SCHOOL OF PUBLIC HEALTH · UNIVERSITY of WASHINGTON

excellent science, shared passion, enduring impact

Investigating Health Effects of Ambient Air Pollution: Focus on Cardiovascular Disease

Joel Kaufman, MD, MPH
Professor, University of Washington
Departments of Environmental & Occupational Health Sciences, Medicine, and Epidemiology
Interim Dean, UW School of Public Health

Why worry about the effects of air pollution on health?

- Historical context
- Recent Research
- Global context
- Evolving understanding
- Research needs

What do we mean by air pollution?

- Particles
- Gases

- Primary air pollutants
- Secondary air pollutants

- Point sources
- Mobile sources (Traffic-related Air Pollution)

Historical Context

- Major air pollution episodes killed people
- Dramatic improvements in US air quality
- Evolving understanding of health effects

Global Burden of Disease

THE WORLD'S TOP 12 HEALTH PROBLEMS
Ranked by Disability-Adjusted Life Years (DALYs)

Rank	1990	2010
1	Lower respiratory infection	Ischemic heart disease
2	Diarrhea	Lower respiratory infection
3	Preterm birth	Stroke
4	Ischemic heart disease	Diarrhea
5	Stroke	HIV
6	COPD	Low back pain
7	Malaria	Malaria
8	Tuberculosis	COPD
9	Protein, energy malnutrition	Preterm birth
10	Neonatal encephalitis	Road injury
11	Low back pain	Major depressive disorders
12	Road injury	Neonatal encephalitis

- Communicable, neonatal/maternal disease
- Noncommunicable disease
- Injury

THE TOP 12 RISK FACTORS
Factors Causing the Greatest "Loss of Health"

Rank	1990	2010
1	Low body weight	High blood pressure
2	Household air pollution	Smoking
3	Smoking	Alcohol
4	High blood pressure	Household air pollution
5	Lack of breastfeeding	Low fruit consumption
6	Alcohol	High body mass index
7	Ambient particulate matter	High fasting plasma glucose
8	Low fruit consumption	Low body weight
9	High fasting plasma glucose	Ambient particulate matter
10	High body mass index	Inactivity
11	Low iron intake	High salt intake
12	High salt intake	Low nut/seed consumption

Lancet, 2012

Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015

*GBD 2015 Risk Factors Collaborators**

Summary

Background The Global Burden of Diseases, Injuries, and Risk Factors Study 2015 provides an up-to-date synthesis of the evidence for risk factor exposure and the attributable burden of disease. By providing national and subnational assessments spanning the past 25 years, this study can inform debates on the importance of addressing risks in context.

Methods We used the comparative risk assessment framework developed for previous iterations of the Global Burden of Disease Study to estimate attributable deaths, disability-adjusted life-years (DALYs), and trends in exposure by age group, sex, year, and geography for 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks from 1990 to 2015. This study included 388 risk-outcome pairs that met World Cancer Research Fund-defined criteria for convincing or probable evidence. We extracted relative risk and exposure estimates from randomised controlled trials, cohorts, pooled cohorts, household surveys, census data, satellite data, and other sources. We used statistical models to pool data, adjust for bias, and incorporate covariates. We developed a metric that allows comparisons of exposure across risk factors—the summary exposure value. Using the counterfactual scenario of theoretical minimum risk level, we estimated the portion of deaths and DALYs that could be attributed to a given risk. We decomposed trends in attributable burden into contributions from population growth, population age structure, risk exposure, and risk-deleted cause-specific DALY rates. We characterised risk exposure in relation to a Socio-demographic Index (SDI).

Lancet 2016; 388: 1659–724

This online publication has been corrected. The corrected version first appeared at thelancet.com on January 5, 2017

See Editorial page 1447

See Comment pages 1448 and 1450

*Collaborators listed at the end of the Article

Correspondence to:
Prof Christopher J L Murray, Institute for Health Metrics and Evaluation, Seattle, WA 98121, USA
cjlm@uw.edu

GBD 2015

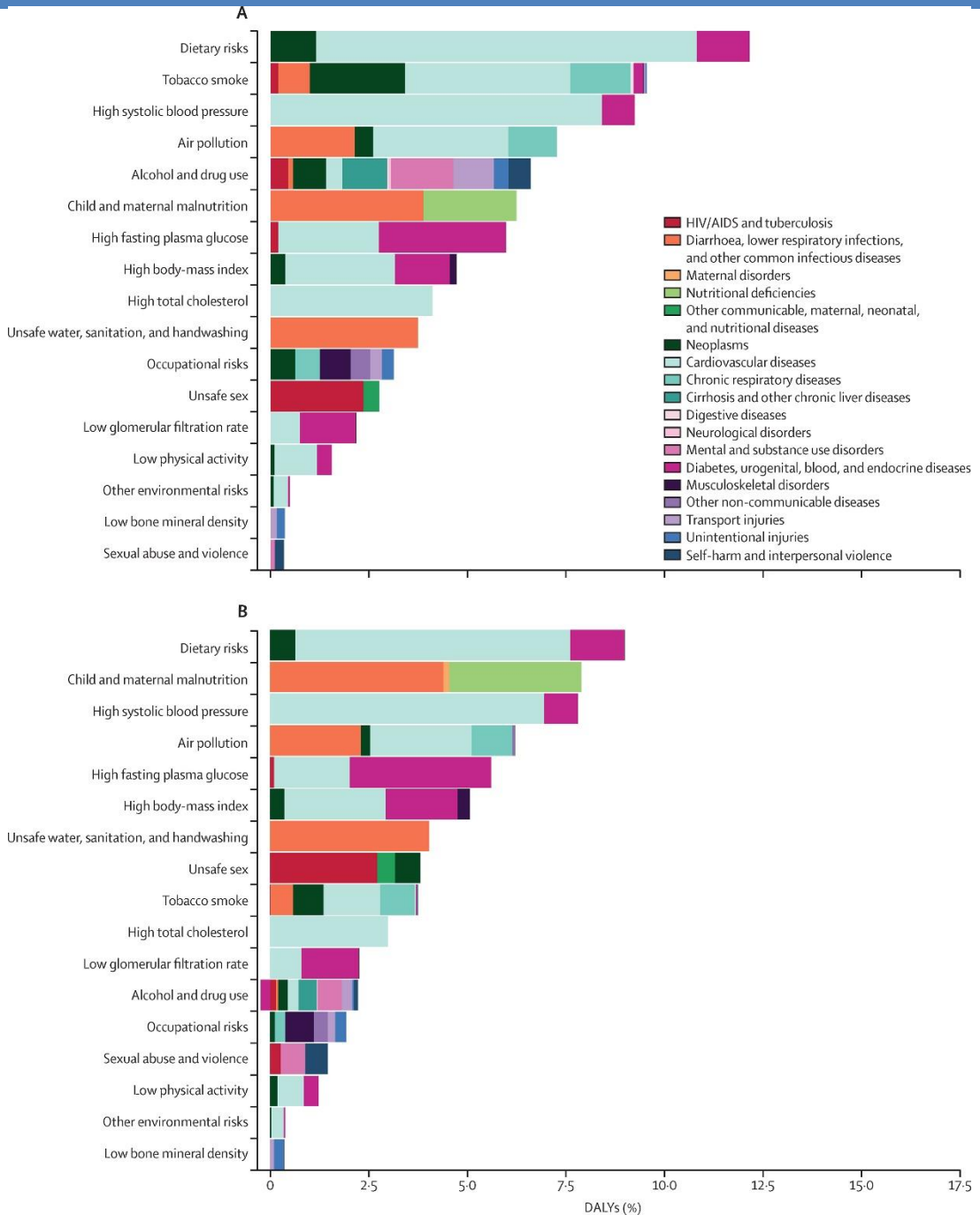
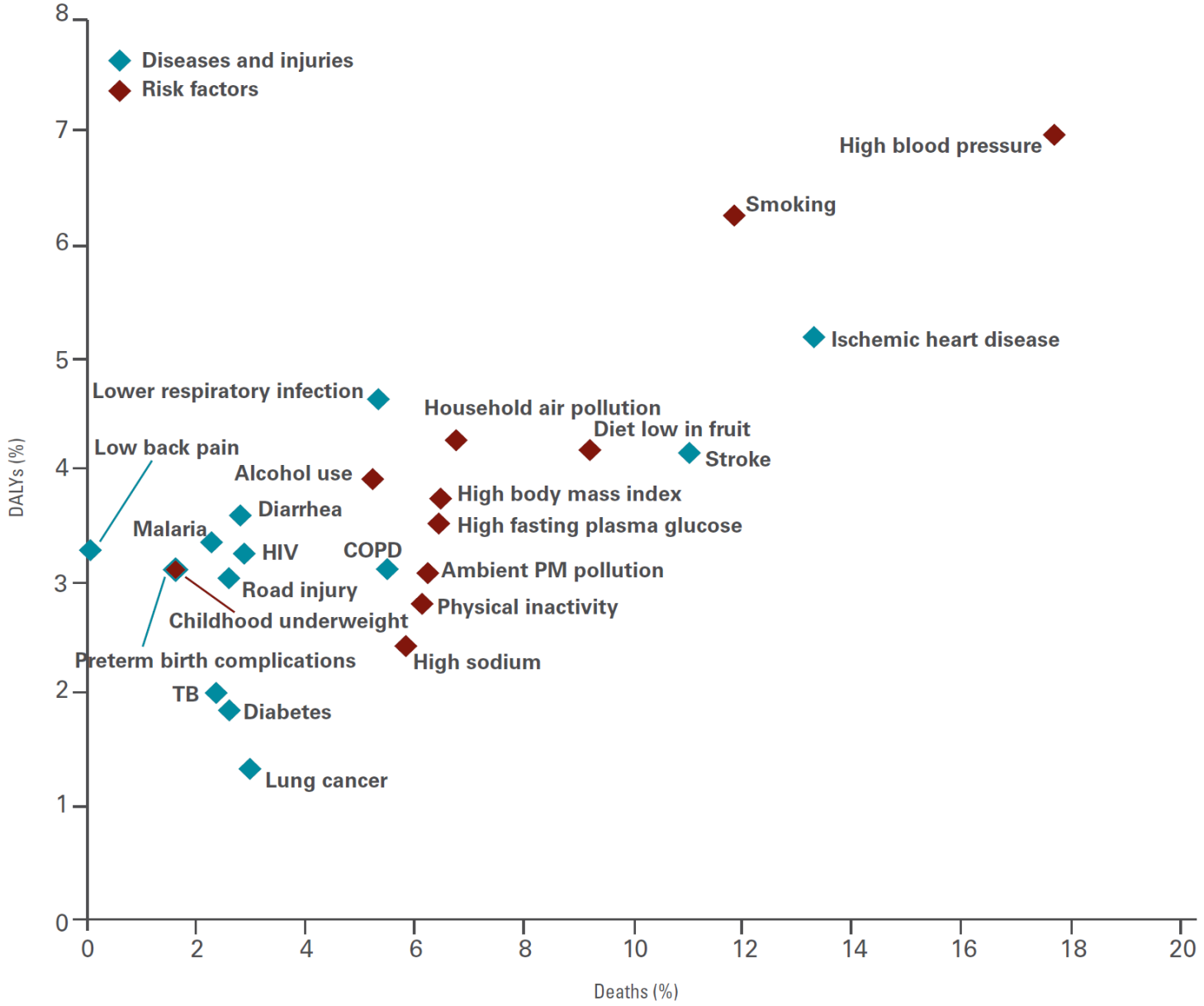

A
Dietary risks
Tobacco smoke
High systolic blood pressure
Air pollution
Alcohol and drug use
Child and maternal malnutrition
High fasting plasma glucose
High body-mass index
High total cholesterol
Unsafe water, sanitation, and handwashing
Occupational risks
Unsafe sex
Low glomerular filtration rate
Low physical activity
Other environmental risks
Low bone mineral density
Sexual abuse and violence
HIV/AIDS and tuberculosis
Diarrhoea, lower respiratory infections, and other common infectious diseases
Maternal disorders
Nutritional deficiencies
Other communicable, maternal, neonatal, and nutritional diseases
Neoplasms
Cardiovascular diseases
Chronic respiratory diseases
Cirrhosis and other chronic liver diseases
Digestive diseases
Neurological disorders
Mental and substance use disorders
Diabetes, urogenital, blood, and endocrine diseases
Musculoskeletal disorders
Other non-communicable diseases
Transport injuries
Unintentional injuries
Self-harm and interpersonal violence
B
Dietary risks
Child and maternal malnutrition
High systolic blood pressure
Air pollution
High fasting plasma glucose
High body-mass index
Unsafe water, sanitation, and handwashing
Unsafe sex
Tobacco smoke
High total cholesterol
Low glomerular filtration rate
Alcohol and drug use
Occupational risks
Sexual abuse and violence
Low physical activity
Other environmental risks
Low bone mineral density
0
2·5
5·0
7·5
10·0
12·5
15·0
17·5
DALYs (%)

Figure 3: The 10 leading diseases and injuries and 10 leading risk factors based on percentage of global deaths and DALYs, 2010



