CD133 and CD34 are considered EPCs.

# HDL Dysfunction and Air Pollution





ALVEOLI

DIRECT PM-INDUCED OXIDATIVE STRESS

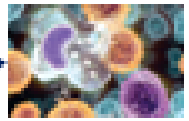
(METALS, ORGANIC CARBON, QUINONES)

ALVEOLAR CELLS, MACROPHAGES

INDIRECT OXIDATIVE STRESS

(CELLULAR PM UPTAKE AND ACTIVTION)

*PULMONARY OXIDATIVE STRESS*



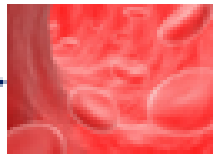
*Lung inflammation*

**PULMONARY CIRCULATION + INTERSTIAL HDL PARTICLES**

*Oxidation of HDL*

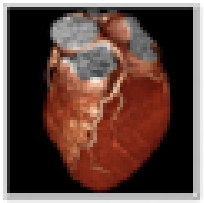
(Lipids, amino acid residues)

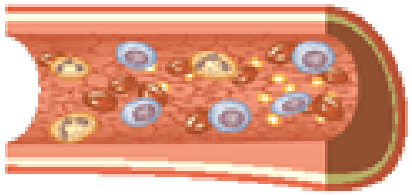
*Systemic "spill-over" of dysfunctional HDL*



*Circulating HDL*

(Dysfunctional properties)





Cardiovascular Damage - Endothelial dysfunction

# Pleiotropic Protective Functions of HDL

## Anti-inflammatory
↓ cytokines, adhesion molecules
↓ macrophages, complement
Bind LPS, Kill parasites

## Anti-thrombotic
↓ platelet activation, ↑ NO, $PGI_2$
PAF acetylhydrolase

## Vascular
Vasodilate via NO, $PGI_2$
↑ eNOS (PI3k-AKT), ↑ EPC

## Metabolic
↑ insulin sensitivity (AMP-K)

## Proteome
Apo's; >75 proteins

## "Lipidome"
Sphingosine-P Rcpt
Vasodilatation
Anti-inflammatory

## Anti-oxidant
Paraoxonase, LCAT
PAF acetylhydrolase
↓ lyso-PC, ↓ ox-LDL

Cytokines, MPO, sPL, SAA

**"Dysfunctional HDL"**

## Pro-fibrinolytic
Promote protein C

## Reverse Cholesterol Transport
↓ Foam cells and atherosclerosis

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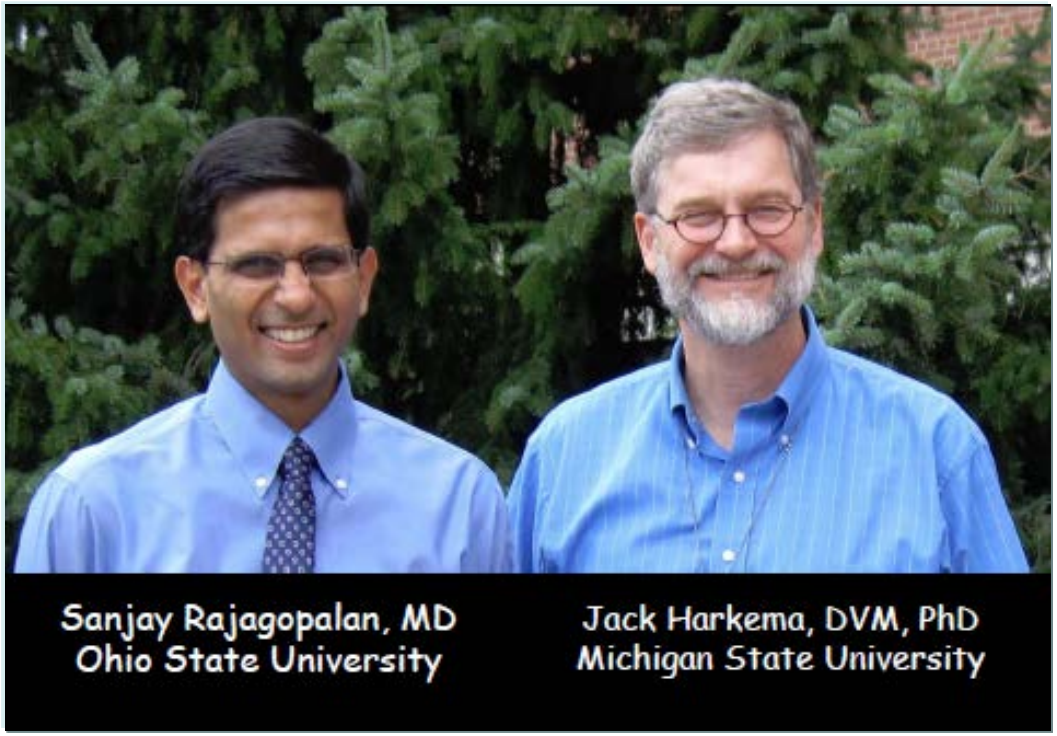
FOR INTEGRATED ENVIRONMENTAL RESEARCH

# URBAN COARSE CAP EXPOSURES



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NIEHS: R01 ES0196166 GRT00019491
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