Air Pollution Mixtures: Health Effects across Life Stages

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Harvard University
Veterans Administration Boston Hospital
and Yale University

Presentation Outline

- Center Overview (Koutrakis)
- Exposure Assessment (Koutrakis)
- Project 1: Toxicology Study (Koutrakis)
- Projects 2,3 and 4: Cohort Studies (Mittleman)
- Project 5: National Study (Dominici)

Harvard CLARC Objectives

Investigate the acute and chronic effects **across the life course** of short- and long-term exposures to individual pollutants, pollution sources and multi-pollutant mixtures:

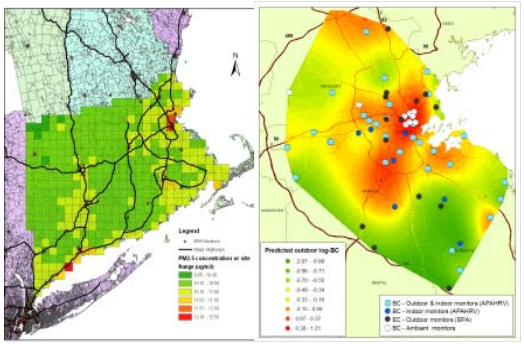
Outcomes:

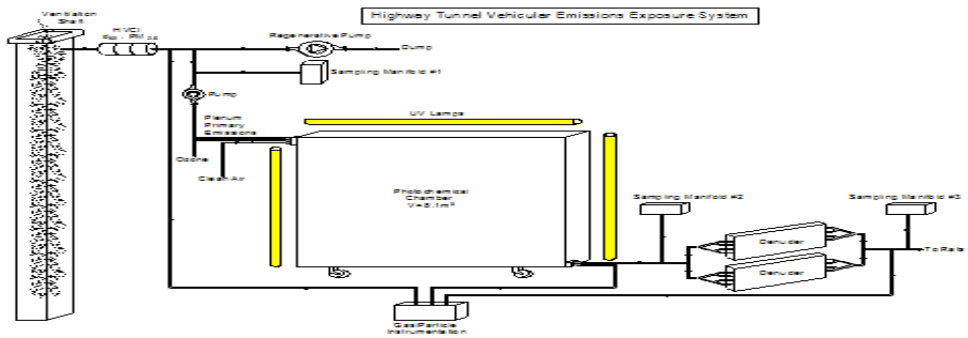
- Cognitive/neuropsychological function
- Cardiovascular/endothelial function
- Inflammation
- Birth weight/growth
- CVD-related hospitalization/mortality

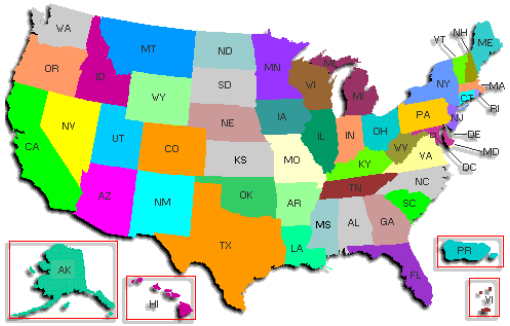
Five Research Projects

- Animal Toxicological Study (Godleski)
- Three New England Cohorts:
  - VIVA/Birth Cohort (Gold)
  - Framingham/Adults (Mittleman)
  - NAS/Elderly Individuals (Schwartz)
- National Study (Domici)

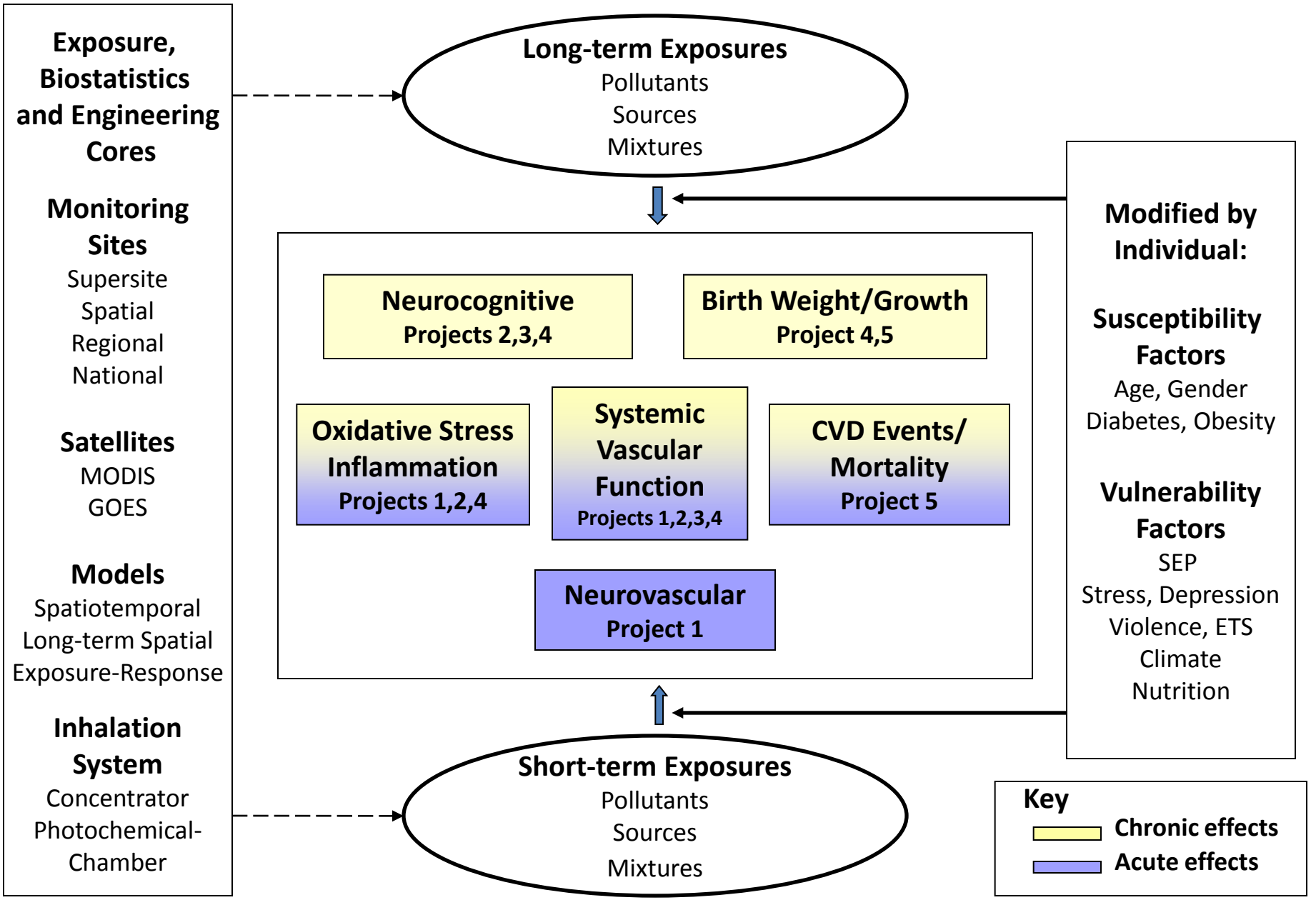
Figure 1: $PM_{2.5}$ levels in the Region (left) and BC levels in the Greater Boston area (right).







Center Framework



Exposure Approach

- Similar Exposure Metrics for all human studies
  - Pollutant Concentrations (Monitoring Sites)
  - Sources Contributions (Receptor Models)
  - Pollutant Mixtures (Cluster Analysis)
- Monitoring Data
  - Boston Harvard Supersite (since late 90s)
  - 40 New England Spatial Sites (years 2-4)
  - Regional and National PM and Speciation Sites

Exposure Approach

- Remote Sensing Data for New England
  - MODIS (10x10, 3x3 and 1x1 km resolution)
  - GOES (4x4 km)
  - New Calibration Approach
- Spatial Models
  - Boston Carbon Model (Ready)
  - PM Prediction Model for days with no satellite data
  - Spatial Model based on Satellite and Land Use Data

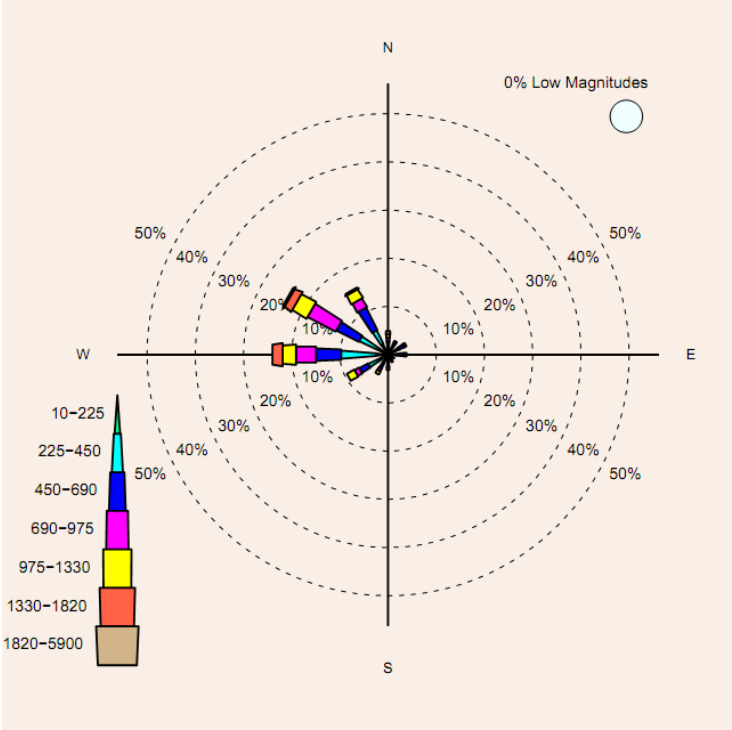
Pollutant Mixtures

- Categorize the days of observation based on their daily gas and particle concentration profiles using cluster analysis (Groups of Days Not Species)
  - Example: Boston Superiste data (2004-09)
- For each group (cluster) we will examine:
  - Chemical and physical characteristics
  - Weather patterns