Environmental factors in cardiovascular disease

Kristen E. Cosselman, Ana Navas-Acien and Joel D. Kaufman

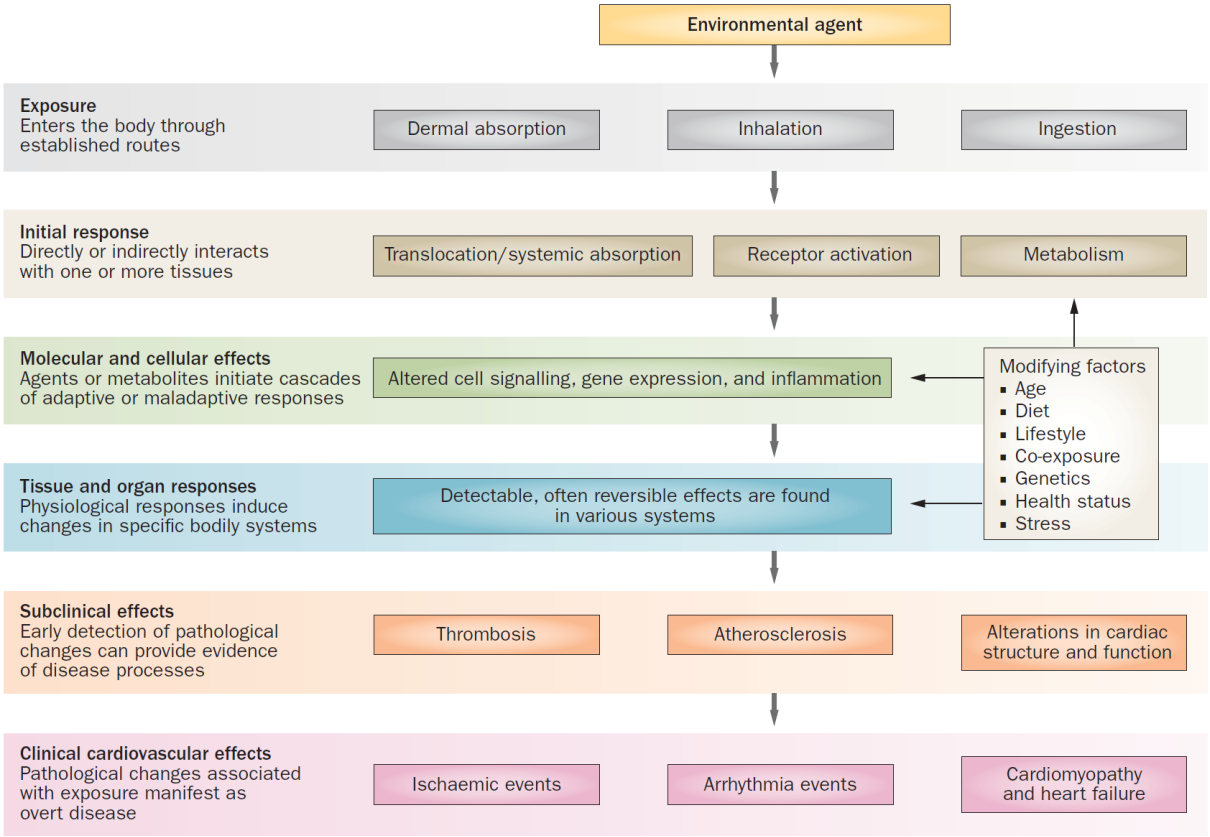


Figure 1 | A framework for the characterization of the effects of environmental factors in cardiovascular disease. A general framework can be constructed to follow the pathways by which the effects of agents are seen. Agents enter the body through established routes, interact with one or more organs and tissues, initiating signalling cascades and physiological responses, leading to subclinical and ultimately clinical pathological changes.

Scientific Background

- Air Pollution Linked to Cardiovascular and Respiratory Disease
  - Short-term and long-term exposures
  - Focus here primarily on long-term exposures

AHA Scientific Statement

Particulate Matter Air Pollution and Cardiovascular Disease

An Update to the Scientific Statement From the American Heart Association

Robert D. Brook, MD, Chair; Sanjay Rajagopalan, MD; C. Arden Pope III, PhD; Jeffrey R. Brook, PhD; Aruni Bhatnagar, PhD, FAHA; Ana V. Diez-Roux, MD, PhD, MPH; Fernando Holguin, MD; Yuling Hong, MD, PhD, FAHA; Russell V. Luepker, MD, MS, FAHA; Murray A. Mittleman, MD, DrPH, FAHA; Annette Peters, PhD; David Siscovick, MD, MPH, FAHA; Sidney C. Smith, Jr, MD, FAHA; Laurie Whitsel, PhD; Joel D. Kaufman, MD, MPH; on behalf of the American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism

Abstract—In 2004, the first American Heart Association scientific statement on "Air Pollution and Cardiovascular Disease" concluded that exposure to particulate matter (PM) air pollution contributes to cardiovascular morbidity and mortality. In the interim, numerous studies have expanded our understanding of this association and further elucidated the physiological and molecular mechanisms involved. The main objective of this updated American Heart Association scientific statement is to provide a comprehensive review of the new evidence linking PM exposure with cardiovascular disease, with a specific focus on highlighting the clinical implications for researchers and healthcare providers. The writing group also sought to provide expert consensus opinions on many aspects of the current state of science and updated suggestions for areas of future research. On the basis of the findings of this review, several new conclusions were reached, including the following: Exposure to PM <2.5 μm in diameter ($PM_{2.5}$) over a few hours to weeks can trigger cardiovascular disease–related mortality and nonfatal events; longer-term exposure (eg, a few years) increases the risk for cardiovascular mortality to an even greater extent than exposures over a few days and reduces life expectancy within more highly exposed segments of the population by several months to a few years; reductions in PM levels are associated with decreases in cardiovascular mortality within a time frame as short as a few years; and many credible pathological mechanisms have been elucidated that lend biological plausibility to these findings. It is the opinion of the writing group that the overall evidence is consistent with a causal relationship between $PM_{2.5}$ exposure and cardiovascular morbidity and mortality. This body of evidence has grown and been strengthened substantially since the first American Heart Association scientific statement was published. Finally, $PM_{2.5}$ exposure is deemed a modifiable factor that contributes to cardiovascular morbidity and mortality. **(*Circulation*. 2010;121:2331-2378.)**

Epidemiological Investigations

- Early Observations
  - Meuse Valley, 1930
  - Donora, PA, 1948
  - London, 1952

- Analytical Epidemiological Approaches
  - Ecological
  - Semi-individual (semi-ecological?)
  - Individual level studies

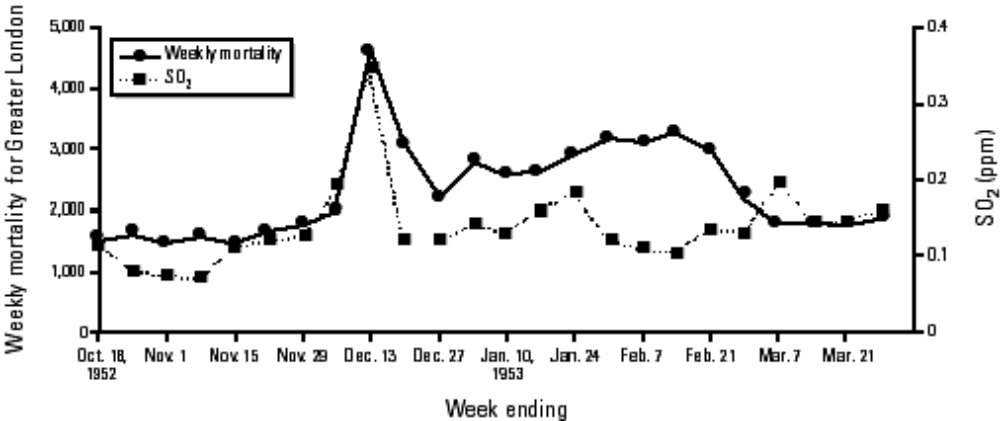
Donora, PA 1948

Los Angeles 1955

Dense fog over the Los Angeles Civic Center, 1955. Note that the buildings project above the base of the inversion layer, while the smog remains below.

Historical Pollution Episodes Established Temporal relationship between PM/Sulfates and Mortality

- Combination of industrialization and weather conditions
  - Meuse Valley, Belgium 1-5 December 1930
    - 60 people died in last 2 days (10x expected)
  - London Smog 5-9 December 1952
    - TSM reached 1500 $\mu g/m^3$
    - 12,000 Excess Deaths Attributed to Event



Harvard Six Cities Study

- Prospective Cohort Study
  - About 8000 subjects selected randomly
  - Six US Cities w/ differing air pollution
  - Subjects followed every two years
    - lung function and questionnaires
  - Ambient air exposures assessed from special fixed-site monitoring stations
    - Particles, sulfates, gaseous pollutants

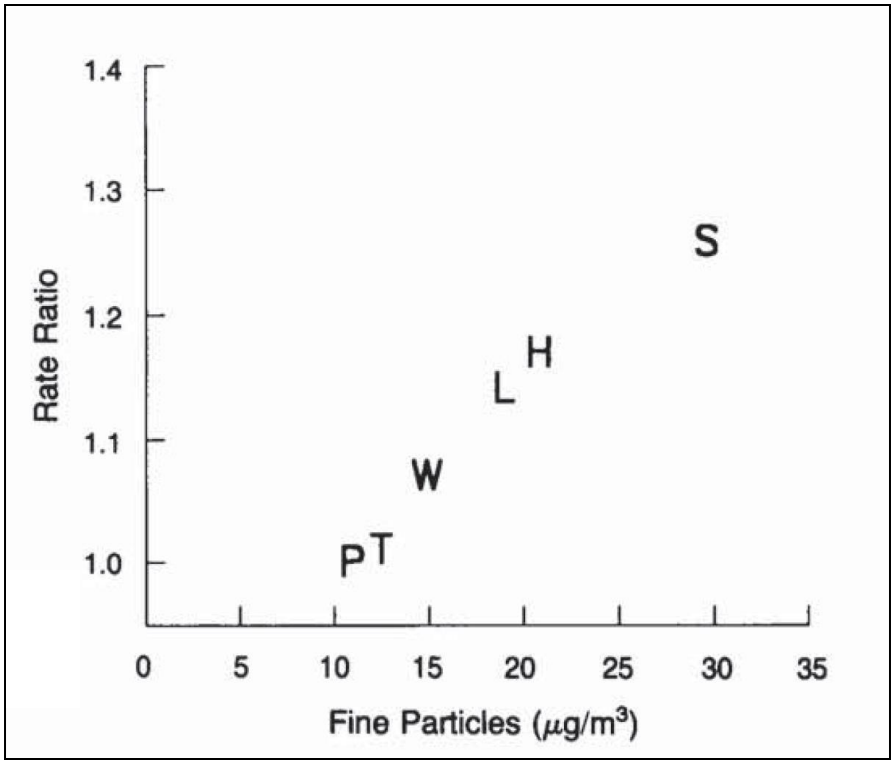
Dockery et al, NEJM 1993; 329:1753-9

The New England
Journal of Medicine

Volume 329 DECEMBER 9, 1993 Number 24

AN ASSOCIATION BETWEEN AIR POLLUTION AND MORTALITY IN SIX U.S. CITIES

Douglas W. Dockery, Sc.D., C. Arden Pope III, Ph.D., Xiping Xu, M.D., Ph.D.,
John D. Spengler, Ph.D., James H. Ware, Ph.D., Martha E. Fay, M.P.H.,
Benjamin G. Ferris, Jr., M.D., and Frank E. Speizer, M.D.



American Cancer Society Cancer Prevention II Study

- 1.2 million adults recruited in 1982
- Link to exposure data for 552,138 residing in metro area, based on zip code at entry
- Vital status 1982-1998
- Cox proportional hazards model
  - Metro area spatial differences random effect
- 2 Updates of study first published in 1995

ACS Study

Table 2. Adjusted Mortality Relative Risk (RR) Associated With a 10-μg/m^3 Change in Fine Particles Measuring Less Than 2.5 μm in Diameter

	Adjusted RR (95% CI)*		
Cause of Mortality	**1979-1983**	**1999-2000**	**Average**
All-cause	1.04 (1.01-1.08)	1.06 (1.02-1.10)	1.06 (1.02-1.11)
Cardiopulmonary	1.06 (1.02-1.10)	1.08 (1.02-1.14)	1.09 (1.03-1.16)
Lung cancer	1.08 (1.01-1.16)	1.13 (1.04-1.22)	1.14 (1.04-1.23)
All other cause	1.01 (0.97-1.05)	1.01 (0.97-1.06)	1.01 (0.95-1.06)

*Estimated and adjusted based on the baseline random-effects Cox proportional hazards model, controlling for age, sex, race, smoking, education, marital status, body mass, alcohol consumption, occupational exposure, and diet. CI indicates confidence interval.

Pope, JAMA, 2002

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 1, 2007 VOL. 356 NO. 5

Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women

Kristin A. Miller, M.S., David S. Siscovick, M.D., M.P.H., Lianne Sheppard, Ph.D., Kristen Shepherd, M.S., Jeffrey H. Sullivan, M.D., M.H.S., Garnet L. Anderson, Ph.D., and Joel D. Kaufman, M.D., M.P.H.

ABSTRACT

BACKGROUND

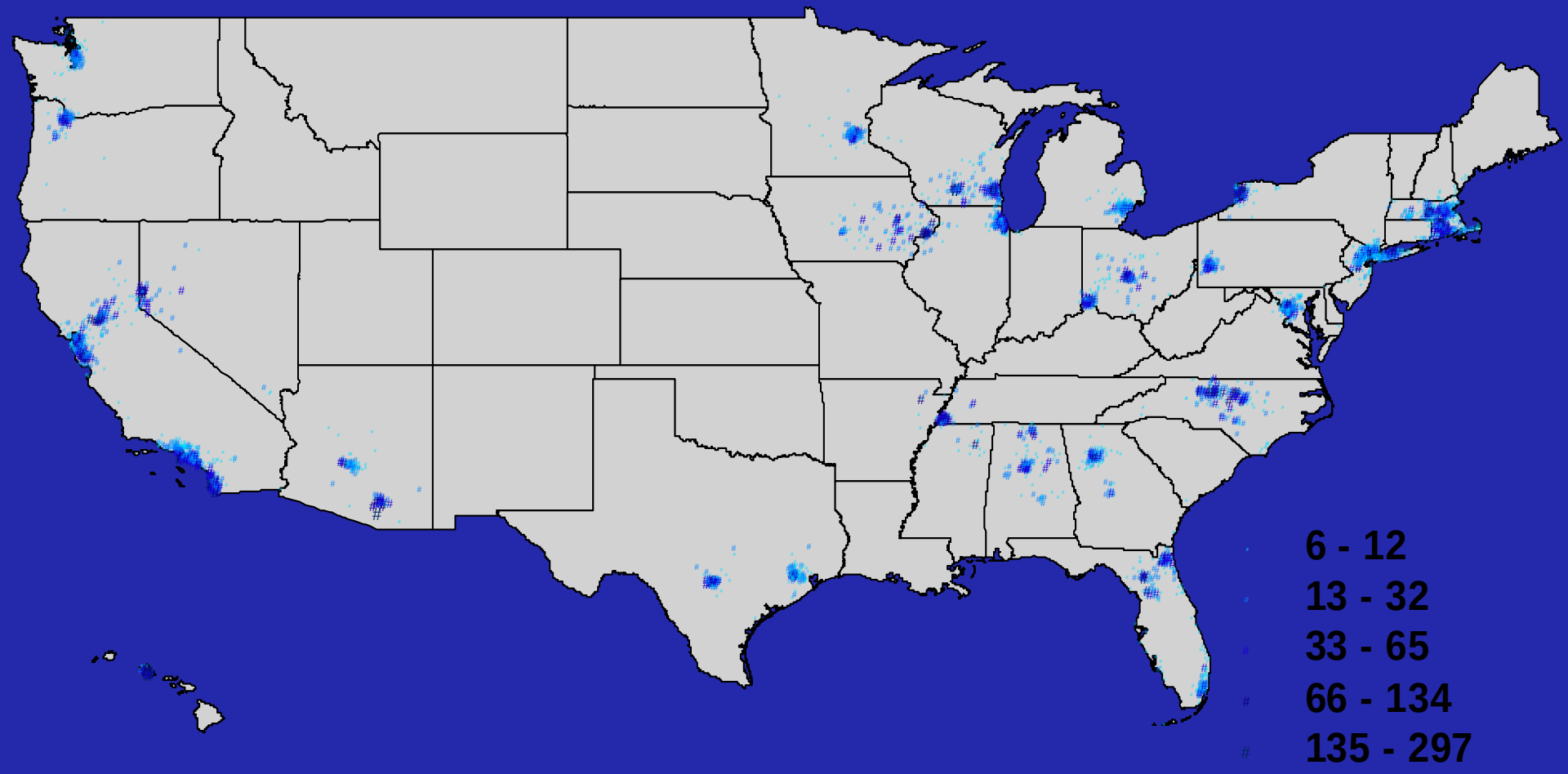
Fine particulate air pollution has been linked to cardiovascular disease, but previous studies have assessed only mortality and differences in exposure between cities. We examined the association of long-term exposure to particulate matter of less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) with cardiovascular events.

