Cardiovascular Effects of Urban and Rural Coarse Particulate Matter in Adults (COARSE-CAP)

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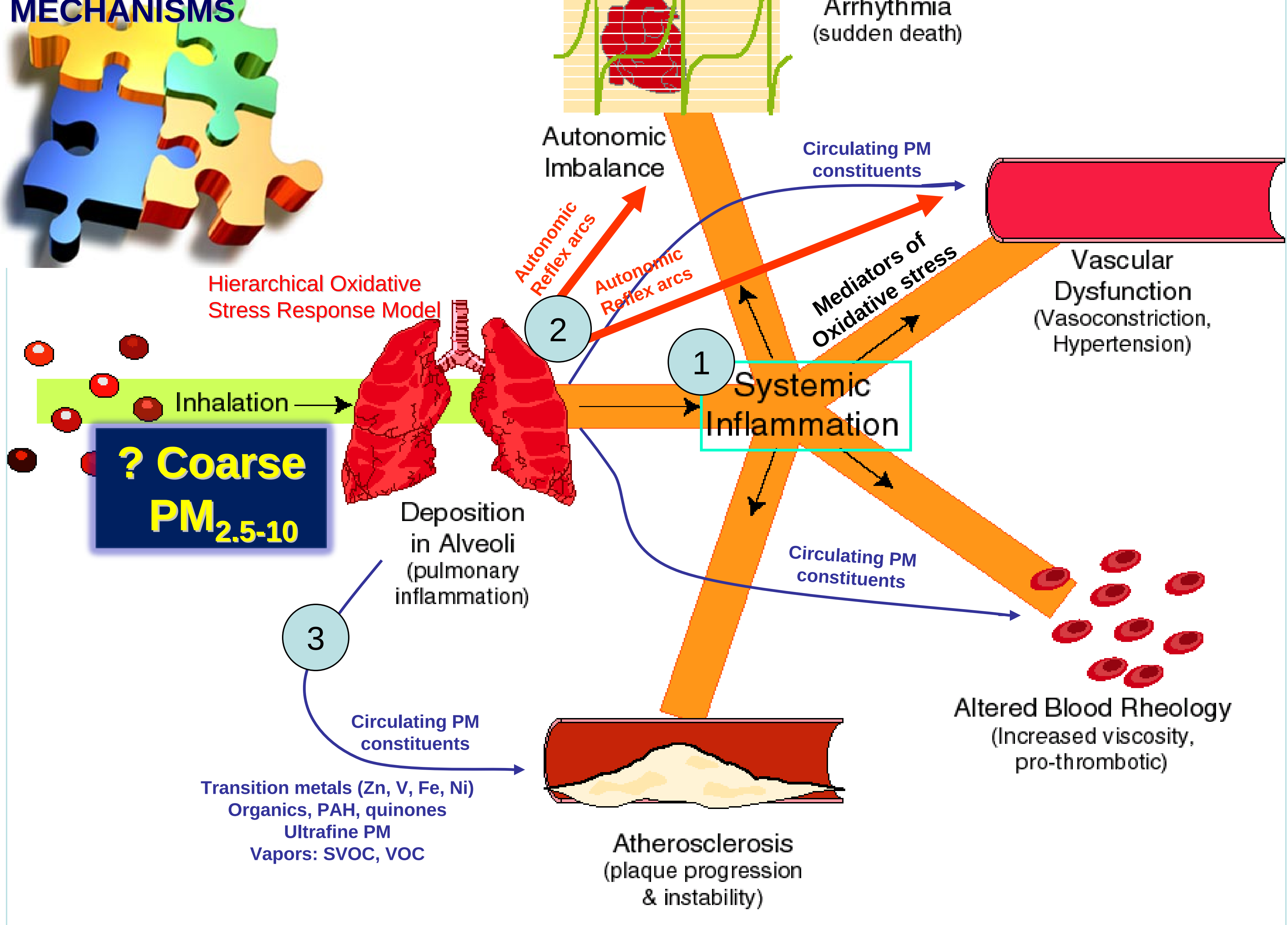
PLAUSIBLE BIOLOGICAL MECHANISMS



Few Studies with Controlled Exposure to Coarse PM

- Exposure to concentrated coarse air pollution particles causes mild cardiopulmonary effects in healthy young adults
  - *Graff DW, et al. Environ Health Perspect 2009; 117: 1089*

    Chapel Hill CAP (2 hr x 89 $\mu g/m^3$) to 14 healthy young adults
    - 20 hrs post ↓ TPA (32.9%), ↓ SDNN (14.4%)
    - No PFT changes, mild increase in lung PMN 20 hrs post-CAP

- Altered heart-rate variability in asthmatic and healthy volunteers exposured to concentrate
  - *Gong H, et al. Inhalant Toxicol 2004; 16: 335*

    Los Angeles suburb (2 hr x 157 $\mu g/m^3$) to 12 asthmatics and 4 healthy adults
    - Small ↑HR and ↓SDNN 4-24 hrs post-CAP(more in healthy)