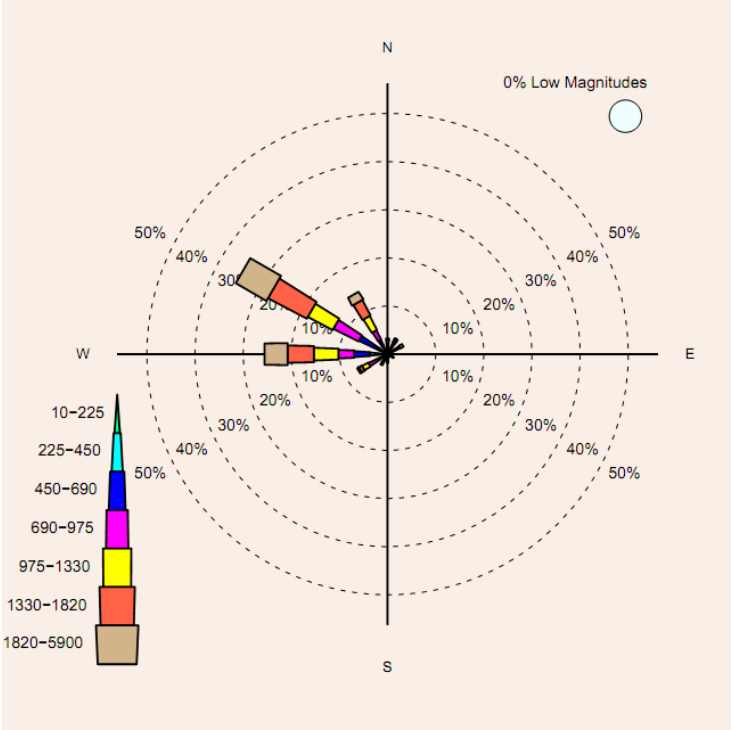
Cluster 2 – 366 Days

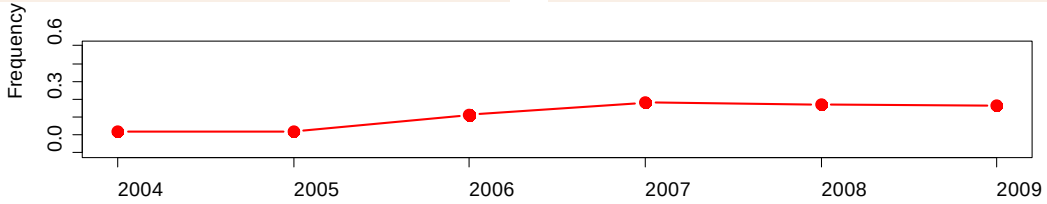
PN (#)	0.9
O3	1.21
NO	0.84
NO2	1.07
BC	1.07
Sulfate	0.88
Ni	0.69
V	0.63
Fe	1.33
Zn	1.13
K	1.16
Si	1.7
Ca	1.4

24h Backwards Trajectory



48h Backwards Trajectory



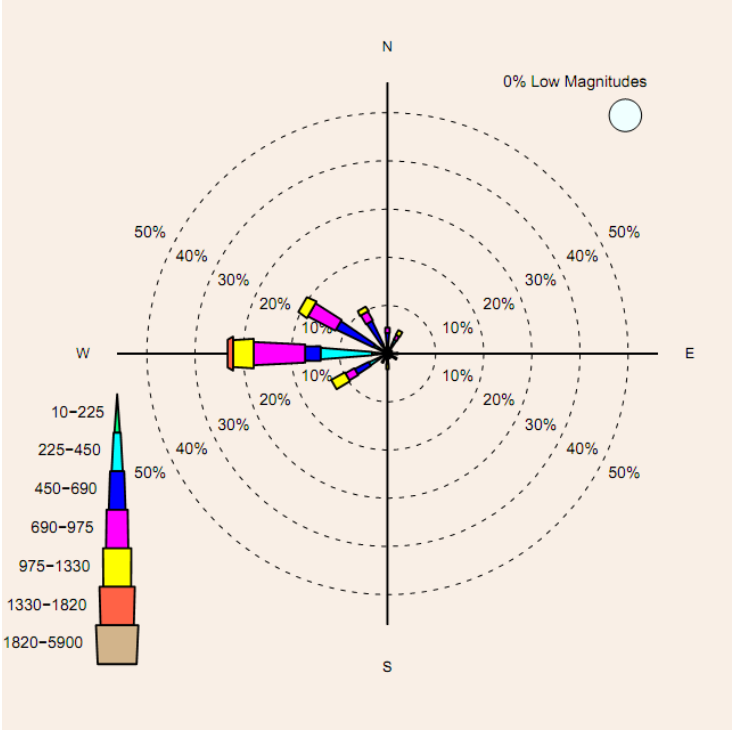


Temp (C)	RH	Wind Speed (m/s)	Water Vapor Pressure	Boundary Layer (m)
13.7	59.4	4.4	10.5	476.6

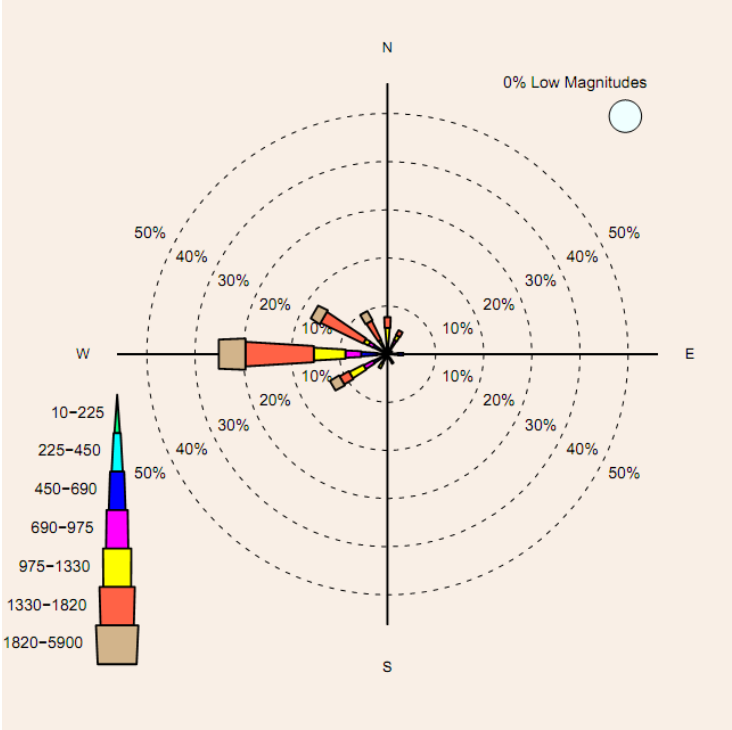
Cluster 3 – 107 Days

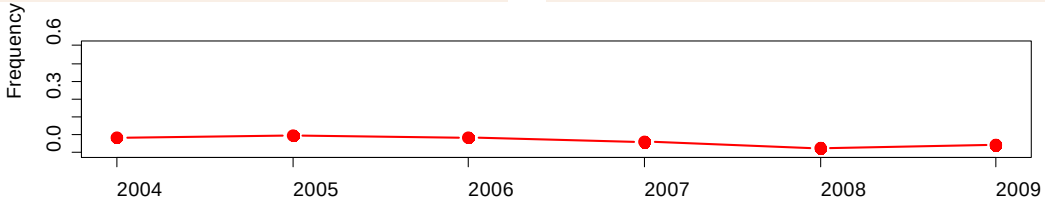
PN (#)	0.85
O3	0.25
NO	1.83
NO2	0.93
BC	1.14
Sulfate	0.81
Ni	1.44
V	1.56
Fe	1.07
Zn	1.35
K	1.04
Si	0.8
Ca	0.85

24h Backwards Trajectory



48h Backwards Trajectory



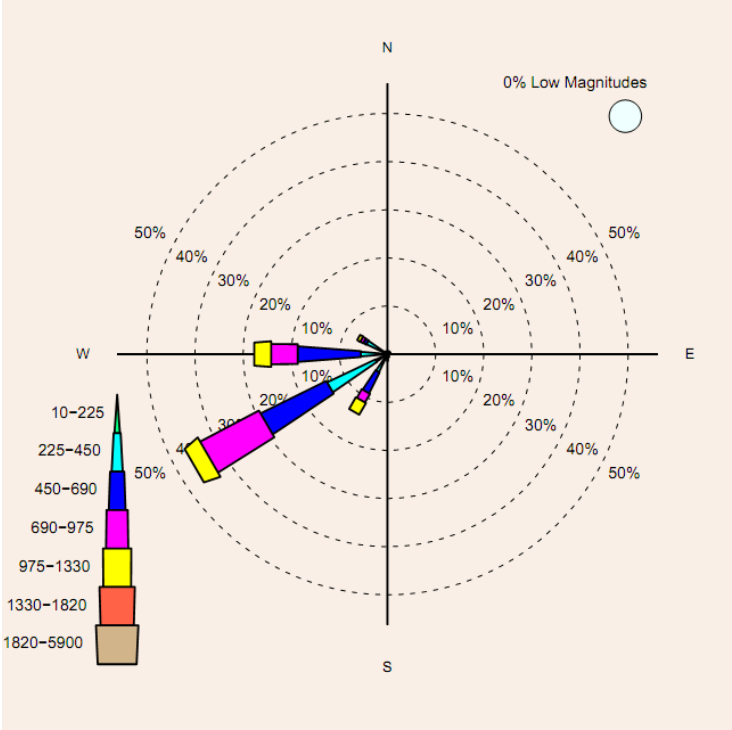


Temp (C)	RH	Wind Speed (m/s)	Water Vapor Pressure	Boundary Layer (m)
5.2	69.5	3.1	6.8	303.5