METHODS

We studied 65,893 postmenopausal women without previous cardiovascular disease in 36 U.S. metropolitan areas from 1994 to 1998, with a median follow-up of 6 years. We assessed the women's exposure to air pollutants using the monitor located near-

From the Departments of Epidemiology (K.A.M., D.S.S., J.D.K.), Medicine (D.S.S., J.D.K.), Biostatistics (L.S., G.L.A.), and Environmental and Occupational Health Sciences (L.S., K.S., J.H.S., J.D.K.), University of Washington; and the Women's Health Initiative Clinical Coordinating Center, Fred Hutchinson Cancer Research Center (G.L.A.) — both in Seattle. Address reprint requests to Dr. Kaufman at the University of Washington Occupational and Environmental Medicine Program, 4225 Roosevelt

WHI-OS Participant Residences



Subjects per zipcode

Exposure Data

- EPA AIRS database
- Annual Average Concentrations, year 2000
- Pollutants:
- $PM_{2.5}$ (PM_{10}, SO_2, NO_2, CO, O_3)
- Closest monitor within 30 miles of subject residential zipcode centroid

Average Concentrations of Fine Particulate Matter (PM2.5) Measured near the Homes of 65,893 Subjects (Year 2000)

Table 2. Average Concentrations of Fine Particulate Matter ($PM_{2.5}$) Measured near the Homes of 65,893 Subjects (Year 2000).*

$PM_{2.5}$ Exposure	Concentration		
	Mean	10th and 90th Percentiles	Range
		$\mu g/m^3$	
Individual exposure	13.5±3.7	9.1 to 18.3	3.4 to 28.3
Citywide average exposure	13.5±3.3	9.3 to 17.8	4.0 to 19.3
Difference between individual exposure and citywide average exposure	0±1.6	−1.6 to 1.7	−11.5 to 11.7

* Plus–minus values are means ±SD. The median distance between the location of monitors and the residences of subjects was 5.6 mi (9.0 km). A total of 573 monitors were used, with a median of 20 (range, 4 to 78) per city.

Miller K et al. N Engl J Med 2007;356:447-458

Estimated Hazard Ratios for the Time to the First Cardiovascular Event or Death Associated with an Exposure Increase of 10 {micro}g per Cubic Meter in the Level of Fine Particulate Matter ($PM_{2.5}$)

Table 3. Estimated Hazard Ratios for the Time to the First Cardiovascular Event or Death Associated with an Exposure Increase of 10 μg per Cubic Meter in the Level of Fine Particulate Matter ($PM_{2.5}$).*

Outcome	No. of Events	Hazard Ratio (95% CI)		
		Overall	Between Cities	Within Cities
First cardiovascular event				
Any cardiovascular event†	1816	1.24 (1.09–1.41)	1.15 (0.99–1.32)	1.64 (1.24–2.18)
Coronary heart disease‡	1268	1.21 (1.04–1.42)	1.13 (0.95–1.35)	1.56 (1.11–2.19)
Cerebrovascular disease§	600	1.35 (1.08–1.68)	1.20 (0.94–1.54)	2.08 (1.28–3.40)
Myocardial infarction	584	1.06 (0.85–1.34)	0.97 (0.75–1.25)	1.52 (0.91–2.51)
Coronary revascularization	949	1.20 (1.00–1.43)	1.14 (0.93–1.39)	1.45 (0.98–2.16)
Stroke	554	1.28 (1.02–1.61)	1.12 (0.87–1.45)	2.08 (1.25–3.48)
Death from cardiovascular cause				
Any death from cardiovascular cause	261	1.76 (1.25–2.47)	1.63 (1.10–2.40)	2.28 (1.10–4.75)
Coronary heart disease				
Definite diagnosis	80	2.21 (1.17–4.16)	2.22 (1.06–4.62)	2.17 (0.60–7.89)
Possible diagnosis	59	1.26 (0.62–2.56)	1.20 (0.54–2.63)	1.57 (0.29–8.51)
Cerebrovascular disease	122	1.83 (1.11–3.00)	1.58 (0.90–2.78)	2.93 (1.03–8.38)

* All analyses evaluated the time until the first event in the category. All estimates were adjusted for age, race or ethnic group, educational level, household income, smoking status, systolic blood pressure, body-mass index, and presence or absence of diabetes, hypertension, or hypercholesterolemia.

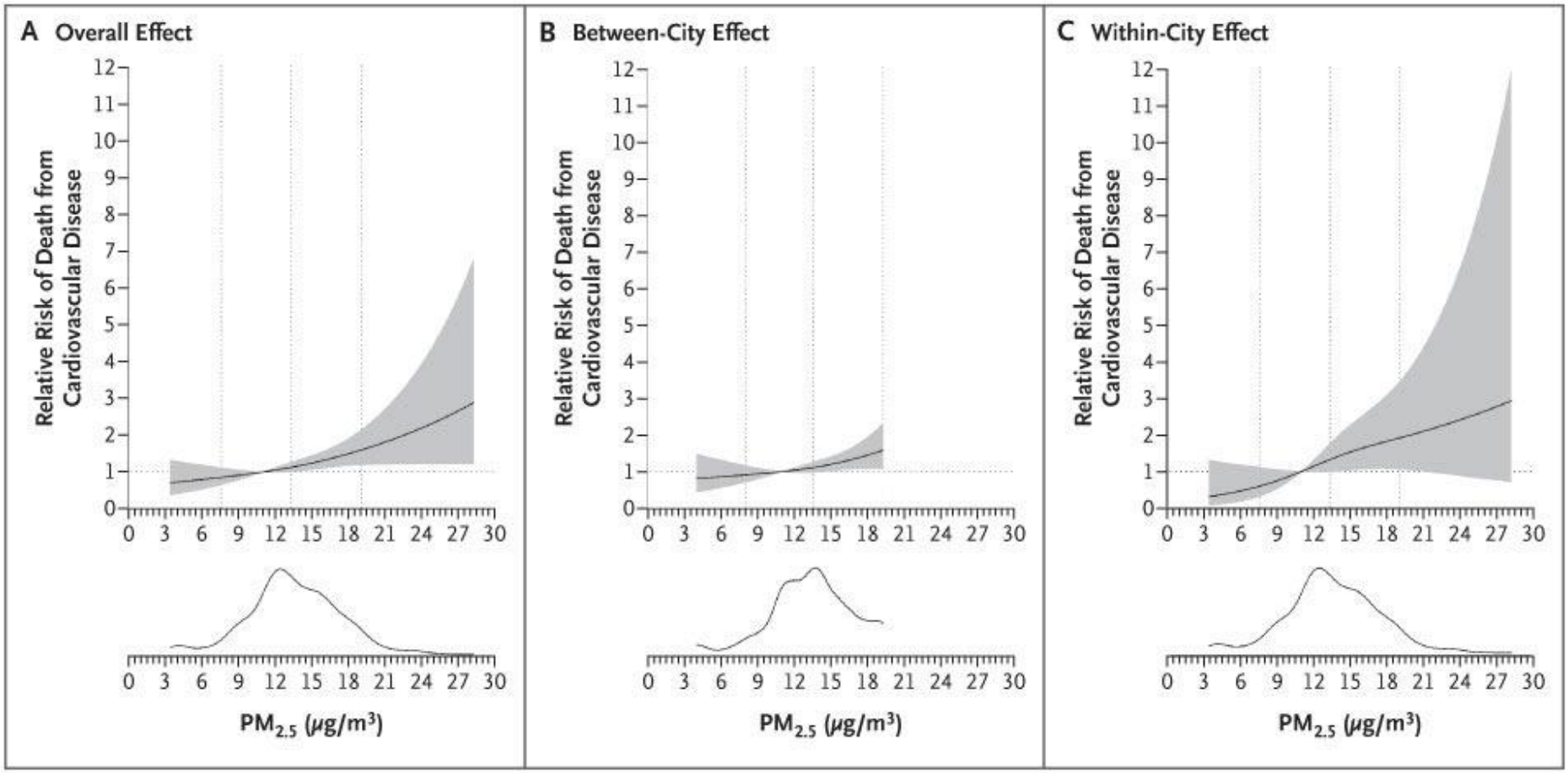
† Events include myocardial infarction, coronary revascularization, stroke, death from coronary heart disease (both definite and possible diagnosis), and cerebrovascular disease. The sum of events in each category may be greater than the total number of events, since some subjects had both coronary and cerebrovascular events.

‡ Events include myocardial infarction, coronary revascularization, and death from coronary heart disease.

§ Events include stroke and death from cerebrovascular disease.

Miller K et al. N Engl J Med 2007;356:447-458

Level of Exposure to Fine Particulate Matter and the Risk of Death from Cardiovascular Causes in Women



Miller K et al. N Engl J Med 2007;356:447-458

Summary

- $PM_{2.5}$ associated with CVD events in postmenopausal women without prior CVD
  - Nonfatal, Fatal
- Association of CVD events and chronic $PM_{2.5}$ exposure similar regardless of most established CVD risk factors
  - age, hypercholesterolemia, hypertension, diabetes
- Increased risk among overweight, obese
  - Overall and central obesity may modify risk of air pollution-related CVD events
- Within-city spatial exposure heterogeneity contributes to risk of cardiovascular events

The Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air)

MESA
Air Pollution

MESA Air Primary Aims

1. To prospectively examine the relation between an individual assessment of long-term air pollution exposures and the *progression* of subclinical CVD
2. To assess the relation between individual assessments of long-term air pollution exposures and incidence of CVD events

MESA Air Primary Aims

1. To prospectively examine the relation between an individual assessment of long-term air pollution exposures and the *progression* of subclinical CVD
2. To assess the relation between individual assessments of long-term air pollution exposures and incidence of CVD events
3. To assess *individual-level exposure* to specific particulate and gaseous ambient-derived air pollutants

Our Approach

- Pair state-of-the-art cardiovascular epidemiology with state-of-the-art exposure estimation
  - Unusual dedication of resources
- Encourage collaborations and promote opportunities for ancillary studies
  - MESA Air as research platform

State-of-the Art Epidemiology

- Multi-city
  - (providing exposure heterogeneity)
- ~7,000 ppts, 45-84 yrs old, CVD-free at baseline

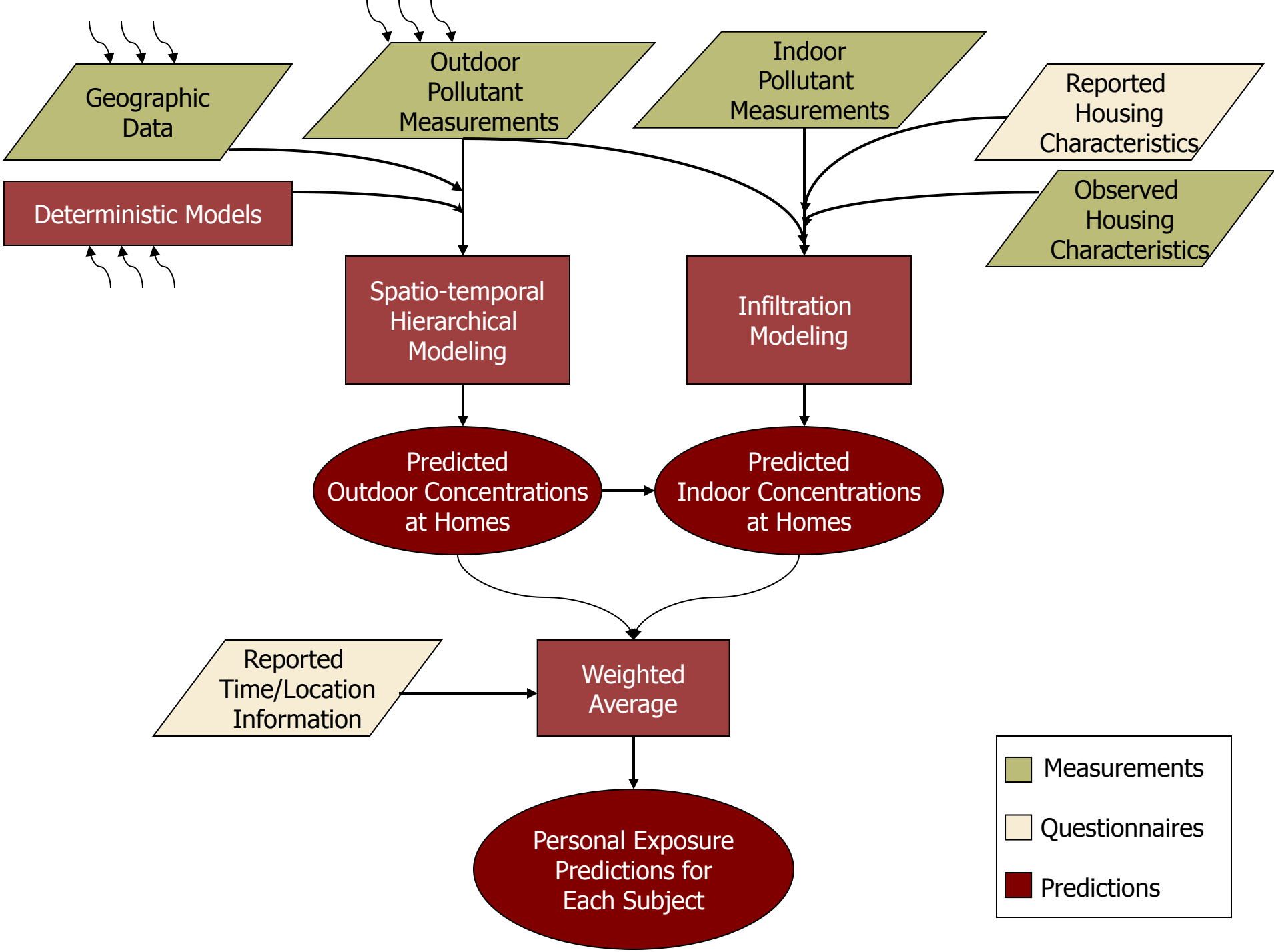
- Multi-ethnic sampling strategy (Caucasian, African-American, Hispanic, Chinese-American)