Coarse-CAP

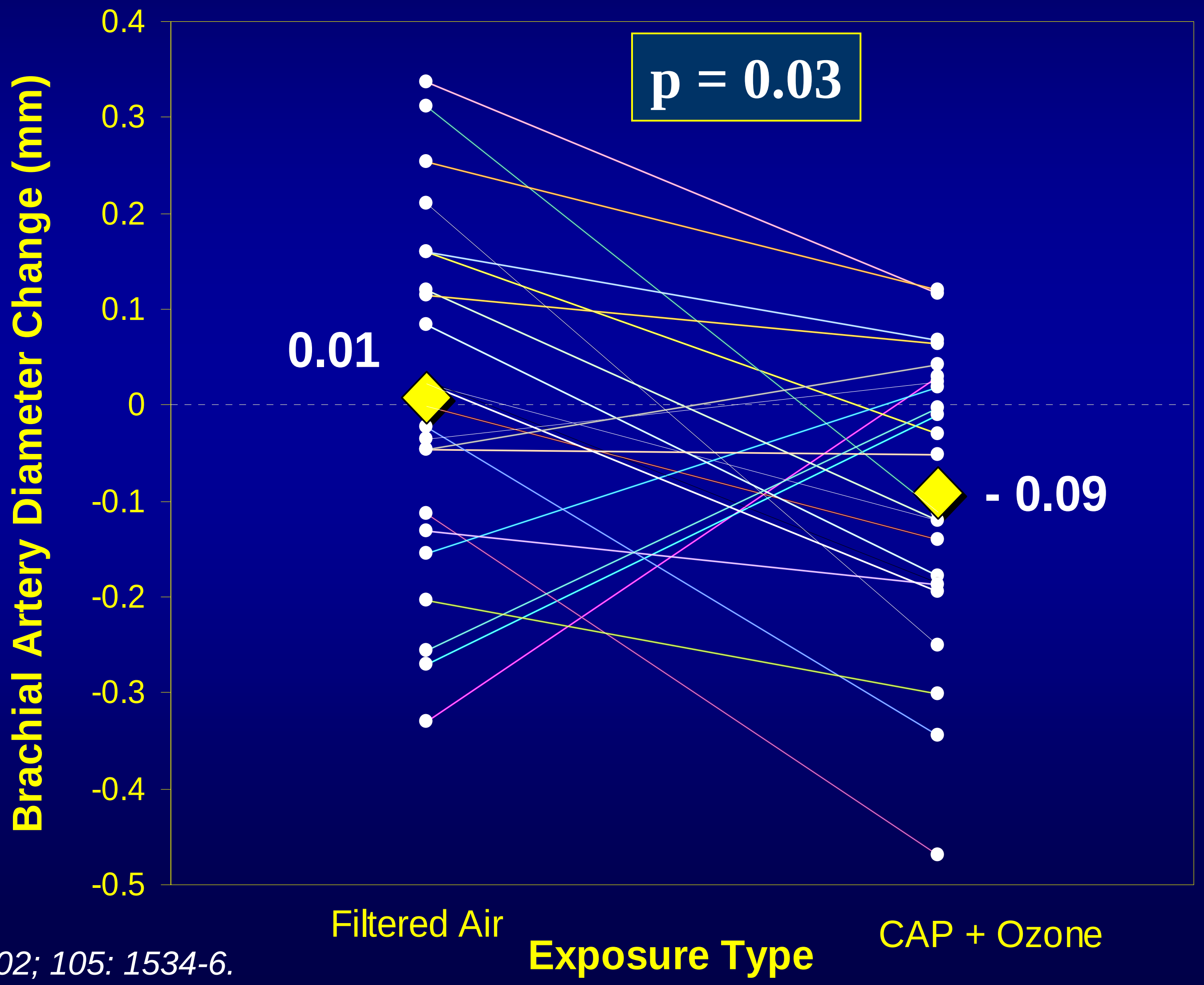
Updated
Overall Hypothesis

Short-term exposure to coarse PM, from both rural and urban sources, promotes pro-vasoconstrictive vascular dysfunctions via biological pathways related to

autonomic imbalance (rapid) and endothelial dysfunction (delayed) with (a) larger effects in obese vs lean subjects and (b) promotes metabolic insulin resistance syndrome

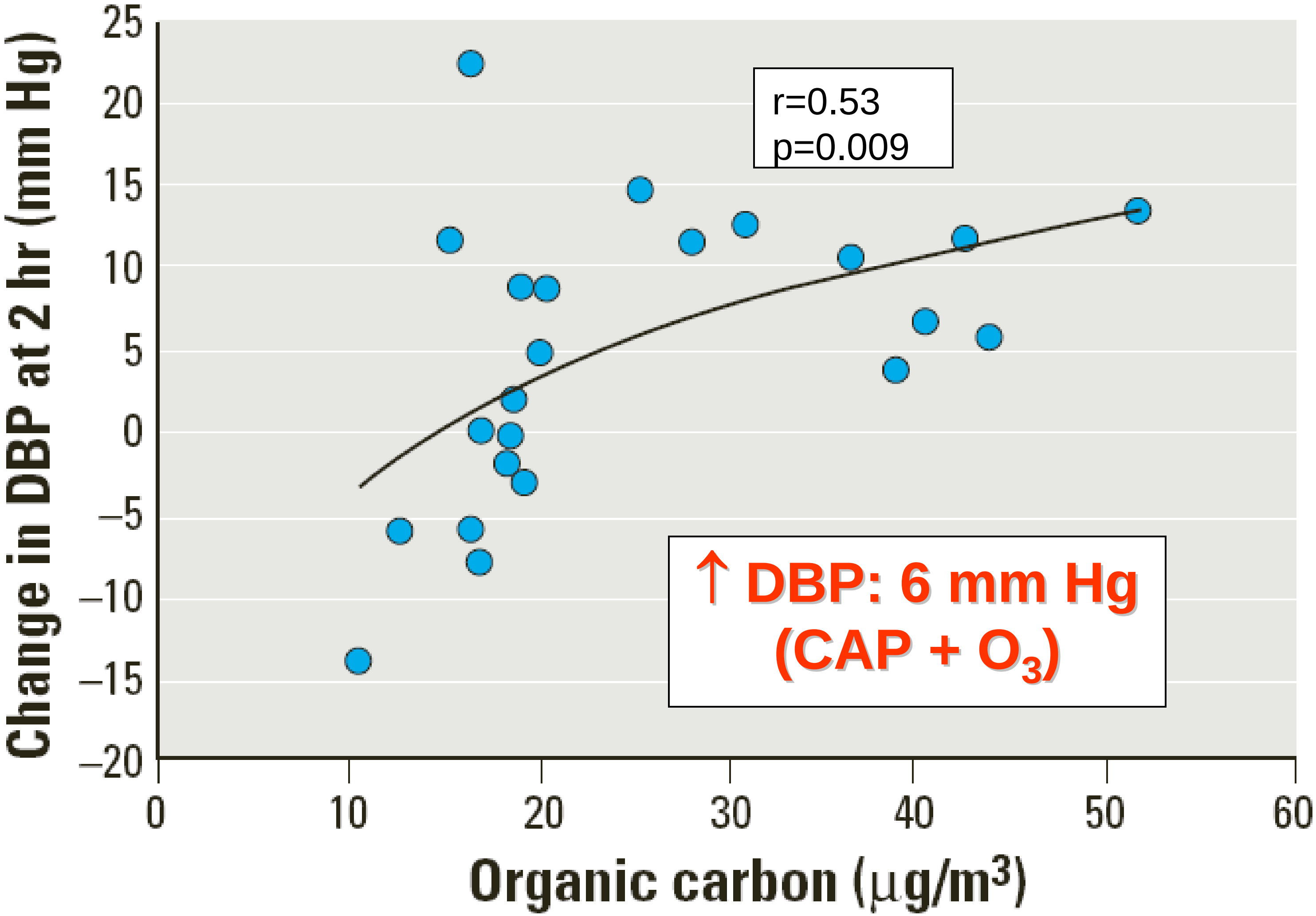
Brachial Artery Diameter Changes in Response to Air Pollution versus Filtered Air

n = 25



Circulation 2002; 105: 1534-6.