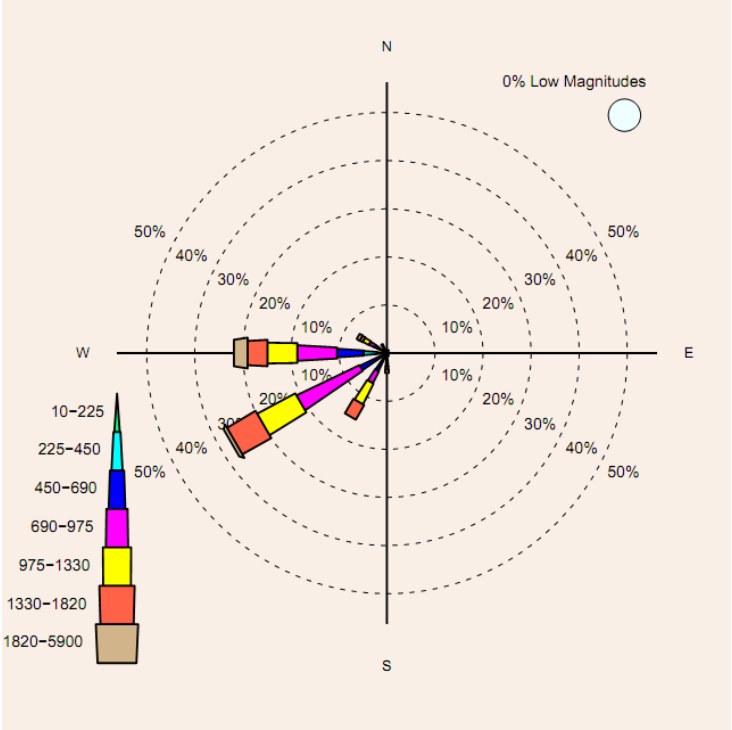
Cluster 4 – 159 Days

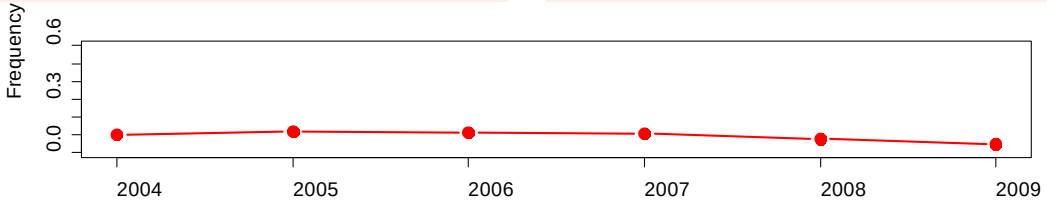
PN (#)	0.25
O3	0.71
NO	0.24
NO2	0.44
BC	0.68
Sulfate	1.29
Ni	0.45
V	0.63
Fe	0.6
Zn	0.48
K	0.6
Si	0.87
Ca	0.62

24h Backwards Trajectory



48h Backwards Trajectory



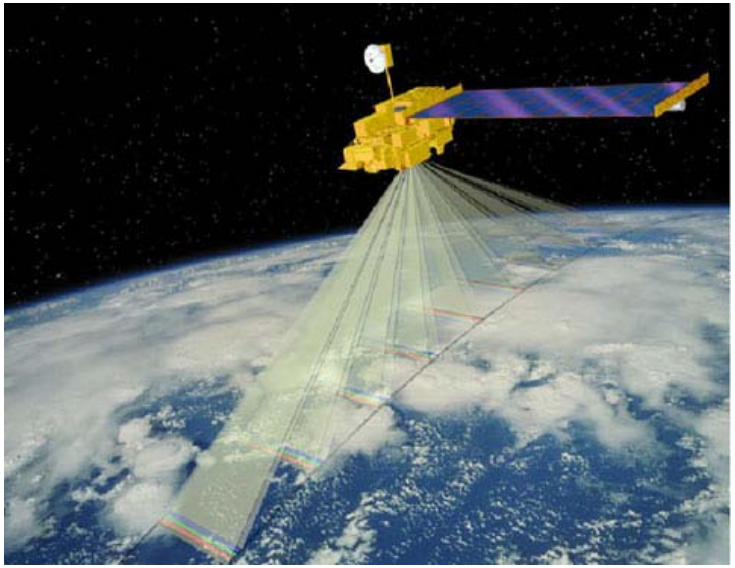


Temp (C)	RH	Wind Speed (m/s)	Water Vapor Pressure	Boundary Layer (m)
22.9	70.0	4.5	19.6	418.2

Future Directions

- Cluster data from multiple locations to identify characteristic profiles
  - Identify groups of cities with similar pollutant profiles (cross sectional studies)
- Use cluster membership as an effect modifier in health effects analysis

Use satellite data to assess acute and chronic exposures to $PM_{2.5}$ in New England



A Novel Calibration Approach of AOD Data to Predict $PM_{2.5}$ Concentrations

Daily Calibration Method of AOD

- There is an inherent day-to-day variability in the AOD-$PM_{2.5}$ relationship which depends on time varying parameters such as particle optical properties, concentration vertical mixing and ground surface reflectance among others
- A daily calibration technique is applied to AOD data to accurately predict $PM_{2.5}$ concentrations within the study region
- This method requires data from multiple ground sites within the study region

Statistical Approach

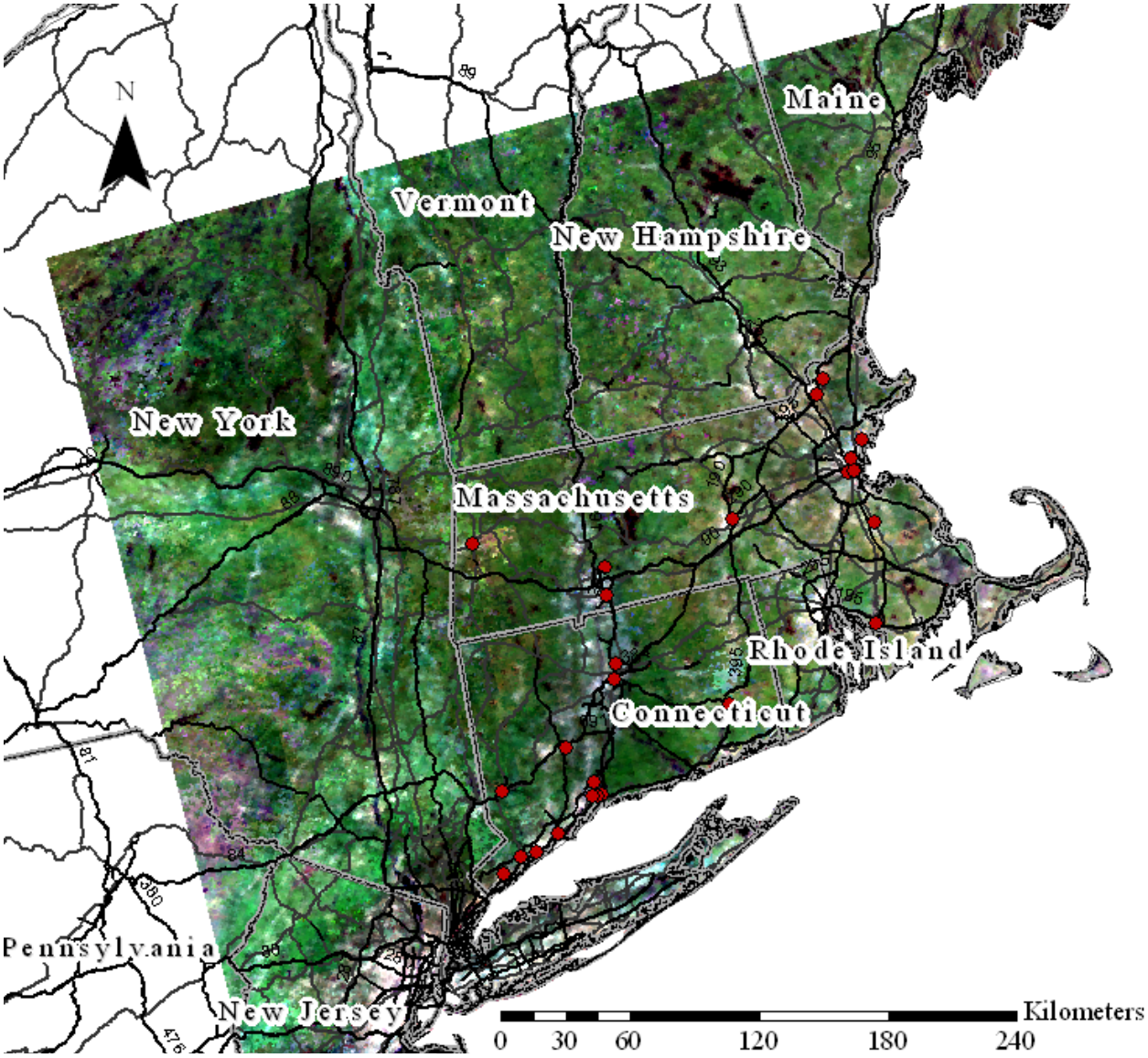
A mixed effects model with random intercepts and slopes is used:

$$PM_{ij} = (\alpha + u_j) + (\beta_1 + v_j) \times AOD_{ij} + w \times Site_i + \varepsilon_{ij}$$