Exposure Modeling Goals

- Outdoor concentrations at all MESA Air participant residences
  - $PM_{2.5}$, NO_2, NO_X, BC
  - Two-week scale
    - Can average up to desired time
  - 1999 – 2012

State-of-the-Art Exposure Assessment

- Over-arching goal: Most accurate estimate possible of each individual study participant's exposure to air pollutants of interest over the period of study
- Focus is on ambient air pollutants
- Concentration vs. exposure
- Emphasize sources of intra-area variation in pollutant concentration and exposure


Geographic Data
Outdoor Pollutant Measurements
Indoor Pollutant Measurements
Reported Housing Characteristics
Deterministic Models
Observed Housing Characteristics
Spatio-temporal Hierarchical Modeling
Infiltration Modeling
Predicted Outdoor Concentrations at Homes
Predicted Indoor Concentrations at Homes
Reported Time/Location Information
Weighted Average
Personal Exposure Predictions for Each Subject
Measurements
Questionnaires
Predictions

Approaches to Outdoor Spatial Concentration Modeling

- Metro-wide annual averages
- Nearest monitor
- Distance to nearest roadway
- Spatial interpolation
- Dispersion modeling
- Land-use regression
- Hybrid approaches
- Likelihood-based spatio-temporal modeling

Outdoor Pollutant Monitoring

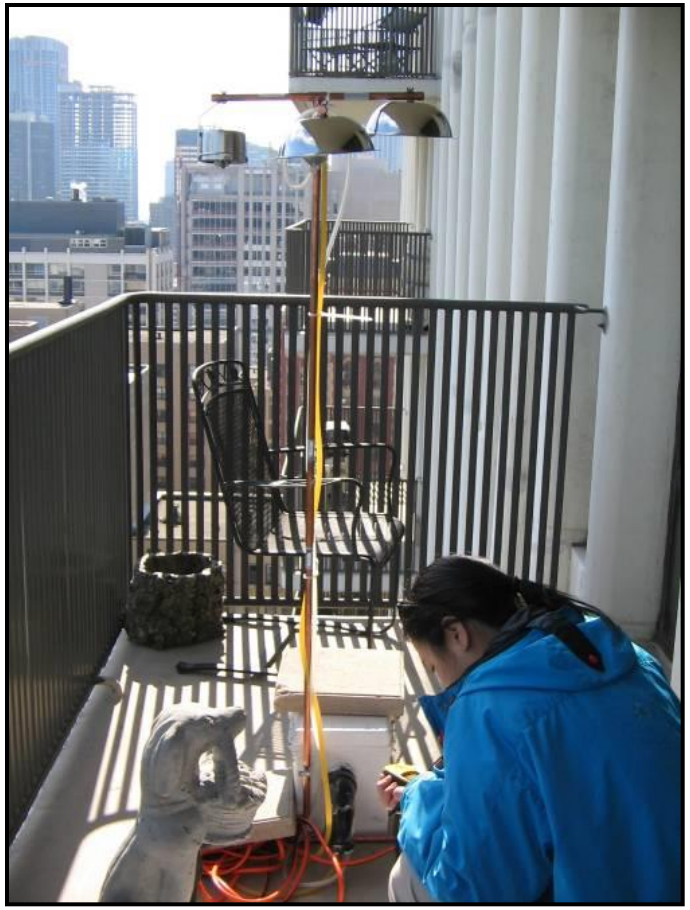
- AQS Network Data

- MESA Air Campaigns
  - Fixed Sites (26 locations, contiguous sampling for 4 yrs)
  - Home Outdoor (100 homes per city, 2x)
  - NO_x Snapshot (100 locations per city, 3x)

Monitoring Data: MESA Air

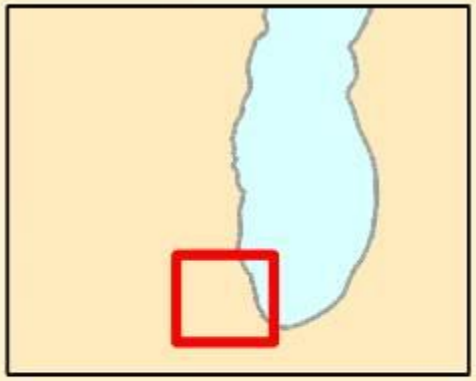
- 2005 – 2009
- $PM_{2.5}$, NO_2, NO_X, BC
- 2-week measurements
- **Fixed** Sites
  - 3 – 7 per city, 1 collocated with AQS site
- **Home** Outdoor Sites
  - 1 – 3 measurements from ~100 participant residence locations in each city
- **Snapshot** Sites (NO_X and NO_2 only)
  - Clusters around roadways

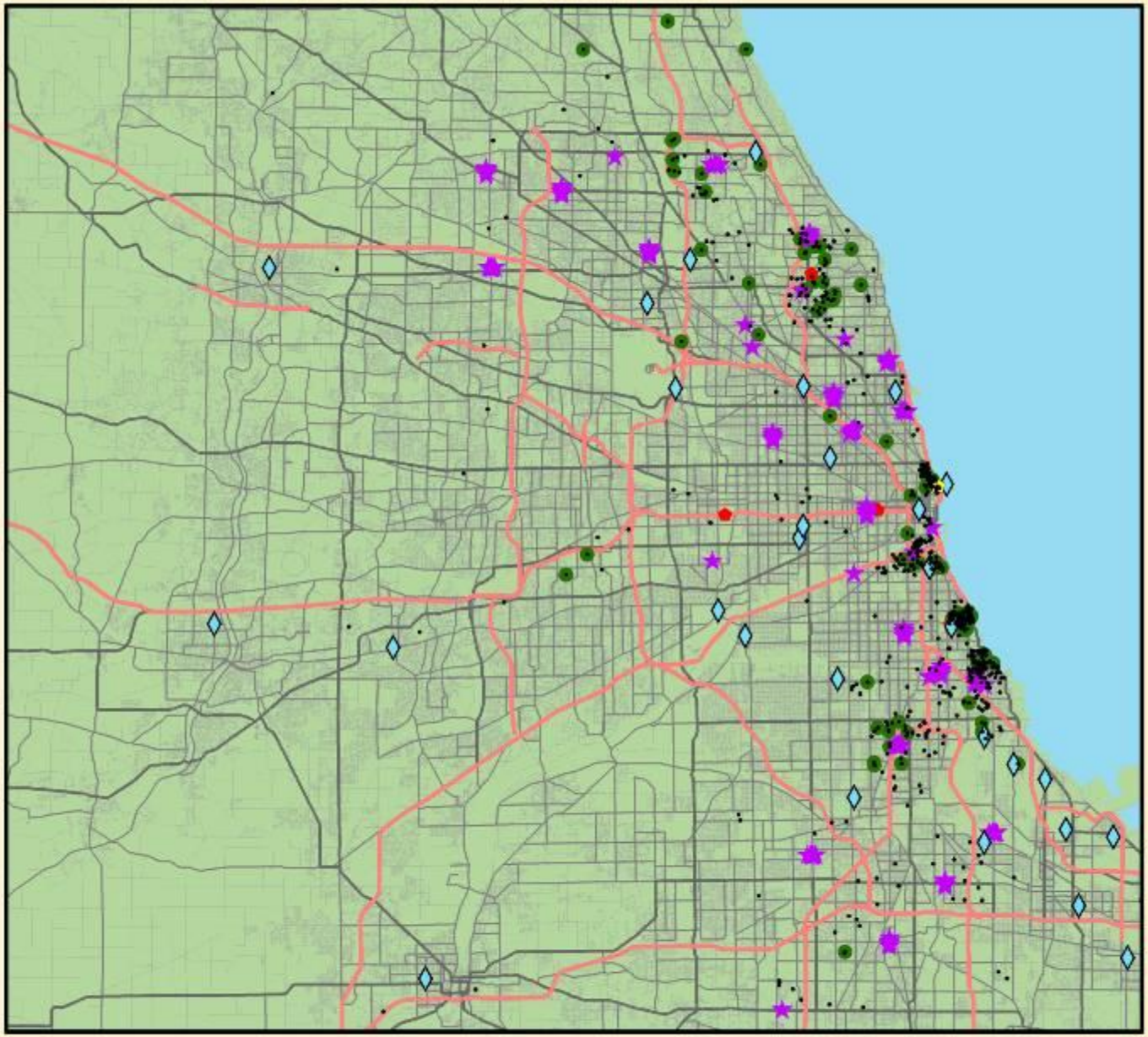
Fixed Sites & Home Outdoor



“Snapshot” Set Up

Focus Area





Legend

- MESA Air Participants
- Home Monitoring Sites
- Community Co-pollutant Monitors
- Fixed Monitoring Sites
- Field Center
- EPA Monitoring Sites
- Primary Interstate highways
- Primary US and State highways
- Secondary State and County highways
- Local, neighborhood, rural streets

All monitoring data are as of December 17, 2007.
Road network data are as of April 1, 2006.
Participant information provided by the Collaborative Health Studies Coordinating Center.

Universal Transverse Mercator Zone 18 (NAD '83)

0 2.5 5 10 15 20

Kilometers

Northwestern University Study Area

Chicago, Illinois

MESA Air Pollution Study
December 17, 2007

Data Source:

MESA Air Pollution

Infiltration Monitoring

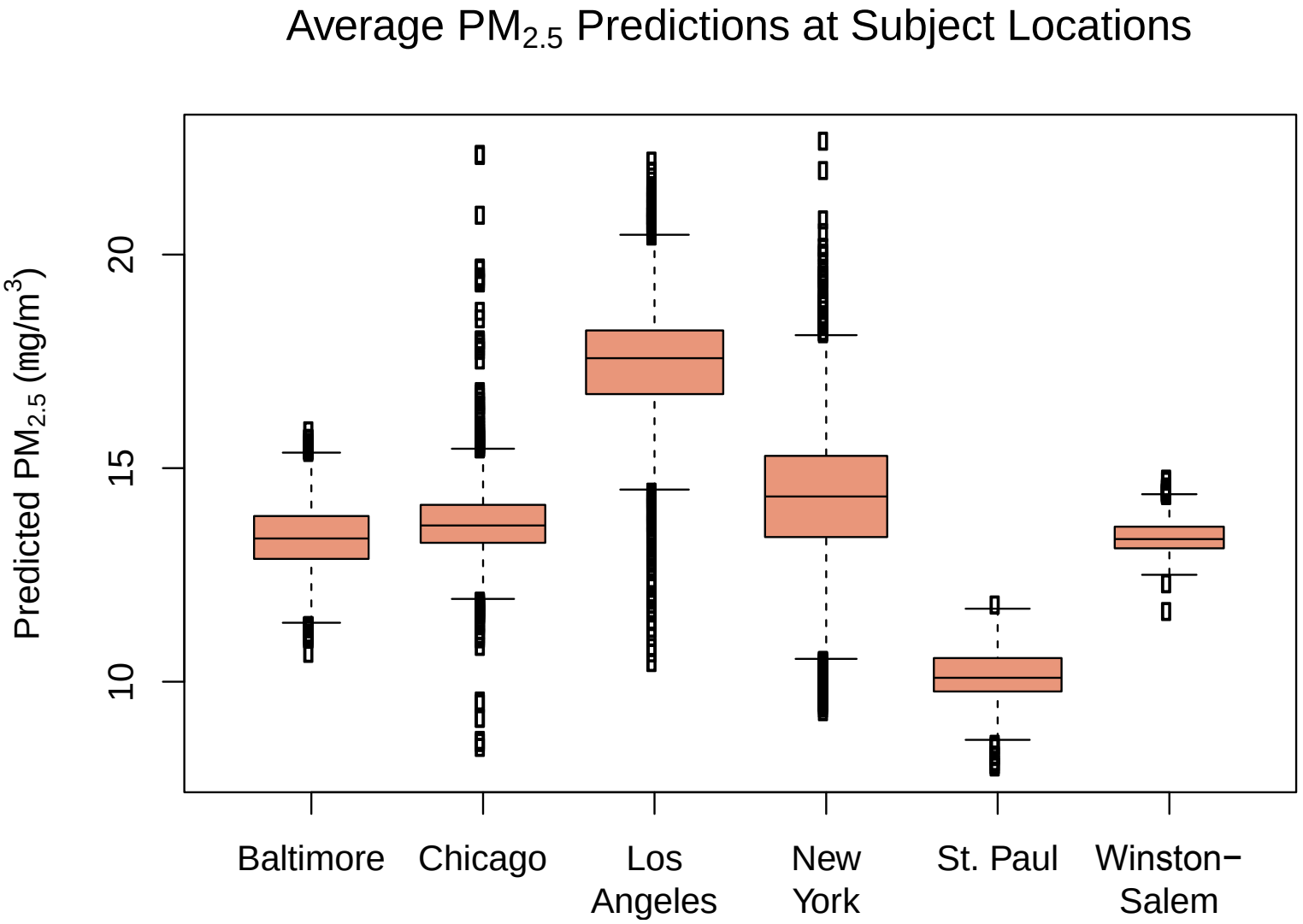
MESA Air Monitoring Campaigns

- Collected 7,420 two-week samples
  - Over 2.3 million hours of active and passive air monitoring
- Samples analyzed for $PM_{2.5}$, LAC, NO_x, O_3, SO_2, and metals
  - Ancillary studies add EC/OC, endotoxin, PM_{10} at a subset of locations