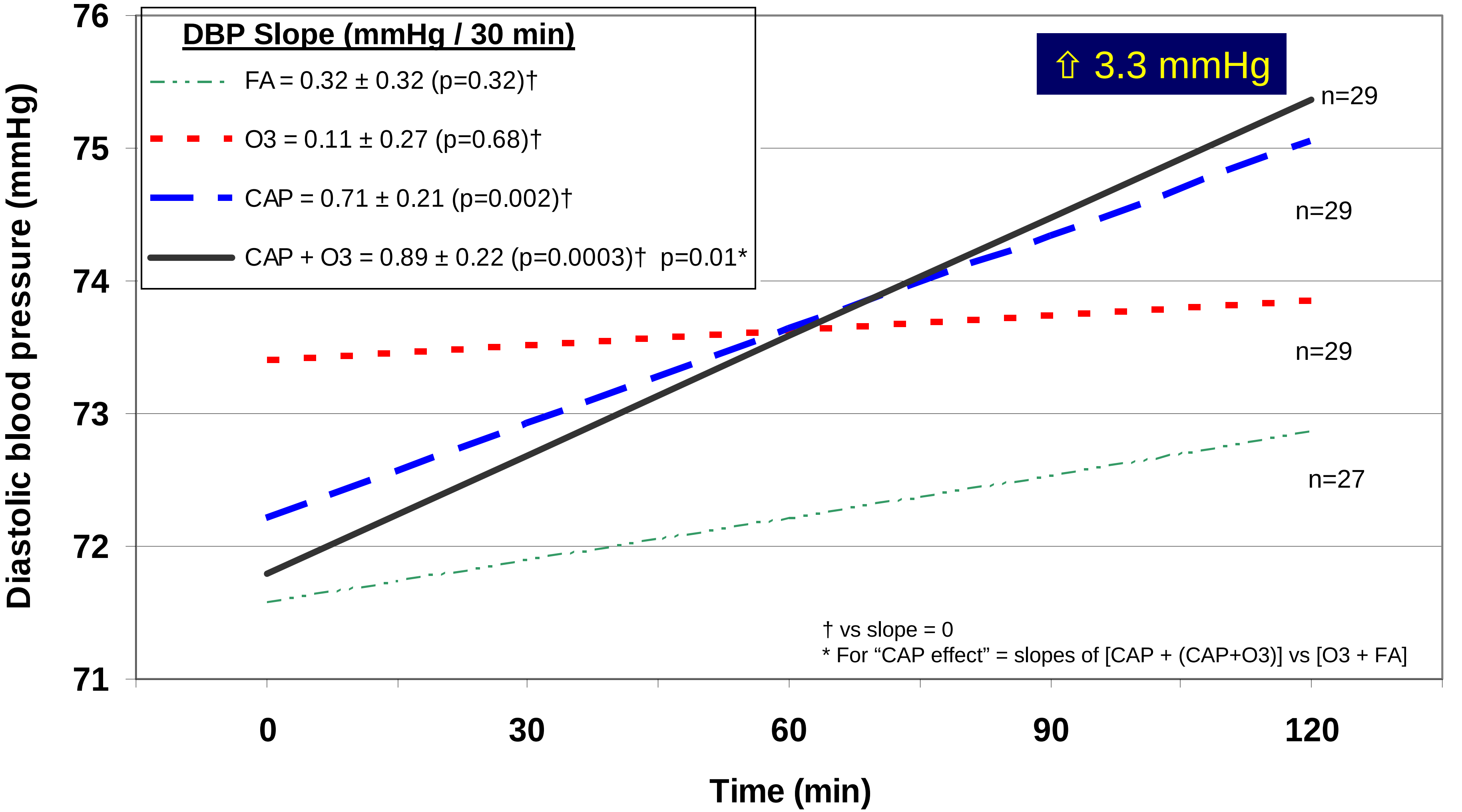
Blood Pressure Responses to Concentrated Ambient $PM_{2.5}$ (CAP) versus Filtered Air



Environ Health Perspectives 2005; 113: 1052-55.

CLEANAIR STUDY: DBP 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)

Hypertension 2009; 54: 659-667

*β =1.6 mmHg per 100 µg/m^3

Endothelial Function (Toronto)

N=31

24 post – pre-exposure FMD changes

- 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

Hypertension 2009; 54: 659-667

Coarse-CAP

Specific Aim 1

To demonstrate that coarse CAP exposure causes acute vascular dysfunctions in health adults (n=50)

– Coarse PM (CAP) [150-300 μg/m^3] for 2 hrs triggers vascular dysfunctions at rural (Dexter) + urban (Dearborn) sites (vs filtered air).

Primary outcomes: ↓ brachial artery diameter (vasoconstriction)
↑ intra-exposure diastolic blood pressure (BP)

– The vascular dysfunctions are mediated by CV autonomic balance

↓ HRV correlated and temporally related to vasoconstriction.

Update: ↑BP related to autonomic Δ; ↓FMD related to systemic inflammation

– To further elucidate the CV impact of coarse PM by novel CV outcomes
- Continuous BP/hemodynamics (Finometer)
- Central aortic hemodynamics, arterial compliance (SphygmoCor)
- Microvascular endothelial function (EndoPAT2000)

Update: Novel metabolic, pro-inflammatory biomarkers and outcomes

Coarse-CAP

Specific Aim 2

To explore potential differences in outcome responses between obese (BMI>30, n=25) versus lean (BMI<27, n=25) adults elicited by both CAP sources (urban vs rural locations).