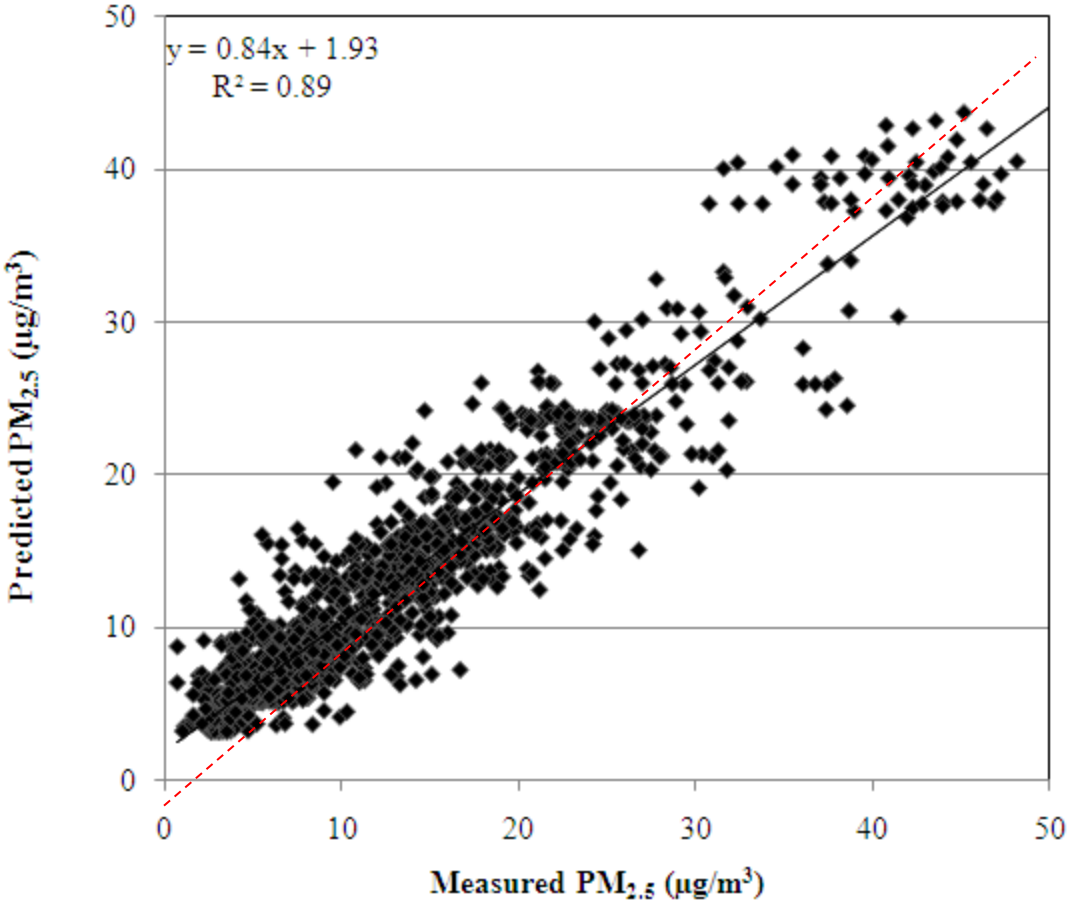
$$(u_j\ v_j) \sim [(0\ 0), \Sigma_\beta]$$

where PM_{ij} is the $PM_{2.5}$ concentration at a spatial site i on a day j; AOD_{ij} is the AOD value in the grid cell corresponding to site i on a day j; a and u_j are the fixed and random intercepts, respectively; β_1 and v_j are the fixed and random slopes, respectively; w is the random slope of site i; and Σ_β is the variance-covariance matrix for the random effects.

$PM_{2.5}$ sites within the study region



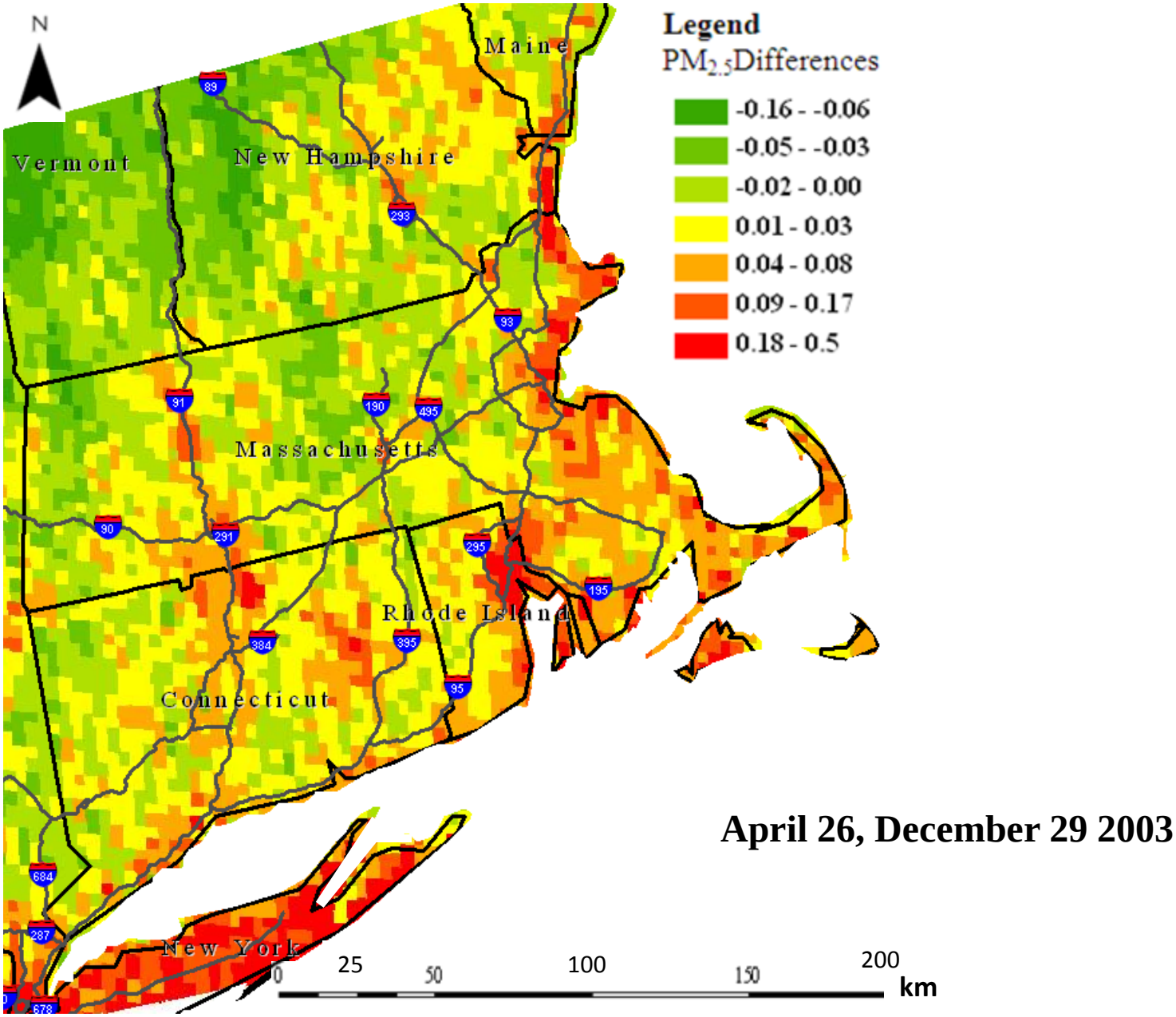
Results (GOES AOD Data)



Model performance as assessed by 576 measured and predicted daily $PM_{2.5}$ concentrations

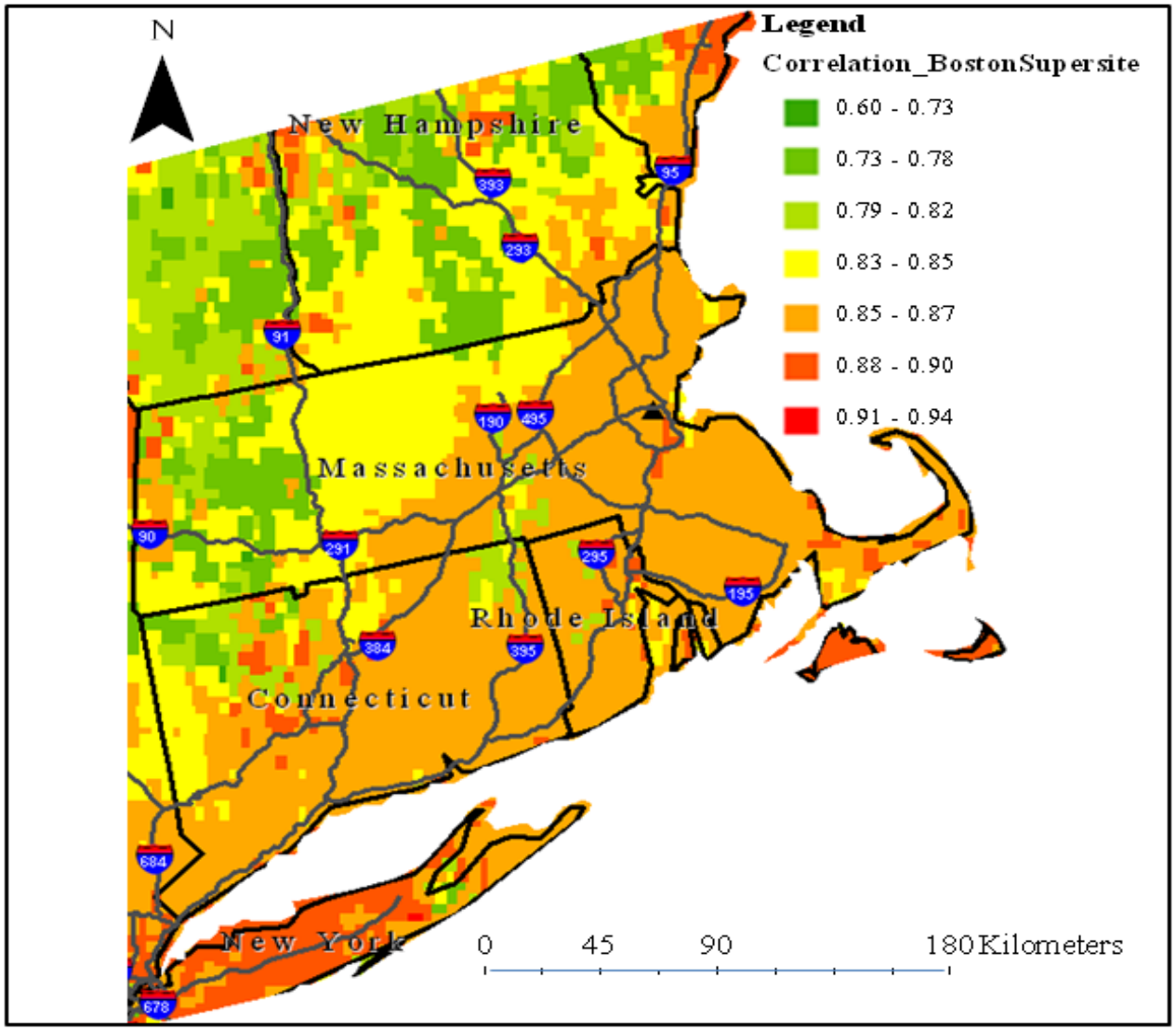
Note: The solid line represents the regression line, and the dashed line displays the 1:1 line.