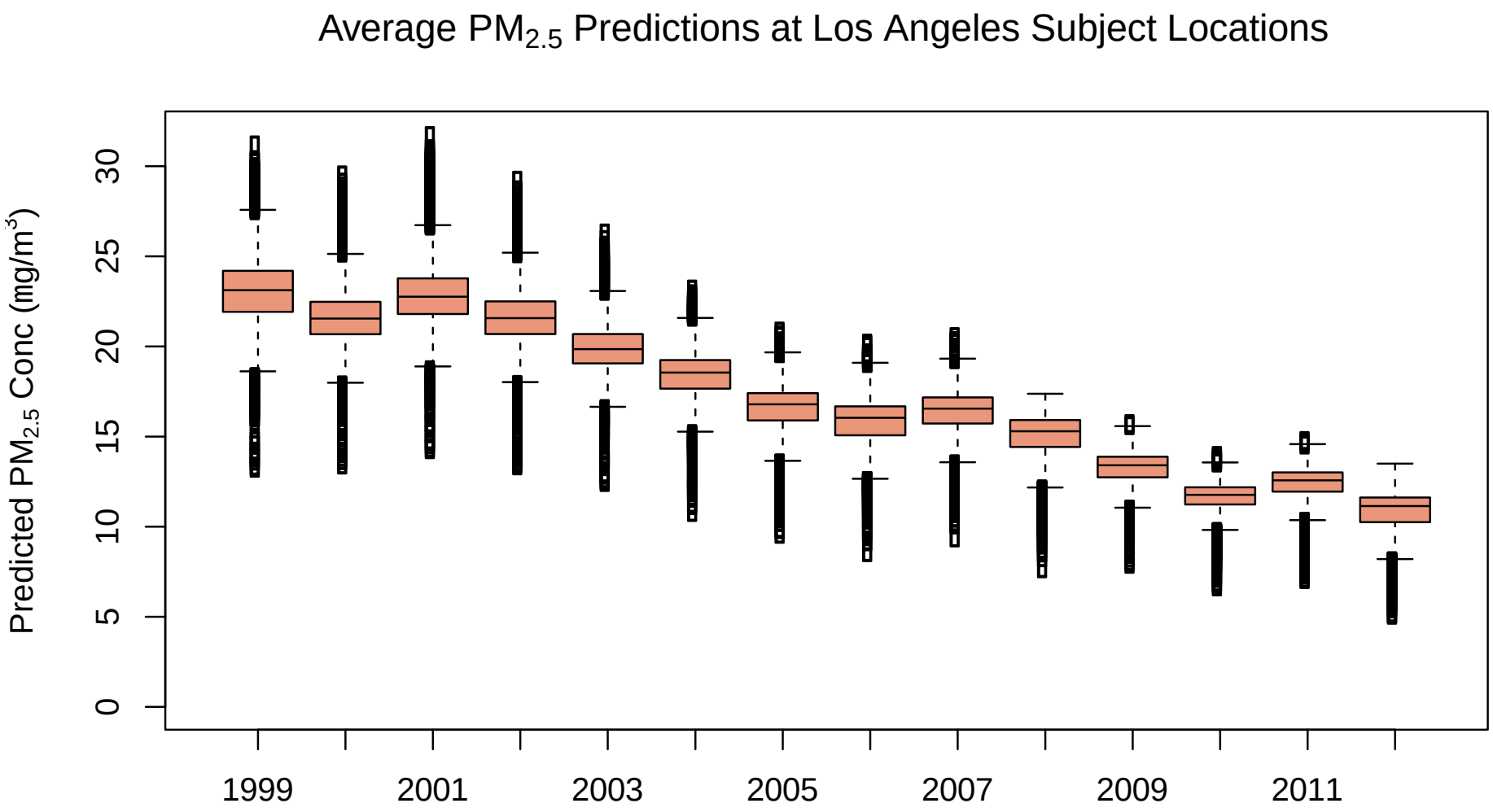
Geographic Inputs

- Traffic volumes (via CALINE)
- Land use (e.g., commercial/industrial)
- Population density
- Distance to coast
- Vegetation index
- Other variables (railyards, airports, ports, etc.)

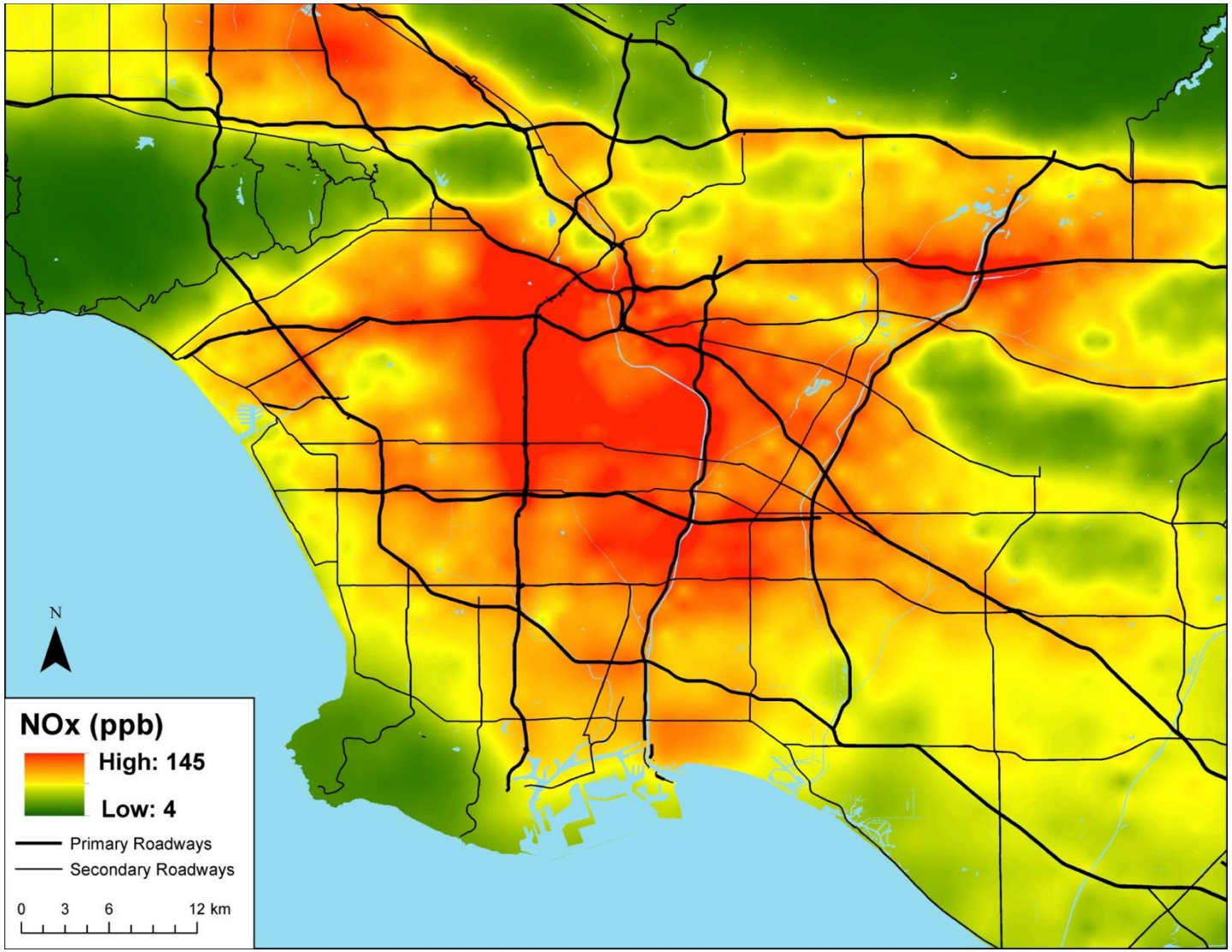
$PM_{2.5}$ Predictions



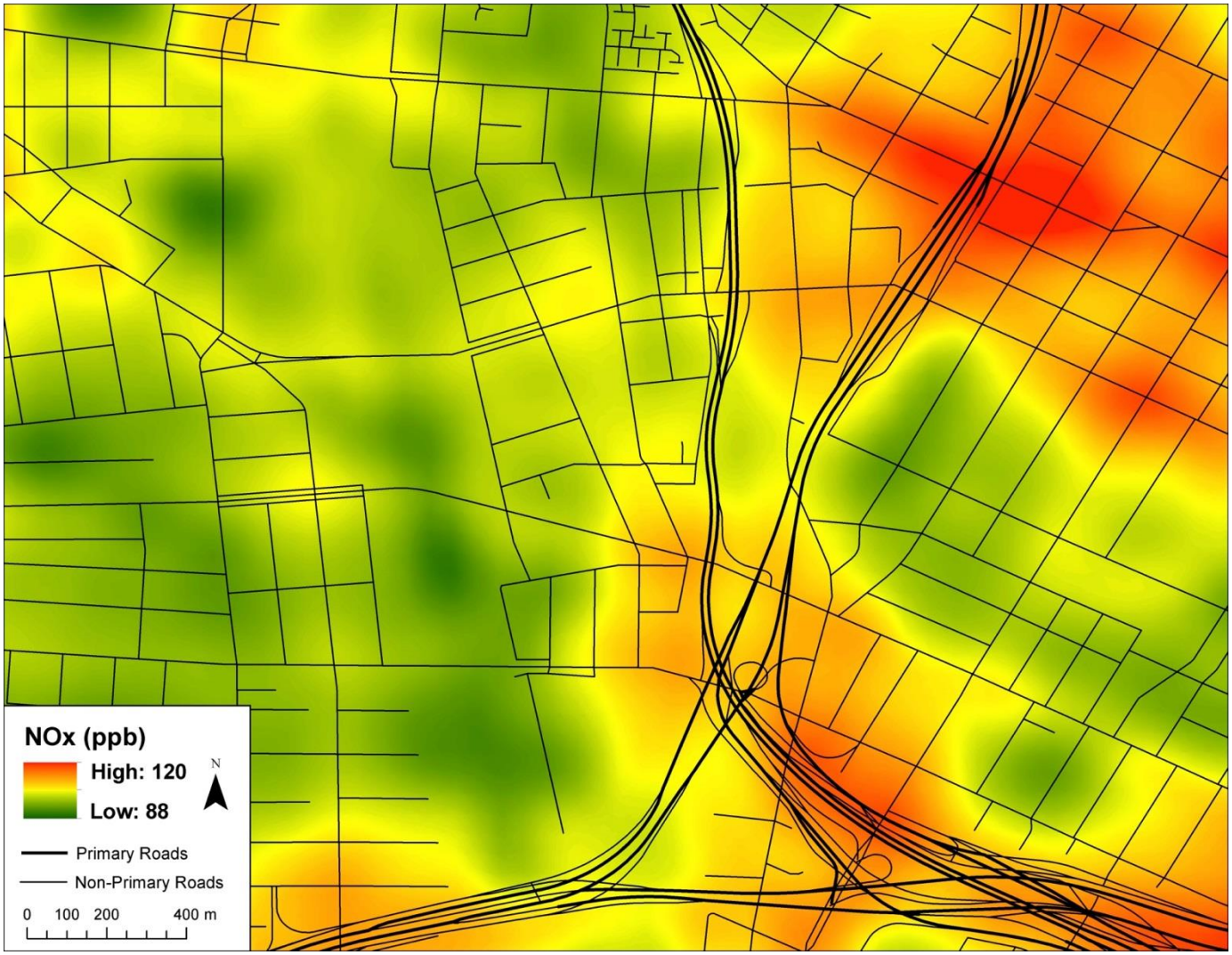
$PM_{2.5}$ Predictions



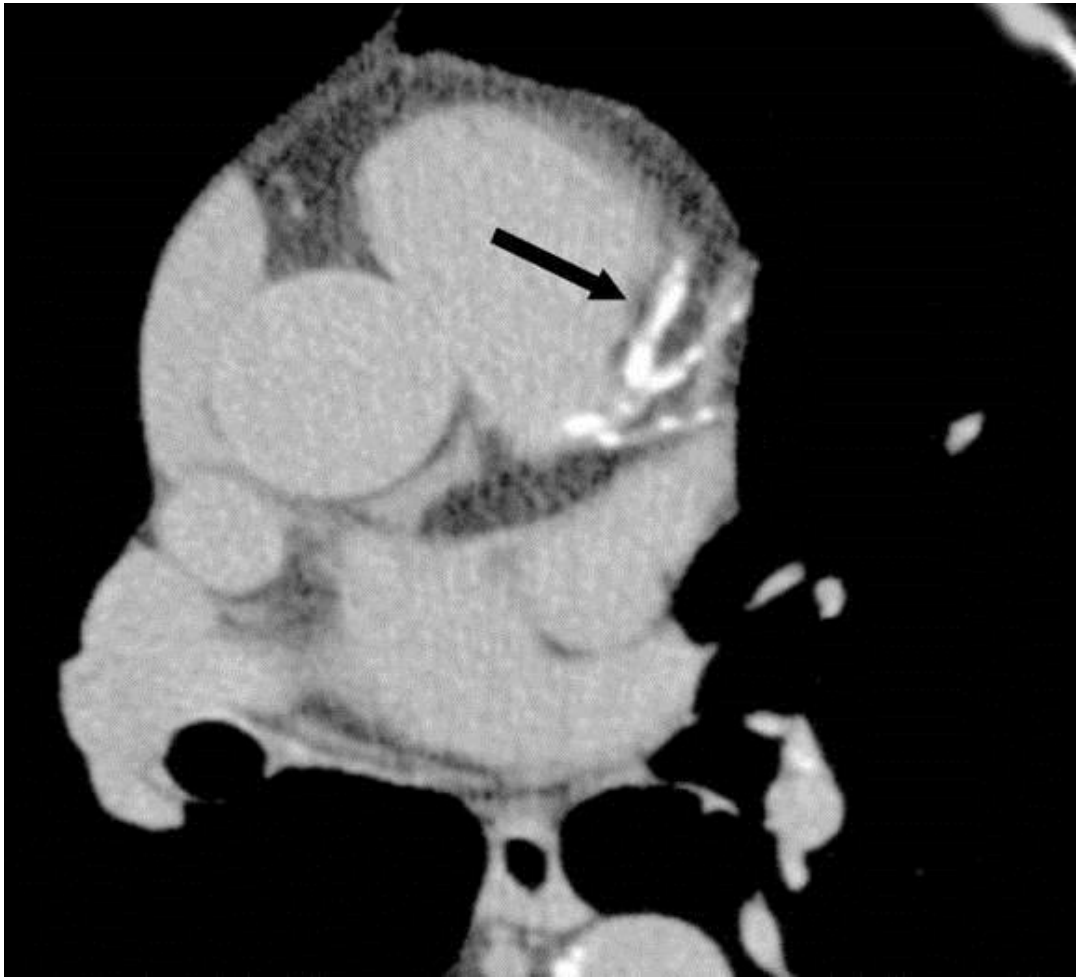
NO_X Predictions: 2000 Average



NO_X Predictions: 2000 Average



Coronary Artery Calcium (CAC)