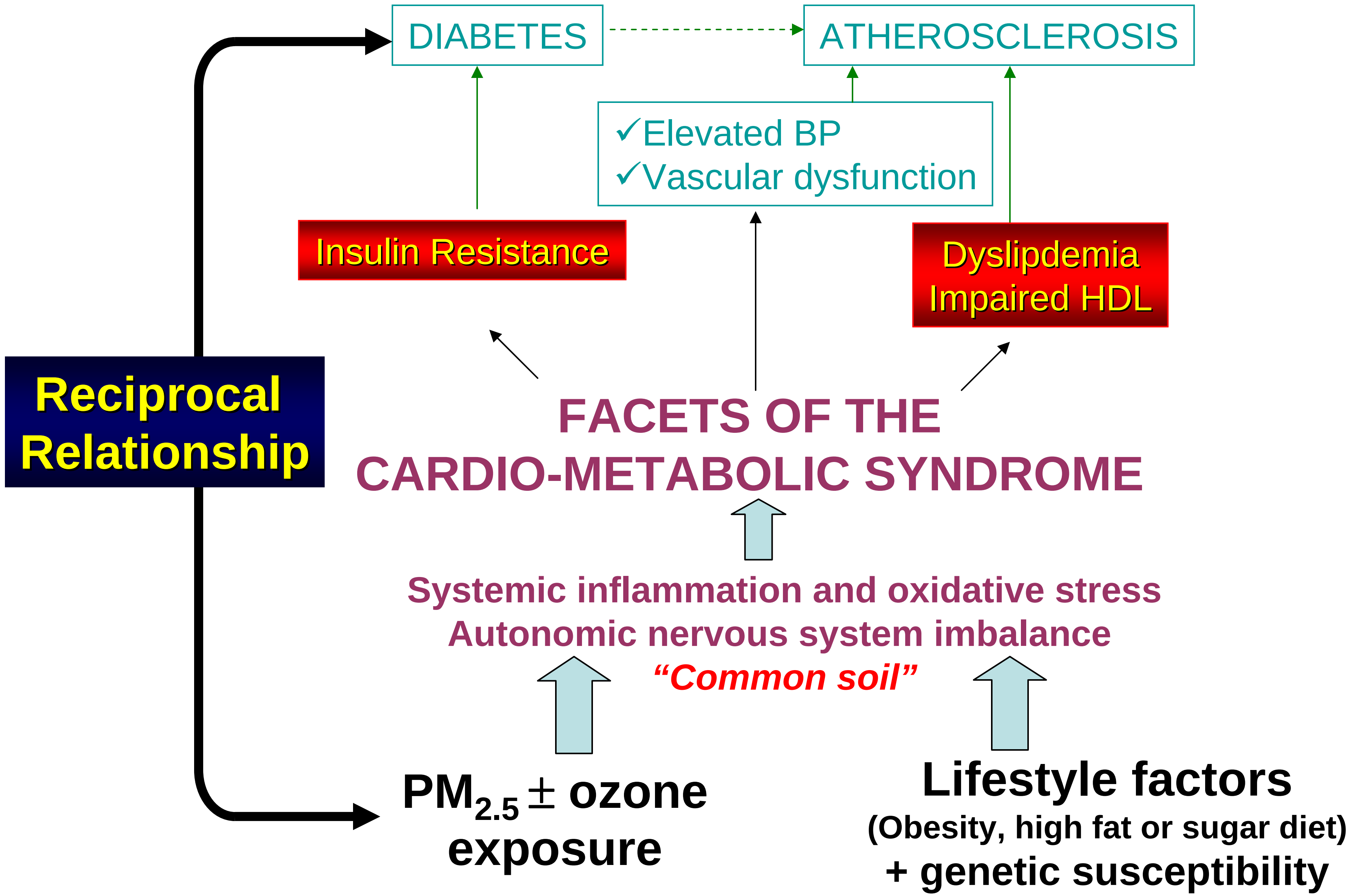
- Compare CV responses due to urban (Dearborn) vs. rural (Dexter) coarse CAP in Michigan [and Toronto – ongoing Harvard EPA Center]
- Compare CV responses between obese and lean subjects and the interaction effects of BMI/metabolic syndrome parameters (e.g. basal BP) on corresponding outcomes

Why Obesity as an Effect Modifier

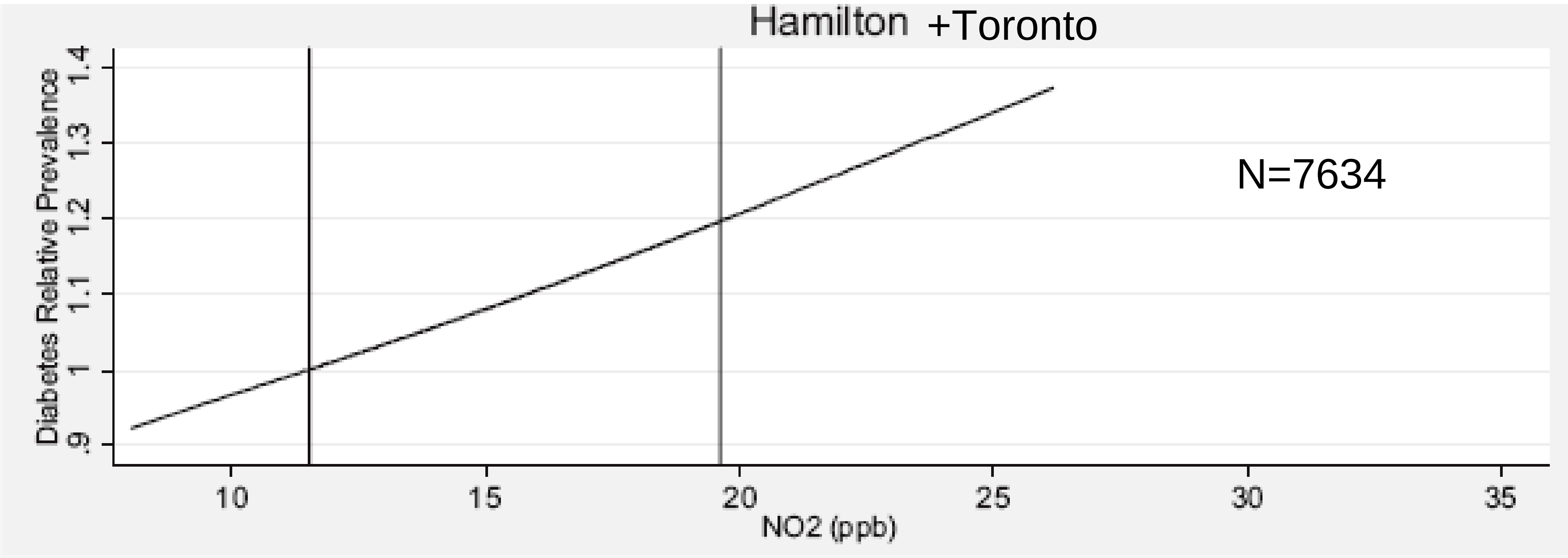
- WHI + Nurses' Health Cohort studies
  - Higher RR in subjects with BMI>30 for CV mortality
- Obese subjects (BMI>30) have larger increase in BP related to ambient PM
  - Detroit Healthy Environments Partnership
    - *Dvonch et al. Hypertension 2009*
  - Traffic exposure in U.S. Boston Puerto Rican cohort
- Obesity increases risk for inflammation related to PM
  - NHANES (WBC); Seniors in St. Louis (CRP)