Spatial variability in $PM_{2.5}$ levels



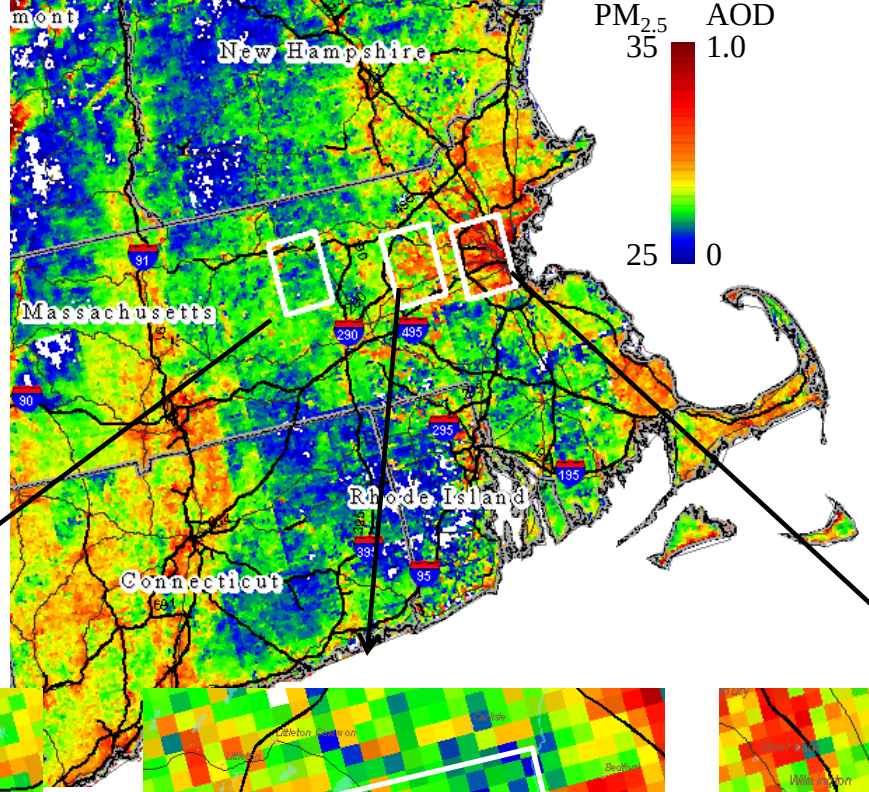
April 26, December 29 2003

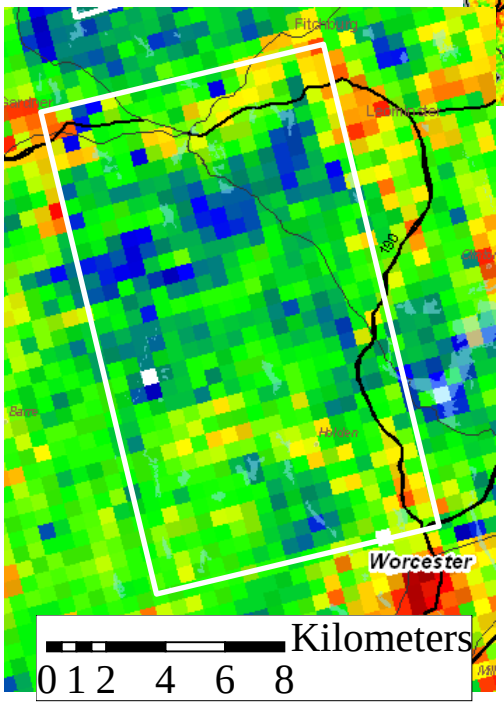
Can Boston Supersite measurements be used to capture the temporal variability of exposures for individuals residing in the Region?

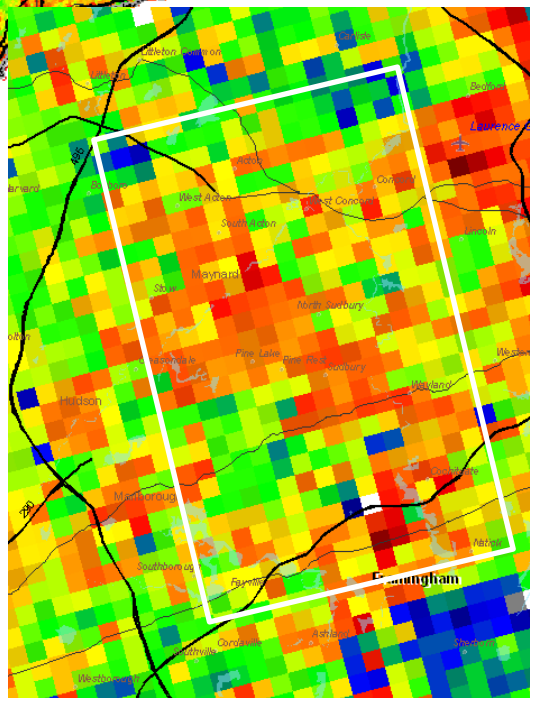


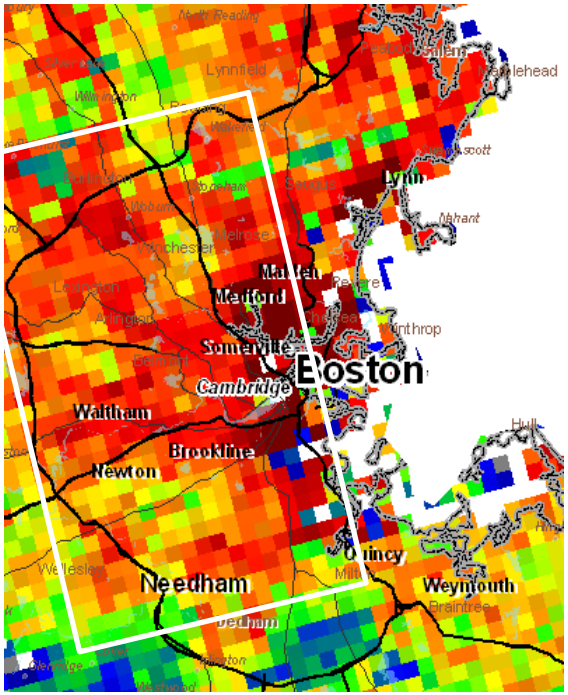
1 km MODIS High Resolution

June 25, 2003



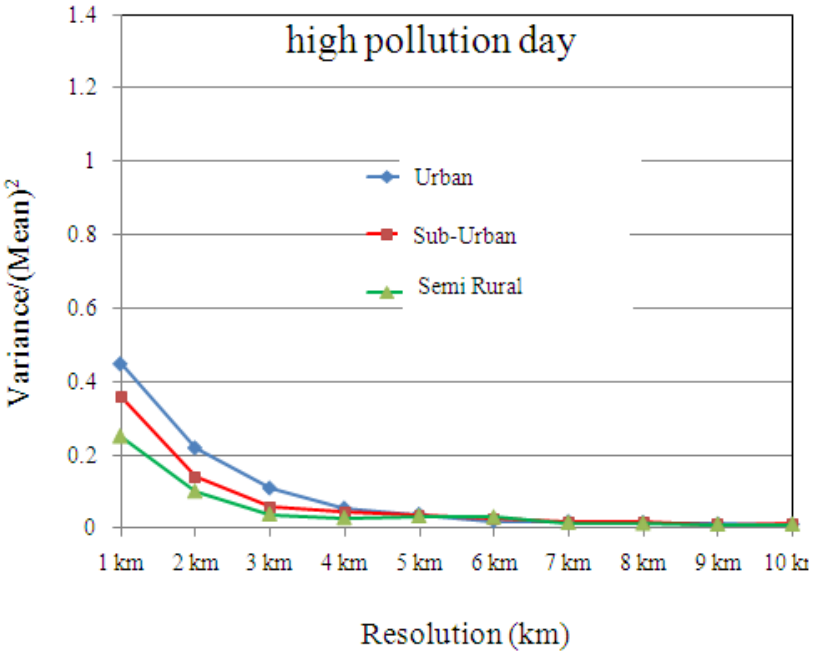






Exposure Spatial Patterns via High Resolution Satellite Imaging

A. Chudnovsky, A. Kostinski, A. Lyapustin, P. Koutrakis. To be submitted to EHP



The variability is characterized here by the scaled variance: Variance normalized by the square of the mean

High resolution data are needed for models that will combine AOD and Land Use data

Project 1: Animal Toxicological Study

- Investigate the toxicity of pollutant mixtures in rats
- Examine the effects of individual components, combinations of components, formation processes or source types
- Assess toxicity by examining changes in: *in vivo* oxidant response, blood pressure, blood flow, inflammation and neurovascular reactivity

Traffic Tunnel

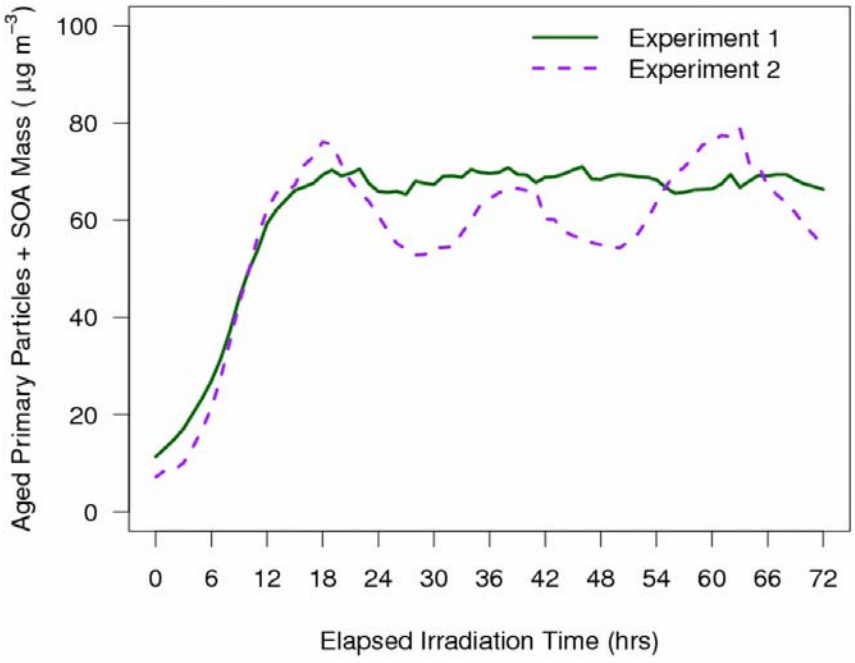
- Moderate-to-heavy traffic density
- 4,000 vehicles (rush hr period)$^{-1}$
- Mostly delivery trucks
- Daily PM_{10}: 350 $\mu g\ m^{-3}$
- Ventilation rate adjusted in response to tunnel CO and NO_x