- CT Scan
- Agatston Score
- Associated with events
- Associated with traditional risk factors

Modeling Strategy

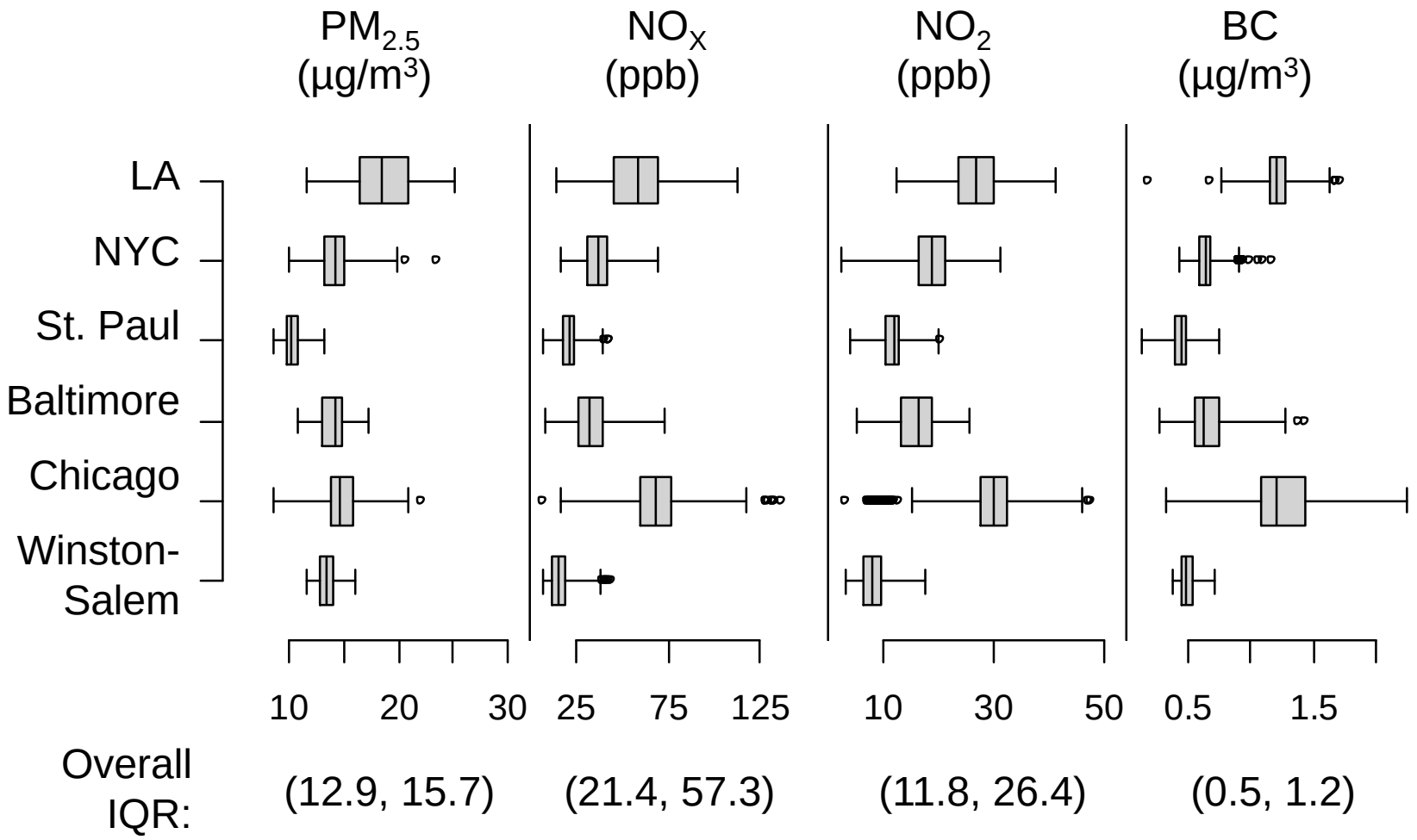
$$Y_{kit} = [\alpha_0 + X_{ki0}\alpha_1 + Z_{ki0}\alpha_2 + a_{ki}] + [\sum_{t'=1}^{t}(\beta_0 + X_{kit'}\beta_1 + W_{kit'}\beta_2 + b_{ki})(v_{kit'} - v_{ki(t'-1)})] + [U_{kit}\gamma_2 + \varepsilon_{kit}]$$

- Model 1: Age, sex, race, site
- Model 2: + smoking, second-hand smoke, adiposity, intentional exercise, cholesterol
- **Model 3: + neighborhood socioeconomic status (SES), income, education, employment status**
- Model 4: + hypertension, blood pressure, diabetes

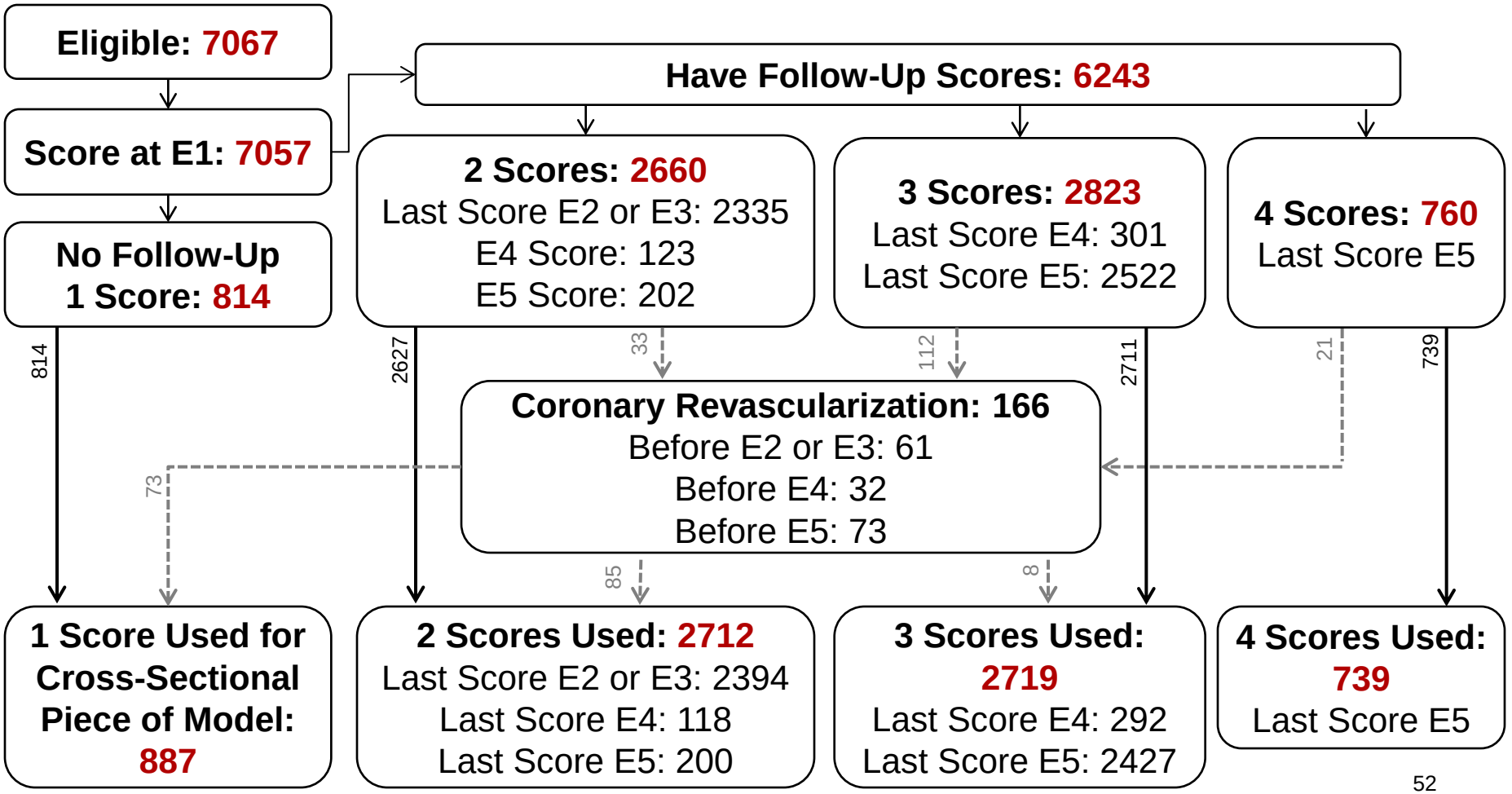
Air Pollution Exposure

- Primary exposures: $PM_{2.5}$, NO_X, NO_2, and BC over period of follow-up
- Two-week predictions aggregated up to nearest full year since baseline exam
- Modeled baseline CAC includes term for year 2000 exposure

Exposure Distribution by Site



Number of CT Scans by Exam

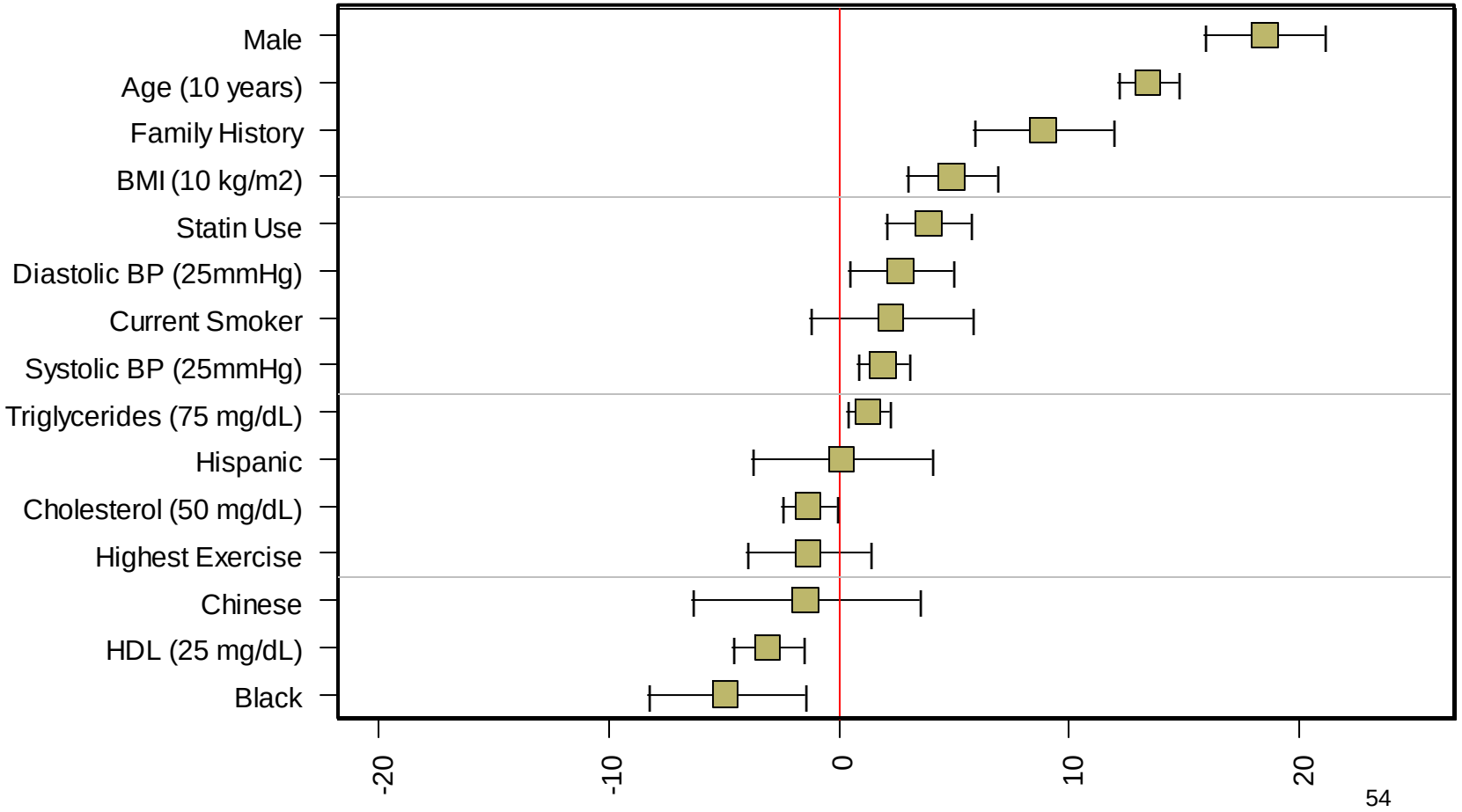


E1: Baseline Exam, E2: Exam 2, E3: Exam 3, E4: Exam 4, E5: Exam 5

Baseline Participant Characteristics by Exposure

	Year 2000 $PM_{2.5}$ ($\mu g/m^3$)	< 14.81	14.81-15.9	15.91-16.64	16.65-19.93	>19.93
	Baseline N	1364	1364	1352	1354	1362
	Baseline Agatston score	165 (445)	123 (355)	168 (475)	146 (379)	125 (364)
	Progression (Agatston/year)	25 (57)	21 (51)	28 (68)	23 (51)	22 (55)
	Age (years)	61 (10)	62 (10)	63 (10)	63 (10)	63 (10)
	Male	50%	47%	48%	43%	47%
Race/ Ethnicity	Caucasian	55%	39%	42%	46%	14%
	African-American	4%	8%	3%	9%	35%
	Chinese	6%	43%	45%	29%	11%
	Hispanic	35%	10%	9%	16%	40%
Smoke Status	Never	43%	49%	40%	46%	60%
	Former	40%	37%	43%	39%	28%
	Current	16%	13%	16%	14%	11%
	BMI (kg/m^2)	29 (5)	29 (6)	29 (5)	28 (6)	27 (5)
	Systolic Blood Pressure (mmHg)	122 (21)	127 (20)	128 (21)	127 (22)	128 (23)
	HDL (mg/dl)	50 (15)	52 (15)	52 (15)	53 (16)	49 (14)
	Total Cholesterol (mg/dl)	198 (36)	194 (35)	191 (35)	193 (36)	196 (37)
	Hypertension	36%	49%	49%	45%	44%
	Statin Use	14%	15%	17%	17%	14%
Diabetes Status	Normal	75%	74%	75%	75%	66%
	IFG	14%	13%	13%	13%	17%
	Diabetic	11%	13%	12%	11%	17%