WHY METABOLIC PARAMETERS

Inter-relationships between the Cardio-metabolic Syndrome and Air Pollution



The Relationship Between Diabetes Mellitus and Traffic-Related Air Pollution



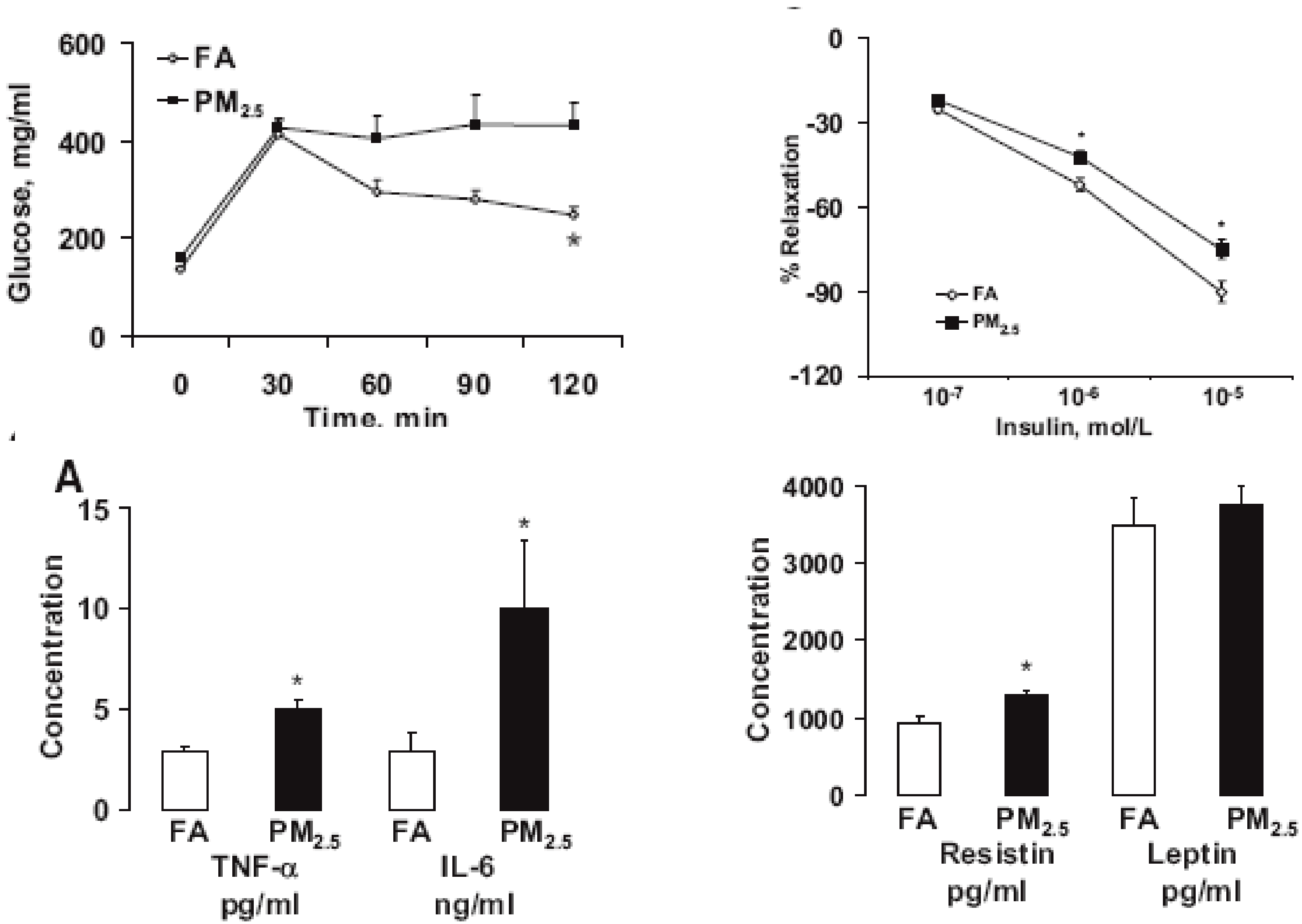
<u>In Women</u>

OR = 1.04 per 1 ppb NO_2

↑ IQR (4 ppb) NO_2 = ↑ 17% DM

J Occup Environ Med 2008; 50: 32

Ambient Air Pollution Exaggerates Adipose Inflammation and Insulin Resistance in a Mouse Model of Diet-Induced Obesity



Circulation 2009; 119:538-46

Coarse-CAP Status

- Construction of Harvard 2-stage coarse concentrator
- Construction with Jack Harkema (MSU) of AIRCARE-2 and installation of concentrator and exposure chamber
- Experimental updates and IRB/University approvals
- Modifications to exposure site locations
- Oct 2010 – Completion of site modifications for electrical powering of AIRCARE-2 facility at Dexter
- Oct 2010 – Study protocols commence at Dexter

Coarse-CAP

Specific Aim 3

To elucidate the coarse CAP constituents and sources responsible for the CV responses.

- **Detailed assessment of the differences in coarse PM composition and sources between the experimental sites.**

- **Correlate CAP composition with CV outcomes for insights into constituents and sources responsible for triggering biological CV responses.**

Coarse-CAP

Coarse PM characterization:

Continuous PM by TEOM and TSI APS.

Teflon filters: gravimetric total mass.

Inductively coupled plasma-mass spectrometry (ICP-MS): trace elements (e.g., Fe, Ni, Zn, Cu)

Ion chromatography: sulfate, nitrate, chloride, potassium, sodium and ammonium.

Thermal-optical-transmission analysis: total organic and elemental carbon.