Photochemical Chamber

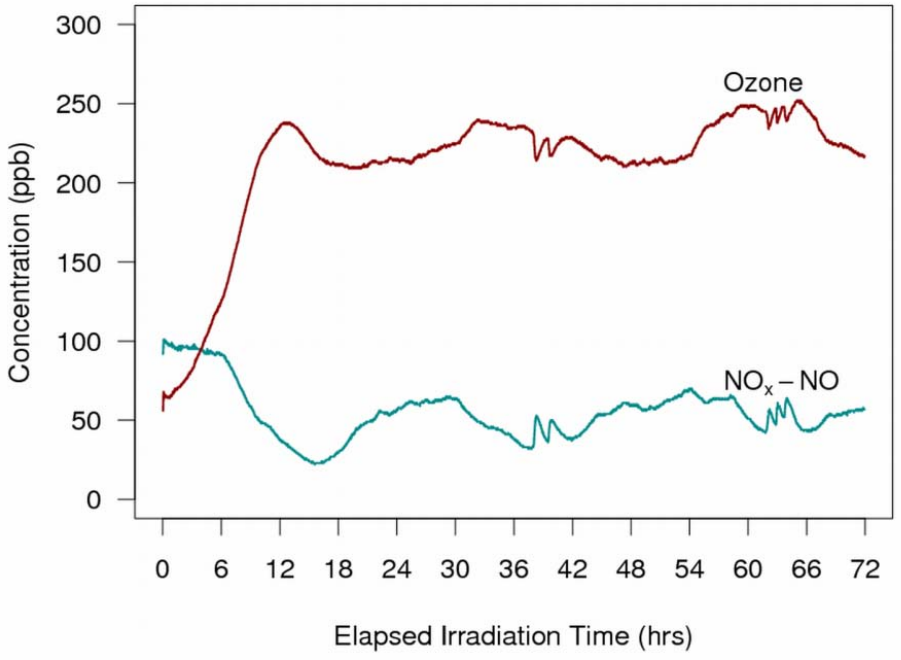
Generate exposures to: Primary, Secondary and Primary plus Secondary traffic exposures

Formation of Secondary Organic Aerosols

Multi-day stability of SOA



Multi-day O_3 and NO_2



Stable and reproducible exposures

Diastolic Blood Pressure (mmHg) ± SE

Experiment	Diastolic BP in Filtered air Control Group	Diastolic BP in Traffic Particles Exposure Group	p-value
Filtered Air	72.6 ± 3.2	77.3 ± 2.5	NS
Primary Particles	72.1 ± 2.9	89.0 ± 4.8	0.02
Filtered Air	65.8 ± 4.1	64.5 ± 2.5	NS
Secondary Particles	63.7 ± 4.9	70.0 ± 2.5	0.03
Primary & Secondary	66.8 ± 4.8	80.7 ± 2.1	0.02

In Rats over 6 hr of the first Two Days of Exposures

THANKS

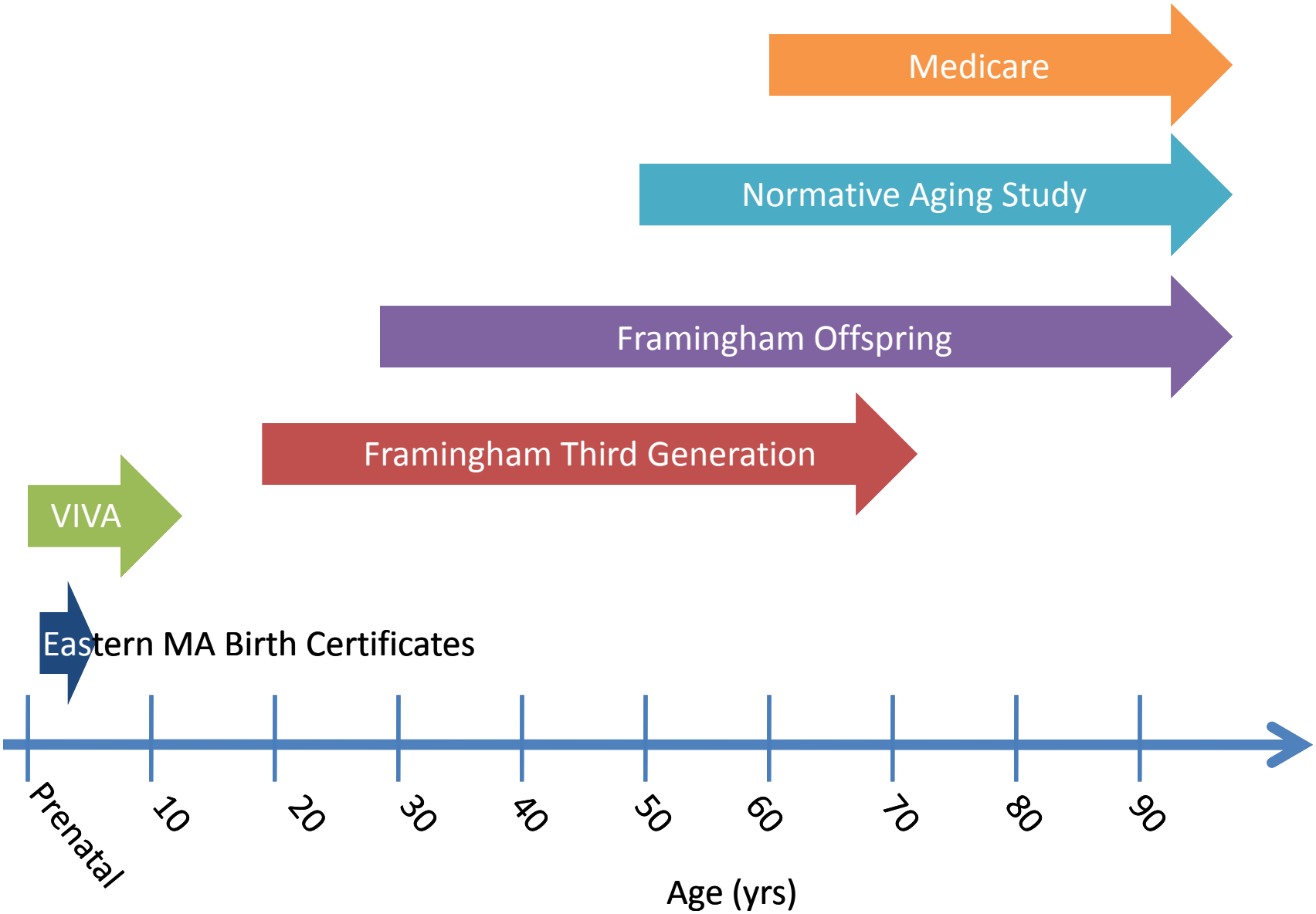
Air pollution Mixtures Across Life Stages: Cohort Studies Projects 2,3, and 4

Murray Mittleman

Diane Gold

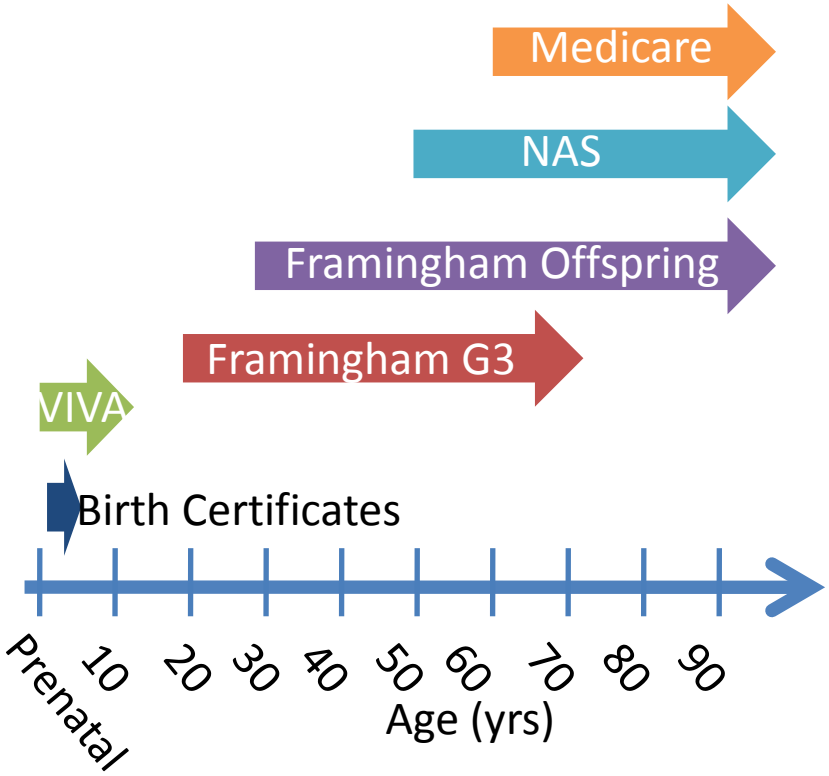
Joel Schwartz

Health Effects Across Life Stages



Health Effects Across Life Stages

Cohort



Health Outcomes

Birth Weight & Growth	Neuro-cog	Oxidative Stress	Vascular Fxn	Hospital Admission	Death
				X	X
	X	X	X		
	X		X		
	X		X		
X	X	X	X		
X					