Risk Factor and Demographic Predictors of CAC Progression

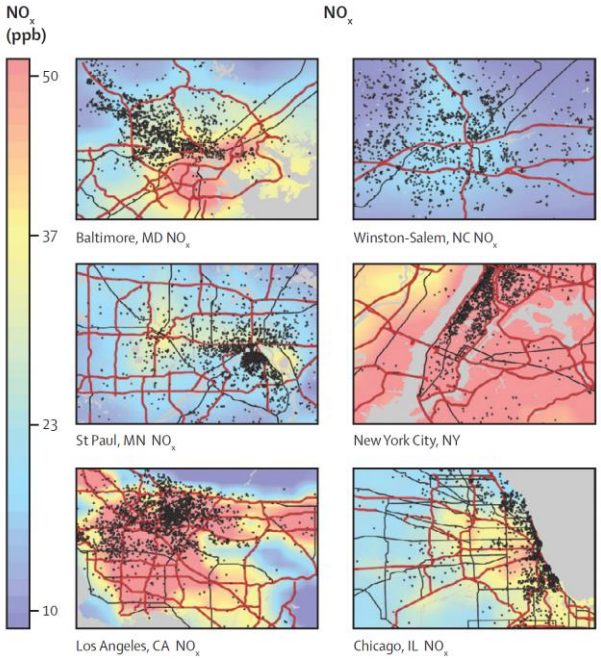


From minimally adjusted models including age, sex, race, and site

Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study

Joel D Kaufman, Sara D Adar, R Graham Barr, Matthew Budoff, Gregory L Burke, Cynthia L Curl, Martha L Daviglus, Ana V Diez Roux, Amanda J Gassett, David R Jacobs Jr, Richard Kronmal, Timothy V Larson, Ana Navas-Acien, Casey Olives, Paul D Sampson, Lianne Sheppard, David S Siscovick, James H Stein, Adam A Szpiro, Karol E Watson

www.thelancet.com **Vol 388 August 13, 2016**



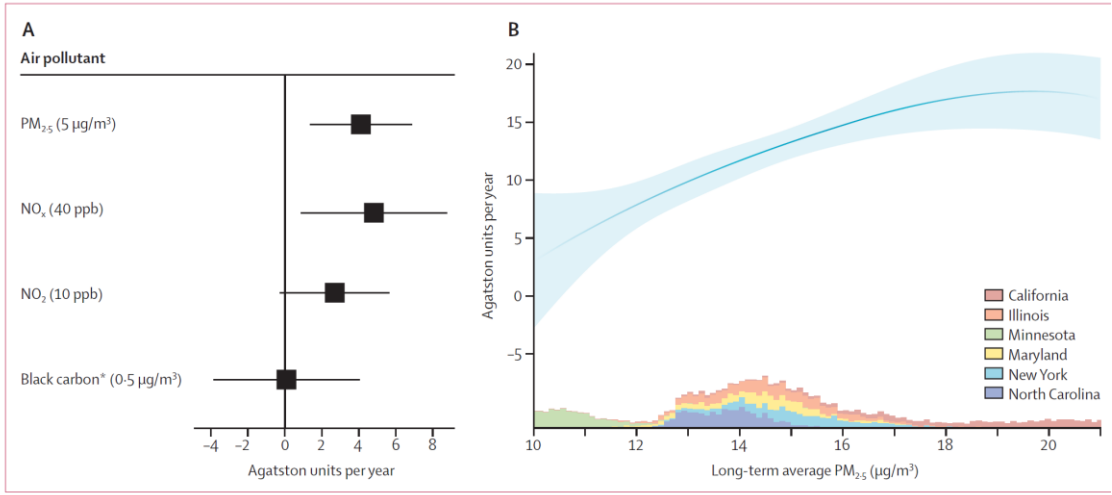


Figure 3: **Long-term average air pollutant concentrations and coronary artery calcium progression**

Summary of Findings

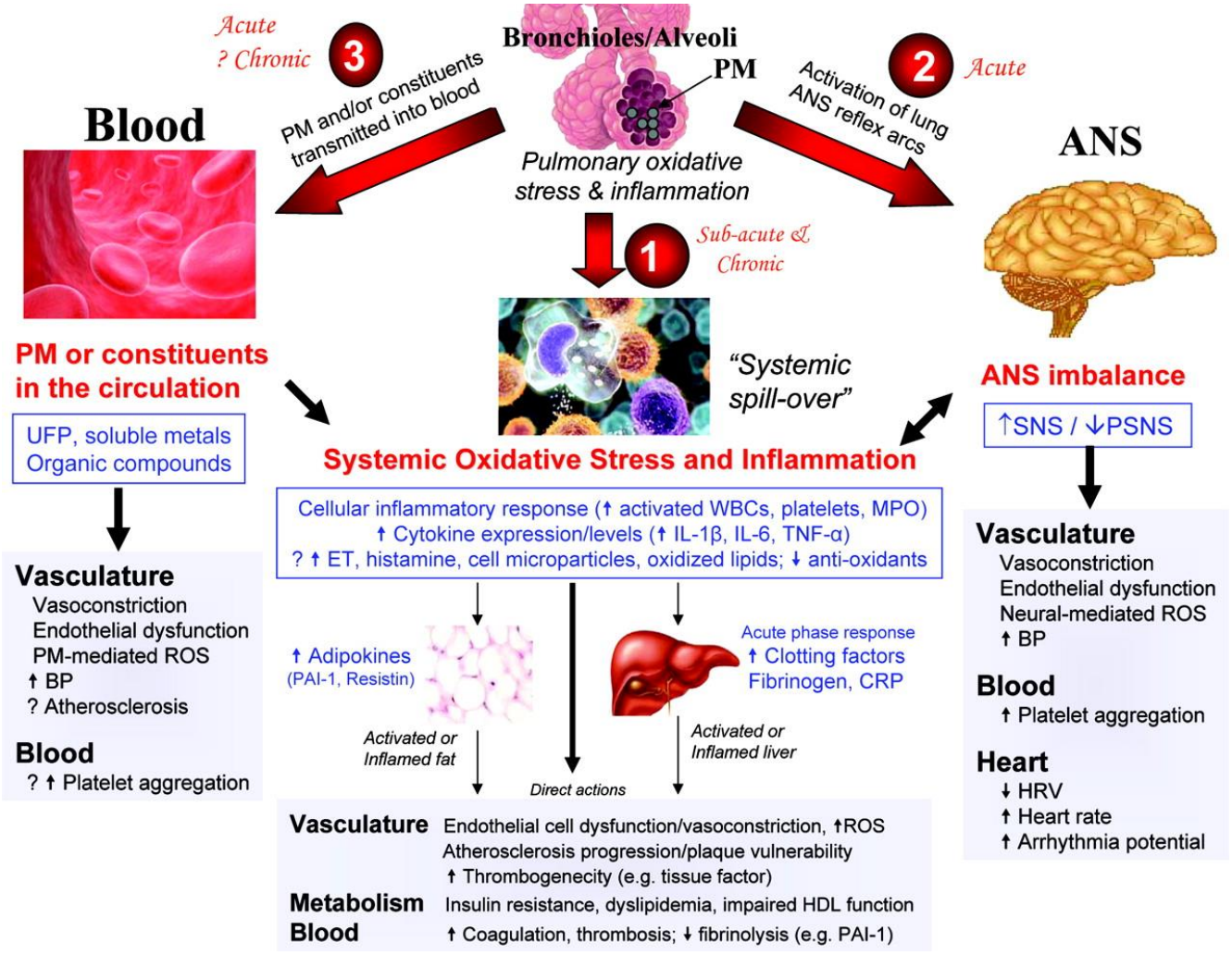
- Strong association between $PM_{2.5}$ and NO_X on CAC progression
- Sensitivity analyses
  - Consistent results between model stages
  - Overall result attenuated compared to site-adjusted
- Effect Modification
  - Stronger associations in older adults and those with diabetes or hypertension
  - No evidence of effect modification by sex, cholesterol, obesity, or SES was observed.

Findings and Conclusions

- Consistent evidence that long-term average predicted outdoor $PM_{2.5}$ and NO_X are associated with an increased progression rate of Coronary Artery Calcium
- This measure of extent of atherosclerosis is strongly related to risk of both myocardial infarction and stroke
- Strongly supports biological plausibility of increased risk of cardiovascular disease due to air pollutant exposures
- Exposures occurred during period of declining PM exposures, but include range of concentrations still common