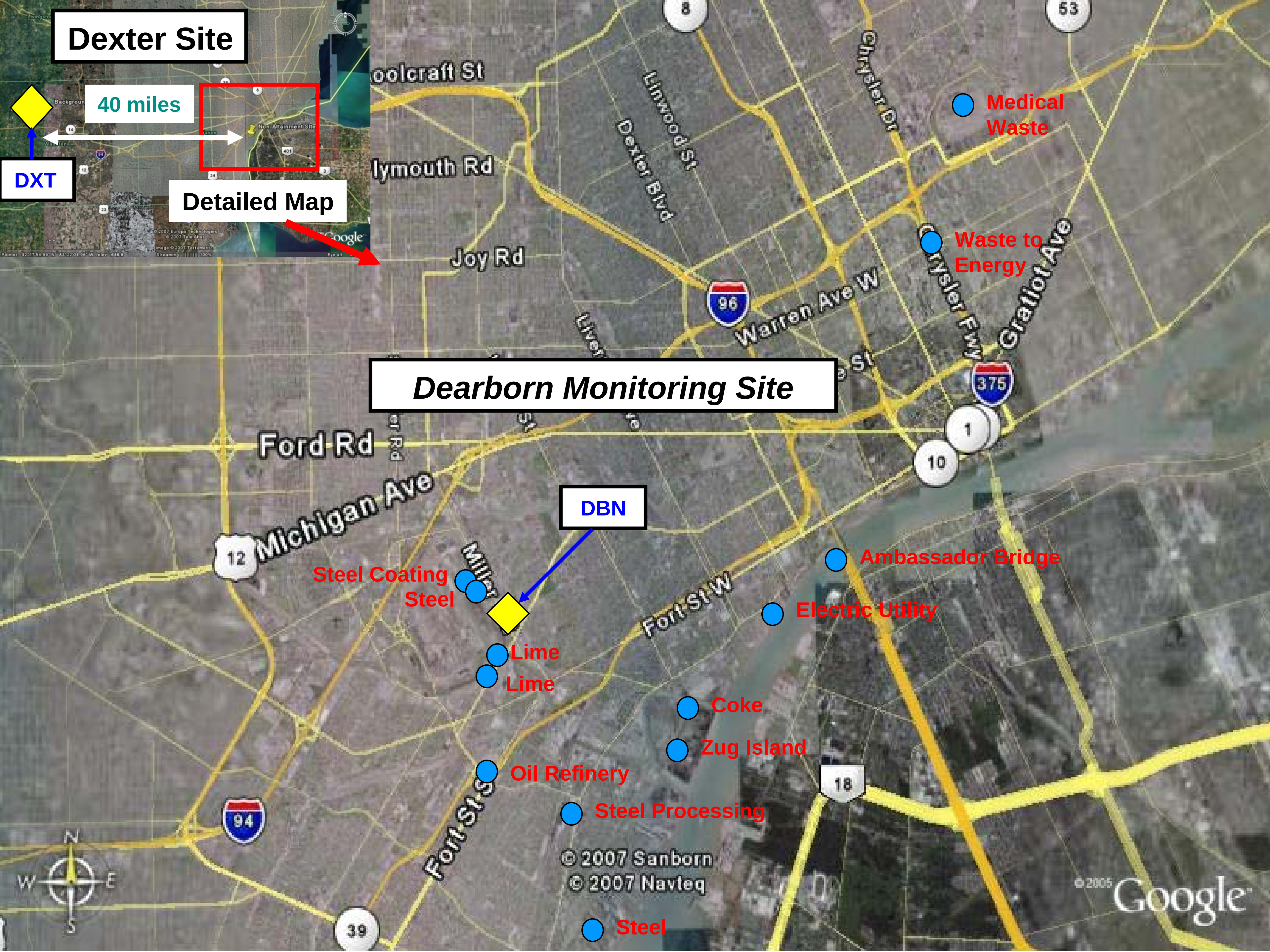
Biological: Endotoxin (LAL)

Source Apportionment:

PM will be quantified and categorized based on the chemical composition

Multivariate receptor modeling methods, Positive Matrix Factorization (PMF)

Associations between the health outcomes and the individual pollutants and CAP components as well as their likely sources


Dexter Site
40 miles
DXT
Detailed Map
Dearborn Monitoring Site
DBN
Medical Waste
Waste to Energy
Ambassador Bridge
Electric Utility
Steel Coating
Steel
Lime
Lime
Coke
Zug Island
Oil Refinery
Steel Processing
Steel
Woolcraft St
Plymouth Rd
Joy Rd
Ford Rd
Michigan Ave
Warren Ave W
Fort St W
Fort St S
Linwood St
Dexter Blvd
Chrysler Dr
Chrysler Fwy
Gratiot Ave
Miller
© 2007 Sanborn
© 2007 Navteq
©2005 Google