Project 2: Normative Aging Study Aims

1. Examine associations between exposures to individual **pollutants, sources, and mixtures** on:
   a) Cognitive and neuropsychological function
      - Mini Mental State Exam (MMSE), CERAD, WAIS-R and NES2
   b) Vascular and endothelial function
      - Pulse wave analysis and blood pressure
   c) Inflammation, endothelial function, and oxidative stress
      - Repeated measurements of serum biomarkers
   d) Telomere length
2. Evaluate whether measures of susceptibility and vulnerability modify these effects
3. Investigate dose-response relationships using flexible modeling techniques

Normative Aging Study (NAS)

- Recruited 2,280 men living in the Boston metropolitan area ages 21-80 beginning in 1963
- Participants visit the center every 3-5 years
- 800+ participating since 1995
- Visits include
  - Physical examination
  - Medical History
  - Blood draw
  - Cognitive testing
  - Self-administered questionnaires

Recent Findings
BC and Cognitive Function

Effect per doubling in BC concentration

	Model 1: Age Adjusted	Model 2: Age and Education Adjusted	Model 3: Multivariable-adjusted[a]
Low MMSE Score (≤25)			
OR (95% CI)	1.4 (1.1, 1.6)	1.3 (1.0, 1.5)	1.3 (1.1, 1.6)
Global Analysis			
Estimate (95% CI)	-0.073 (-0.122, -0.023)	-0.052 (-0.100, -0.004)	-0.054 (-0.103, -0.006)

Abbreviations: confidence interval, CI; odds ratio, OR; Mini-Mental State Examination, MMSE

[a]Adjusted for age, education, first language, computer experience, physical activity, alcohol consumption, diabetes, dark fish consumption, percent of residential census tract that is non-white, percent of residential census tract adults with a college degree, indicator for first cognitive assessment, and indicator for part-time resident

Power et al. EHP 2011

Project 3: Framingham Offspring and Third Generation Cohorts

Aims

Examine associations between exposures to individual **pollutants, sources, and mixtures** on:

1. **Cognitive function among** middle-aged **and older adults**
   - MMSE,CERAD, Stroop
2. **Vascular and endothelial function**
   - FMD, PAT, blood pressure
3. Modifying effects of **measures of susceptibility, pollutants, sources, and mixtures**

Framingham Cohorts

Offspring

- 5,124 adult children (and spouses) of the Original Cohort
- Examined every 4-8 years beginning in 1971
- Our analyses start with Exam 6 (1995-1998)
- Routine physical exam, anthropometry, and risk factor assessment

Third Generation

- 4095 participants recruited 2002-2005
- Children of Offspring participants
- Exam 2 finished December 2010
- Addresses currently being processed for geocoding

Offspring and Third Generation Characteristics

	Offspring Cohort, Exam 6+ (1995-1998)		Third Generation Cohort (2002–2005)	
	Men (*n* = 1,657)	Women (*n* = 1,875)	Men (*n* = 1,912)	Women (*n* = 2,182)
Age (years)	59 (10)	59 (10)	40 (9)	40 (9)
Current smoking (%)	15	16	19	16
Systolic BP (mmHg)	130 (17)	127 (20)	121 (13)	113 (14)
Diastolic BP (mmHg)	77 (9)	74 (9)	78 (9)	73 (9)
Antihypertensive medication (%)	31	26	10	7
Hypertension (%)	35	29	22	12
Body mass index (kg/m^2)	28.5 (4.4)	27.4 (5.7)	27.9 (4.7)	26.0 (6.1)
Blood glucose (mg/dl)	108 (28)	101 (27)	99 (18)	92 (18)
Lipid-lowering medication (%)	16	10	11	4

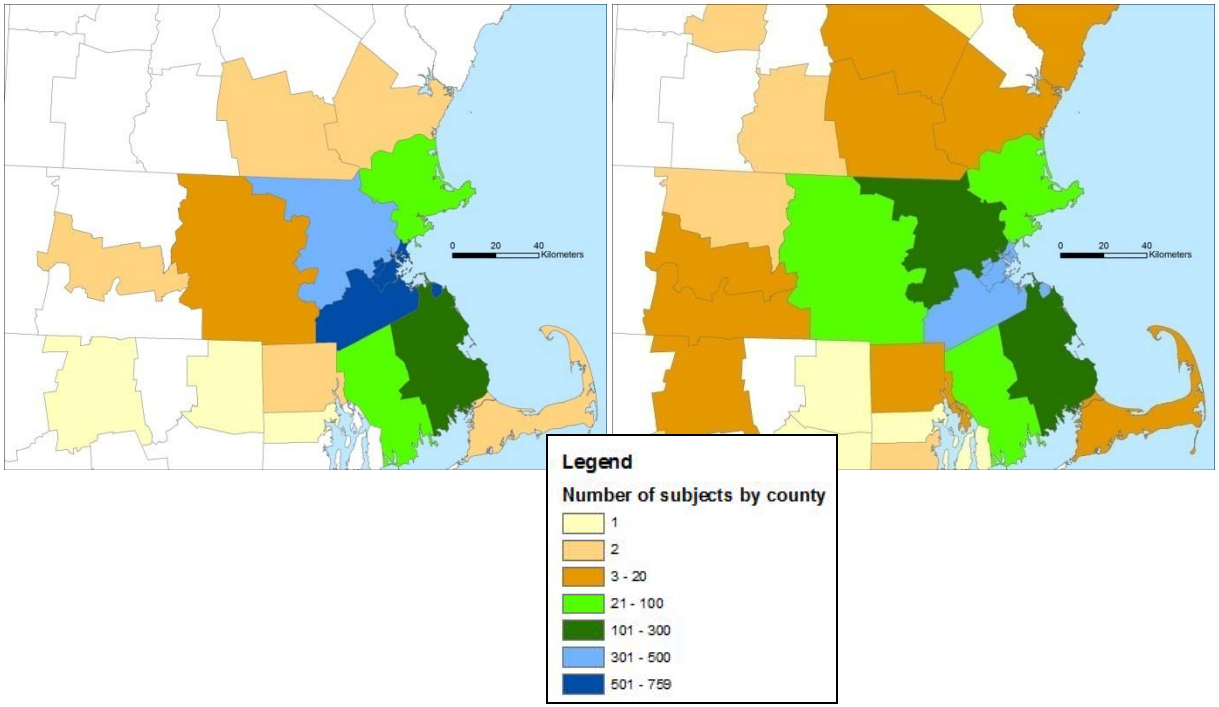
Project 4: Project Viva
Aims

- To determine the health effects of prenatal and postnatal exposures to individual **pollutants, sources, and pollutant mixtures** on:
  - Somatic growth
  - Cardiovascular risk (blood pressure, exercise tolerance)
  - Cognition
- Outcomes are measured longitudinally from birth up through age 7-9 in 1300 children living throughout greater Boston, whose mothers were recruited in the first trimester of pregnancy from 1999 through 2002
- Viva has measures of biomarkers that may be in pathways related to growth, blood pressure or cognition (e.g, cytokines, inflammatory markers, leptin, adiponectin; cord blood methylation)
- Viva has measures of social support, stress, SES and other factors that may modify pollutant effects

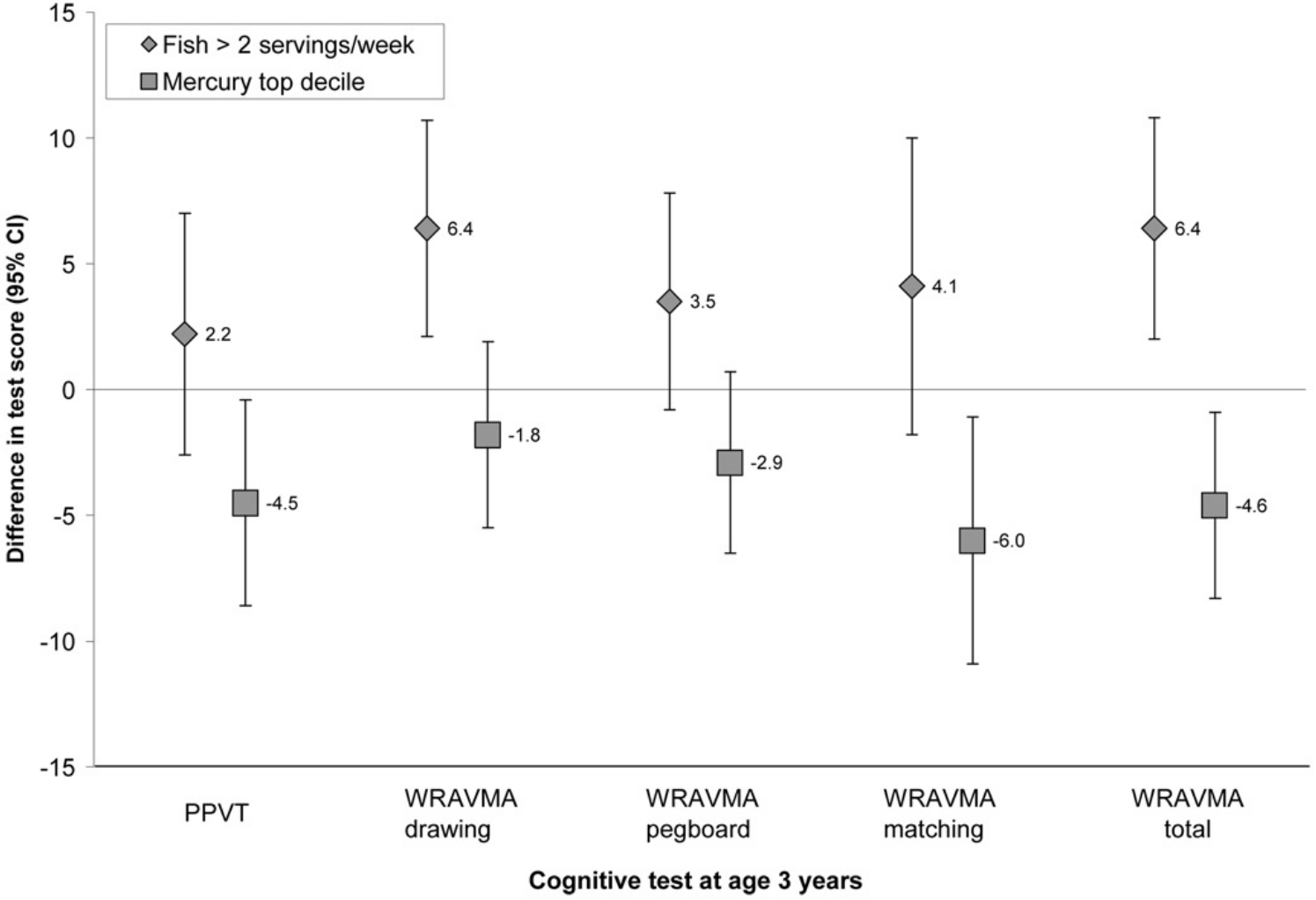
Using geocoded enrollment (pregnancy) addresses, in preliminary analyses adjusting for potential confounders, closer distance to roadway and increased urbanness of residence was associated with:

-reduced fetal growth
-greater infant weight gain,
-increased infant obesity at 6 months of age
-increased bronchitis, croup, and eczema by age 3
-reduced FEV_1 at age 7
-increased asthma with wheeze by age 7

Distribution of Project Viva children at enrollment and in 2010

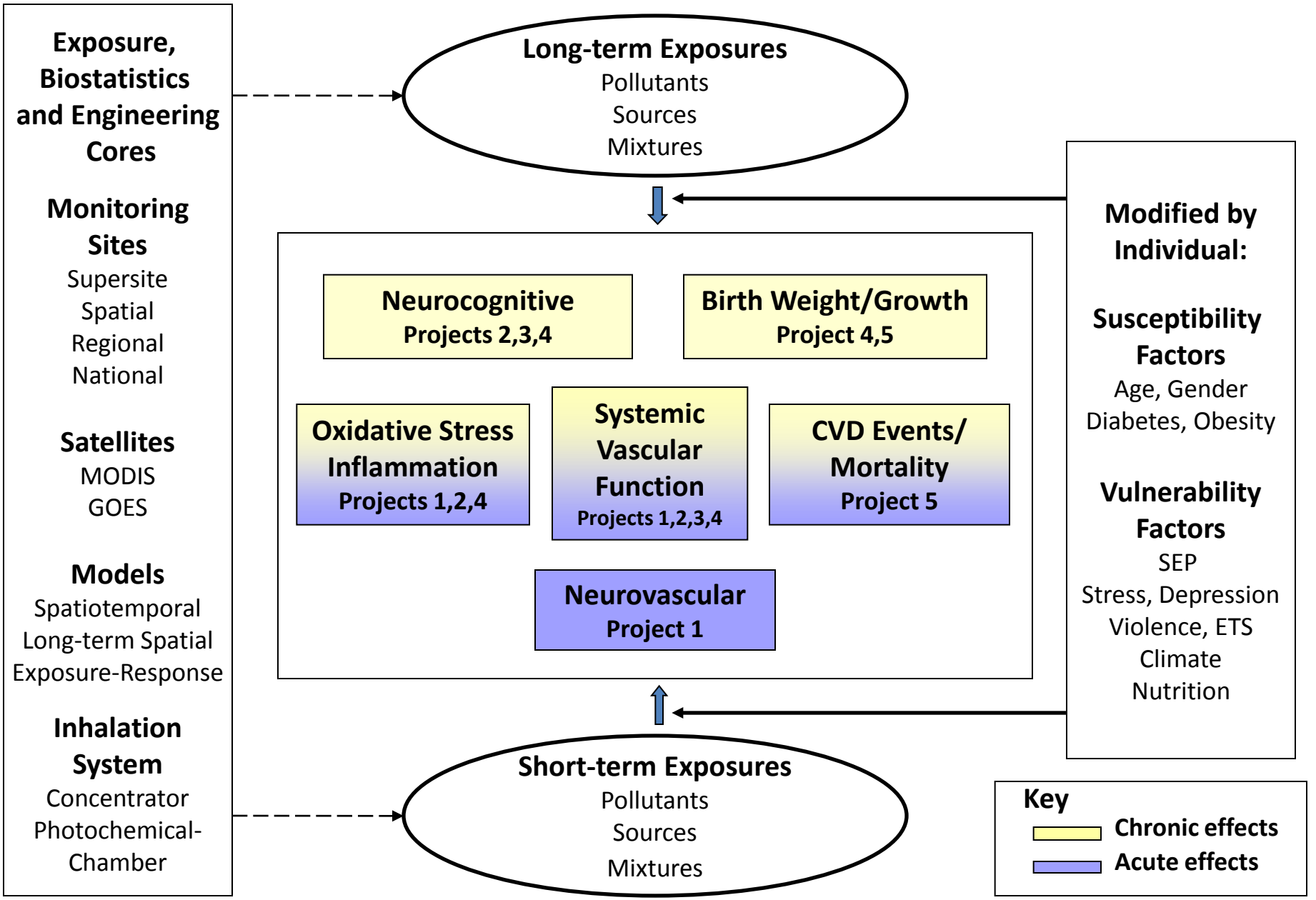


Project Viva: Known predictors of impaired cognition: Maternal fish consumption in pregnancy improves cognitive function, whereas mercury exposure reduces cognitive function at age 8



Oken et al. Am J Epidemiol 2008

Center Framework



A National Study to Assess Susceptibility, Vulnerability, and Effect Modification of Air Pollution Health Risks

Francesca Dominici, Joel Schwartz, Michelle Bell, Antonella Zanobetti

Goals

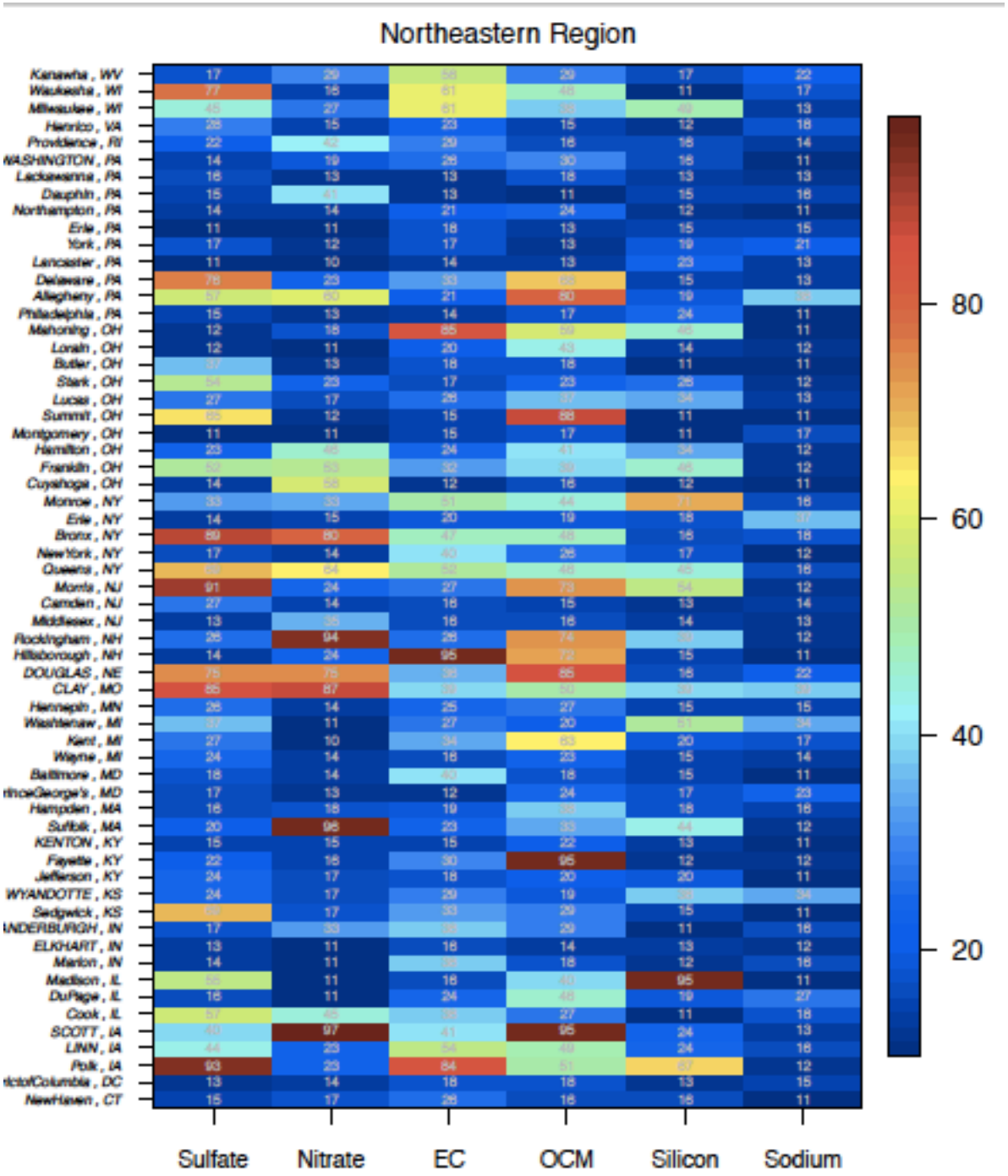
- Conduct national studies aimed at identifying individual and area-level factors that explain the geographical and temporal heterogeneity of the air pollution health risks across the US.

Aims

- In Aims 1 and 2, we will conduct national studies of short- and long-term exposures of individual pollutants, sources, and mixtures.
- In Aim 3, we will establish a cohort of 2.3 million Medicare enrollees residing in the same New England region and following them prospectively for cause-specific hospital admissions and mortality for from 2000 to 2014.
- We will also complement the Viva study by studying on all live births in Eastern Massachusetts geo-coded to the exact address.

Posterior inclusion probabilities by component
and by county in the Northeast US

CVD admissions for the period 1999 to 2008 linked by county to chemical component data from the STN



$PM_{2.5}$ chemical components and mortality rates: 1999-2008