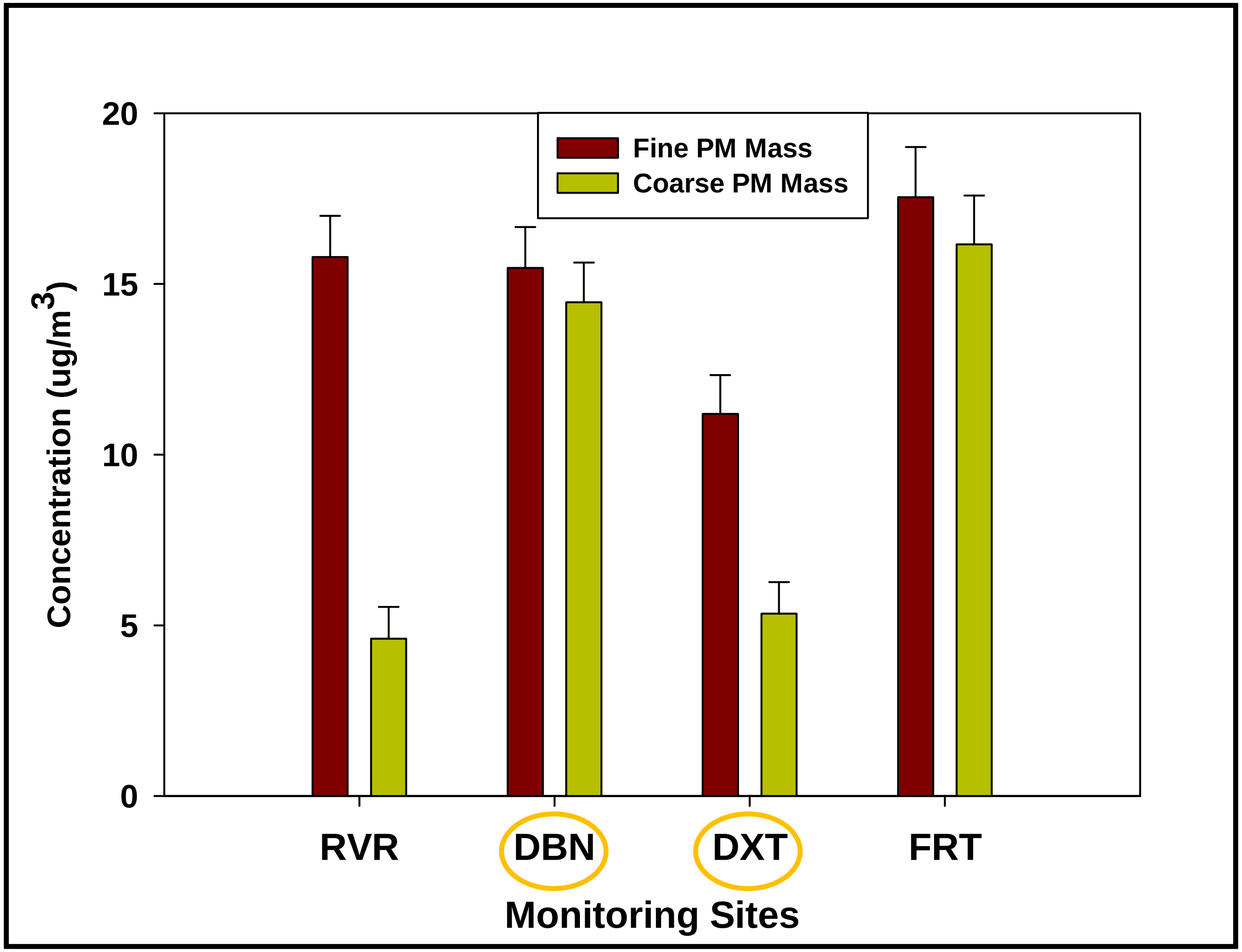
Monitoring Sites

Dexter

Dearborn

Dearborn Site

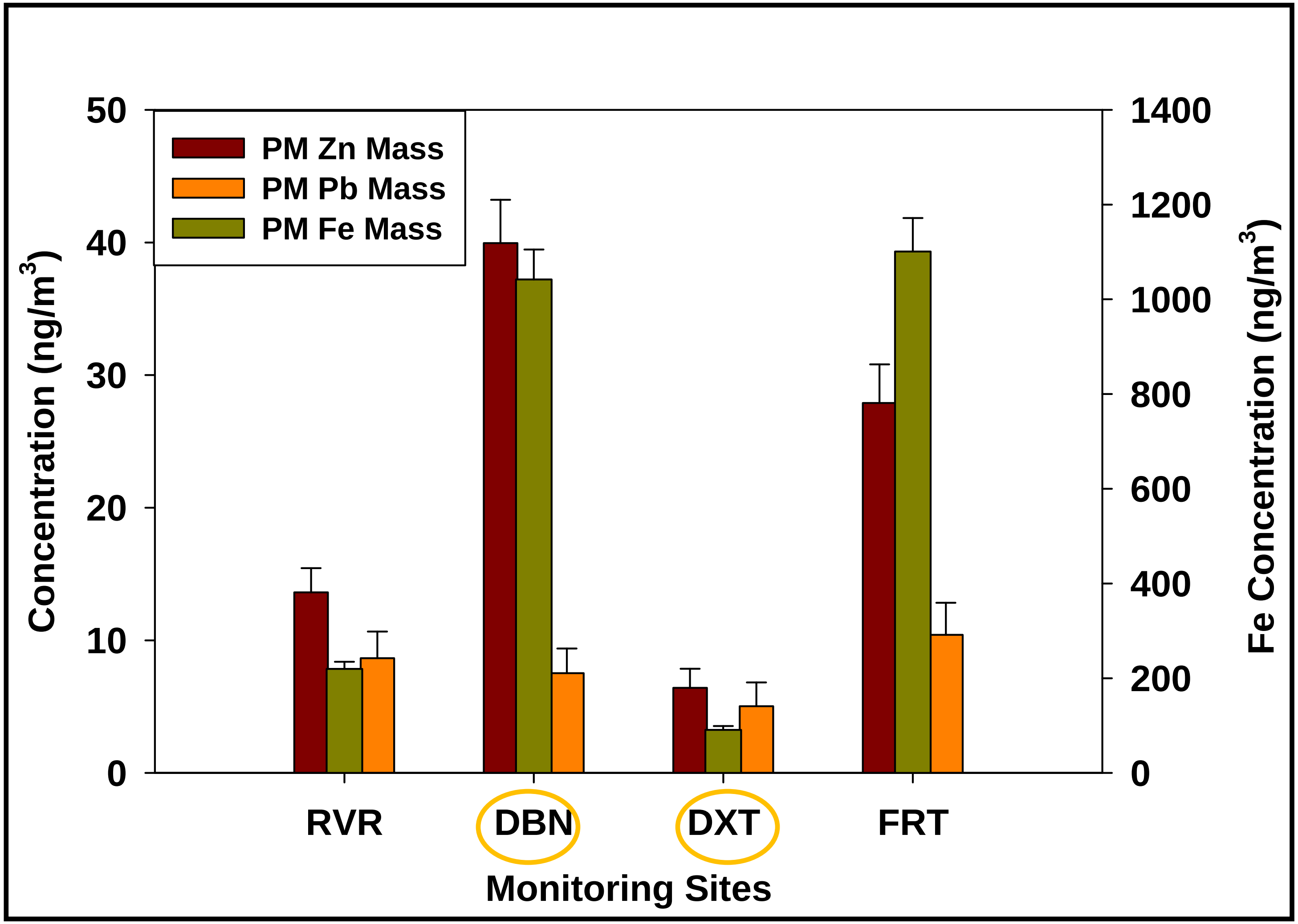
PM Dichot Mass - Spatial Results



USEPA-NERL / Univ-Michigan Collaborative Study (July-August 2007)

Spatial Results

Coarse PM Species (XRF)

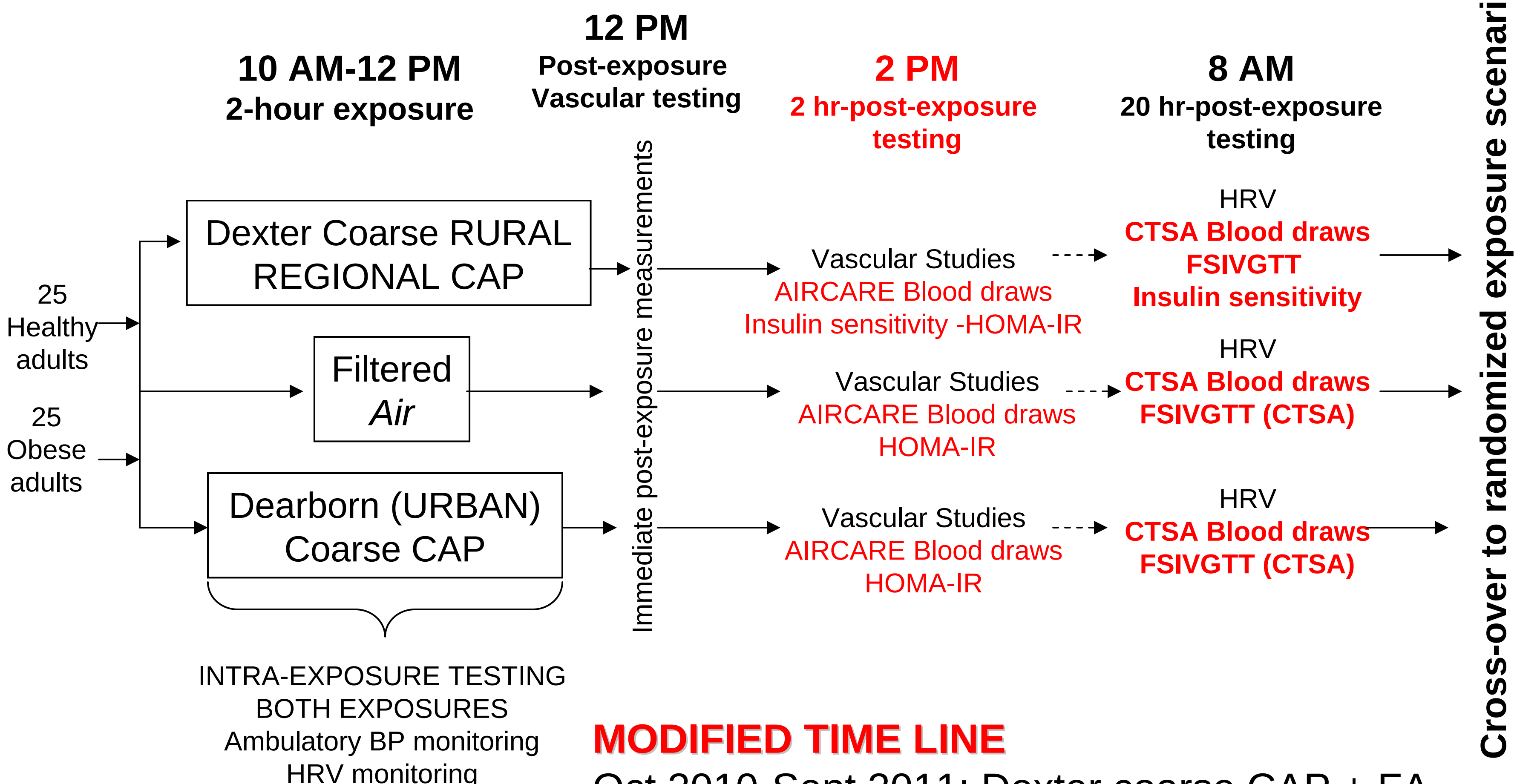


USEPA-NERL / Univ-Michigan Collaborative Study (July-August 2007)

Updated Coarse-CAP Protocol

Coarse CAP = *150-300 µg/m³*

Exposure dose allowed to change along with ambient levels



MODIFIED TIME LINE

Oct 2010-Sept 2011: Dexter coarse CAP + FA

Oct 2011- April 2012: Dearborn coarse CAP

Method	Effect Assessed	Specific Parameter Measured
Ultrasound	Basal vascular tone	Brachial artery diameter
Finometer	Arterial hemodynamics	Cardiac output and Systemic Vascular Resistance
Omron 780	Systemic BP	Brachial BP: Average of 2^{nd} and 3^{rd} arm BP
SphygmoCor	a) Arterial compliance b) Pulse wave analyses	a) Carotid-femoral PWV b) Central aortic BP levels, augmentation index Aix)
Terason Ultrasound	Brachial (conduit) vascular function	Flow-mediated dilatation (endothelial function) Nitroglycerin-mediated dilation (NMD)
EndoPAT	Microvascular endothelial function	Finger tonometer-determined microvascular endothelial-dependent dilatation (RI)
CV outcomes to take place while subject is <u>intra-chamber during 2-hour long exposure</u>		
AMBP	Continuous BP/HR	Rapid systemic arterial BP change during exposure
Holter ECG	Continuous ECG/HRV	Time/frequency domain heart rate variability metrics.

UPDATED BIOMARKERS AND OUTCOMES

Plasma Endotoxin level	**Circulating blood endotoxin concentrations**
CARDIAC and VASCULAR BIOMARKERS	
EPC levels/function (flow cytometry)	**Endothelial progenitor cell vascular repair function**
Cardiac echo – RF tissue Doppler	**Novel cardiac diastolic function parameter**
PRO-INFLAMMATORY AND METABOLIC	
TLR-2 and TLR-4 (flow cytometry) Monocytes $CD^{14+}CD^{16+}$ vs $CD^{14+}CD^{16-}$	**Monocyte Toll-like receptor expression** **Circulating monocyte pro-inflammatory sub-types**
Adipocytokines/cytokines/CBC *Adiponectin, IL-1beta, IL-6, TNF-alpha*	**Adipocyte function and cytokine changes**
HDL function; PON-1 activity *Prevention of LDL oxidation*	**Dysfunctional HDL particles**
Lipoproteins *(NMR lipoprofile)*	**Lipoprotein phenotypes** (LDL-P#; LDL-P size)
HOMA-IR (glucose x insulin/405)	**Metabolic insulin sensitivity**
****FSIVGTT using MinMOD (S_I)**	**Metabolic insulin sensitivity**

Coarse-CAP

- **Principal Investigator:**
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  Co-investigators:
  - J. Timothy Dvonch, Gerald Keeler (School of Public Health, UM)
  - Niko Kaciroti (Biostatistics, UM)
  - Diane R. Gold (Harvard School of Public Health)

- Consultants/collaborators:
  - Bruce Urch, Jeffrey R. Brook, Frances Silverman (GAGE Toronto)
  - Sanjay Rajagopalan (Ohio State) Monocyte biomarkers
  - Marianna Kaplan (UM, Rheumatology) EPC testing
  - Elif Oral (UM, Endocrinology) Metabolic testing
  - Jesus Araujo (USC) HDL function
  - Ted Kolias (UM, Cardiology) Echo diastolic function