Extra Slides

Biological pathways linking PM exposure with CVDs



Brook, R. D. et al. Circulation 2010;121:2331-2378

Circulation

American Heart Association
Learn and Live

Environmental factors in cardiovascular disease

Kristen E. Cosselman, Ana Navas-Acien and Joel D. Kaufman

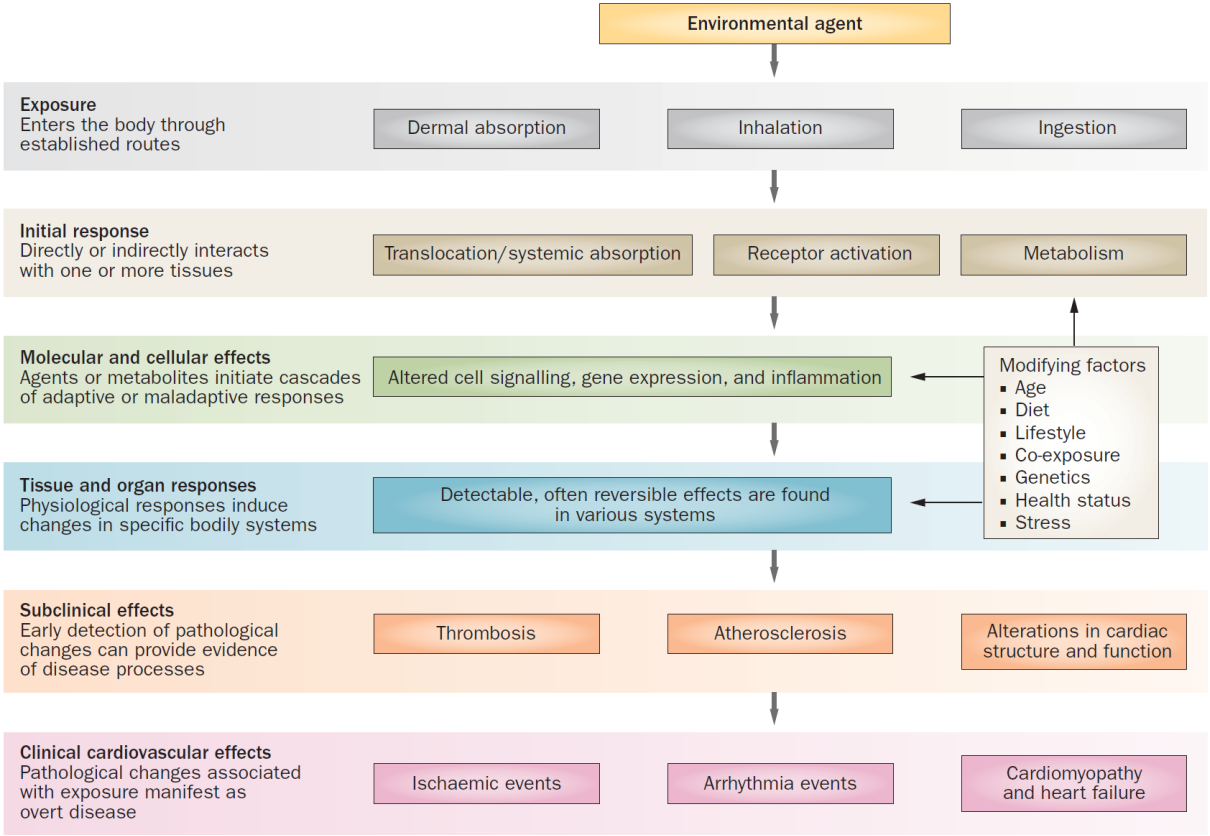
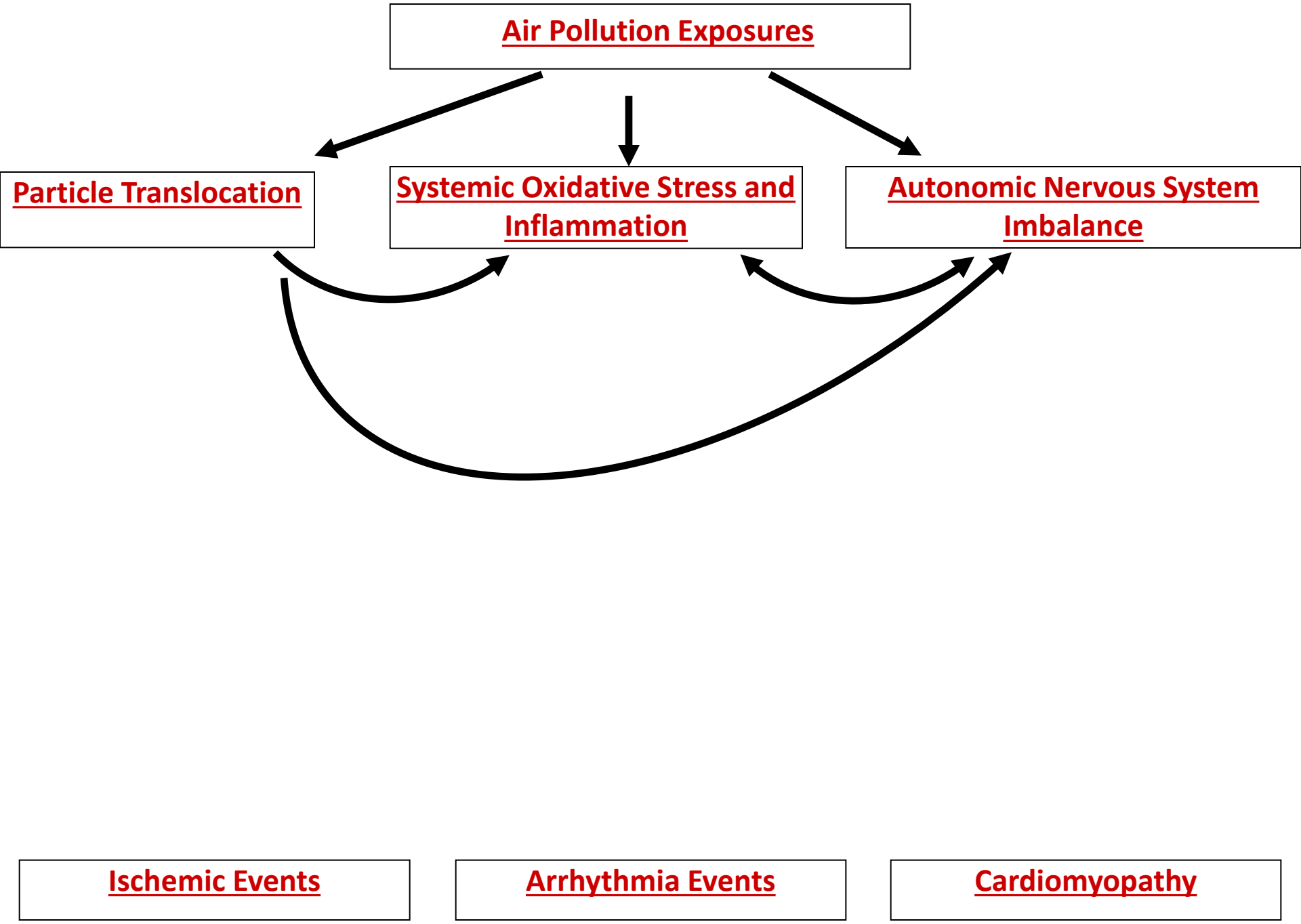
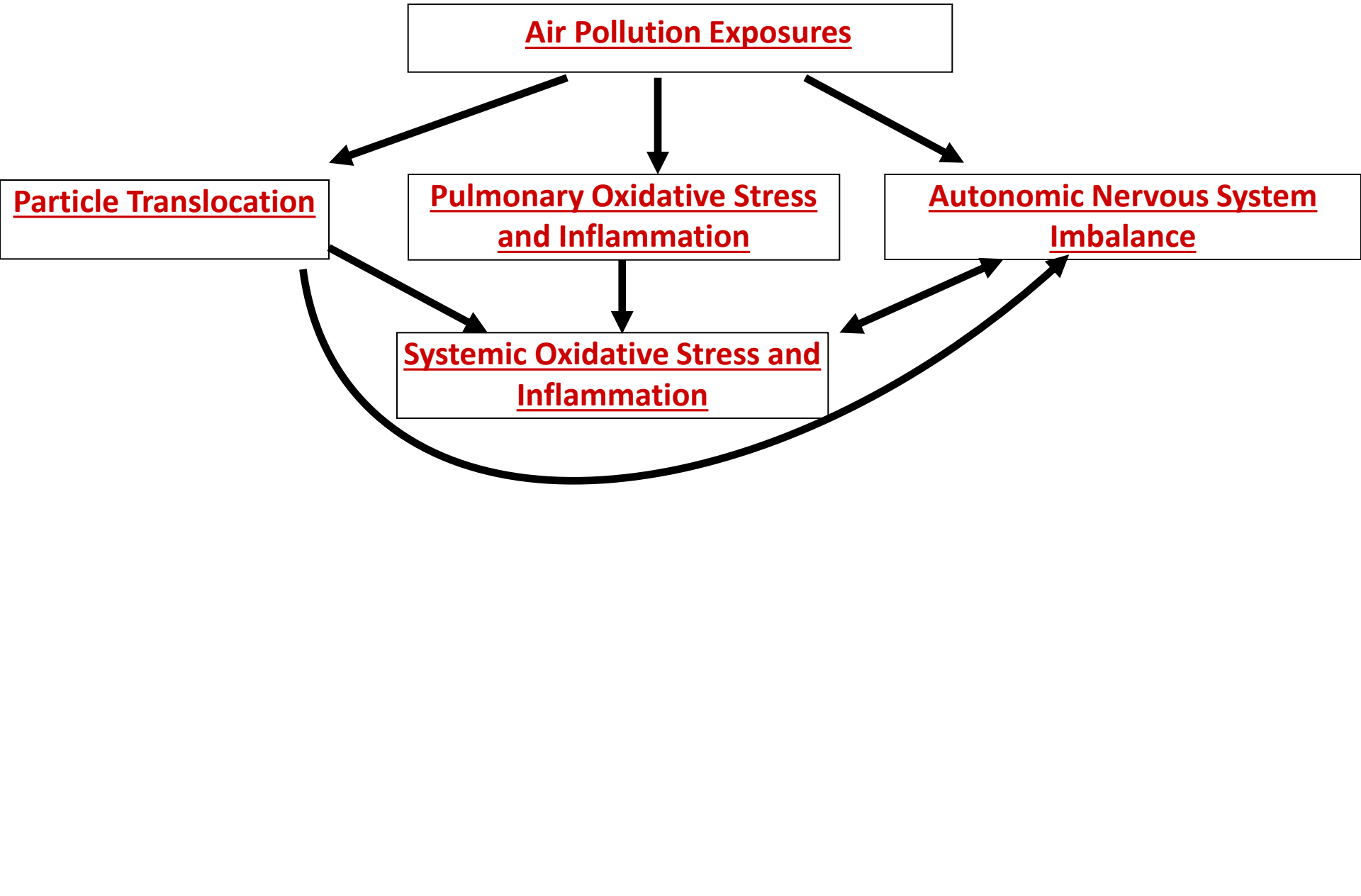
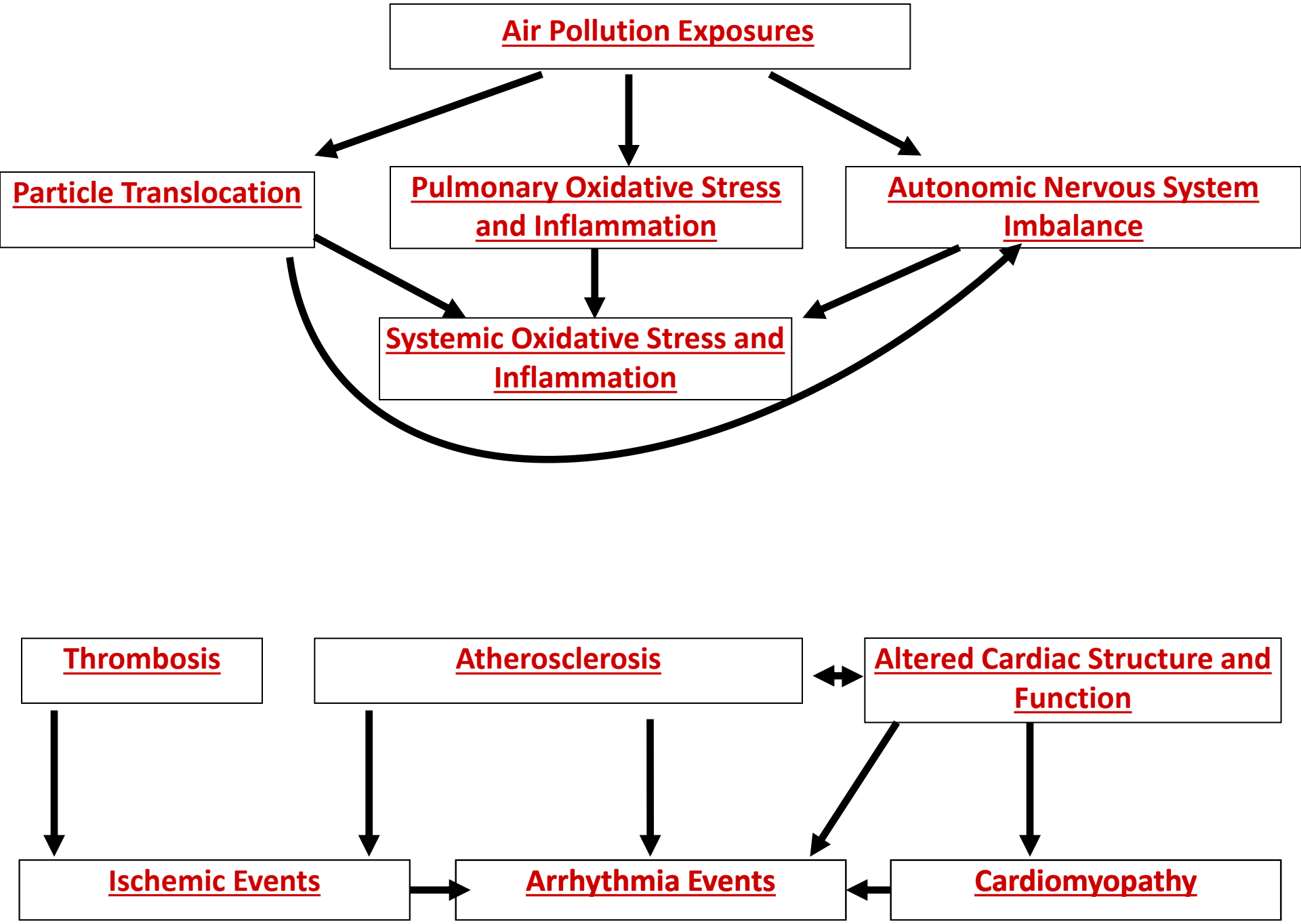
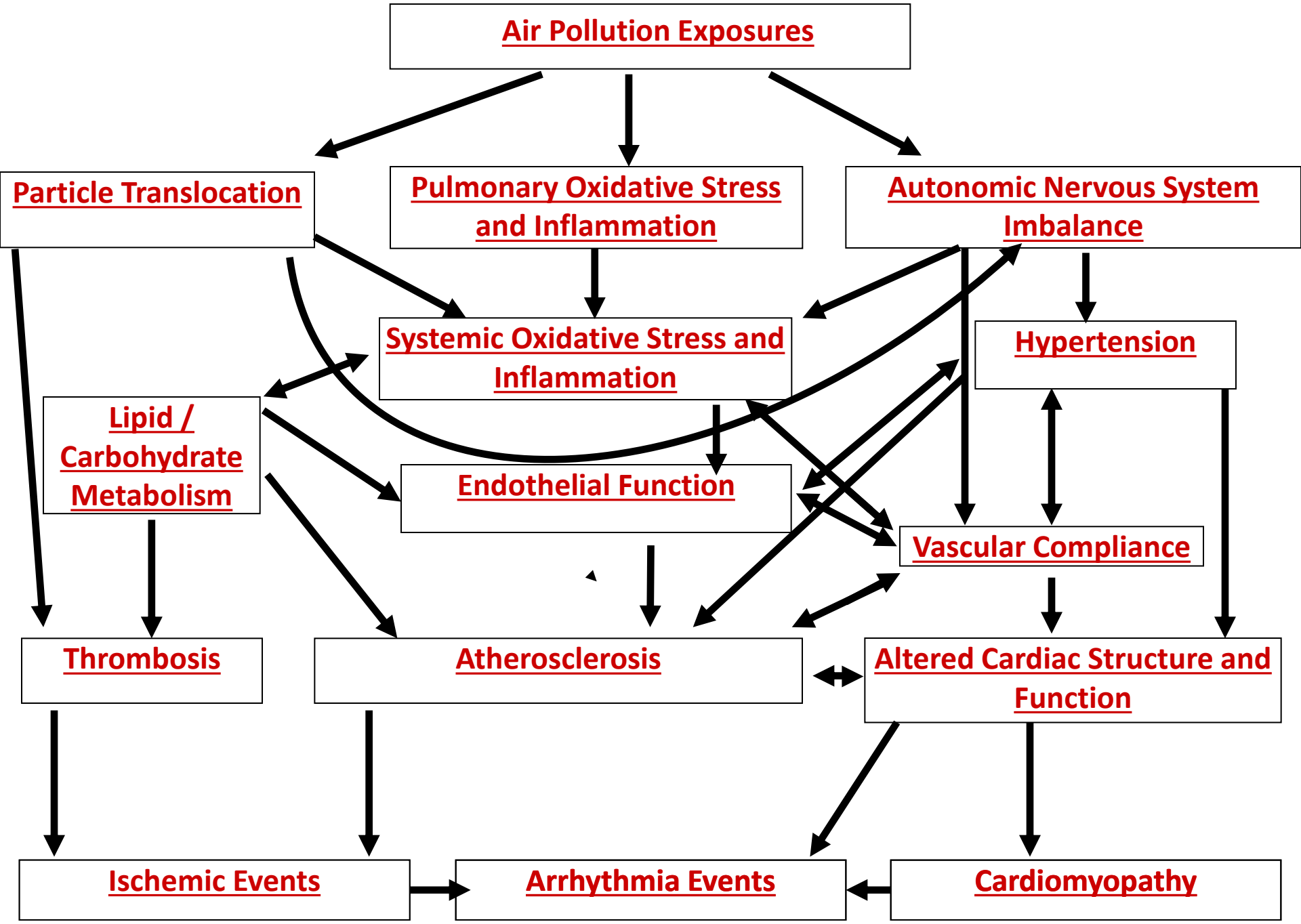


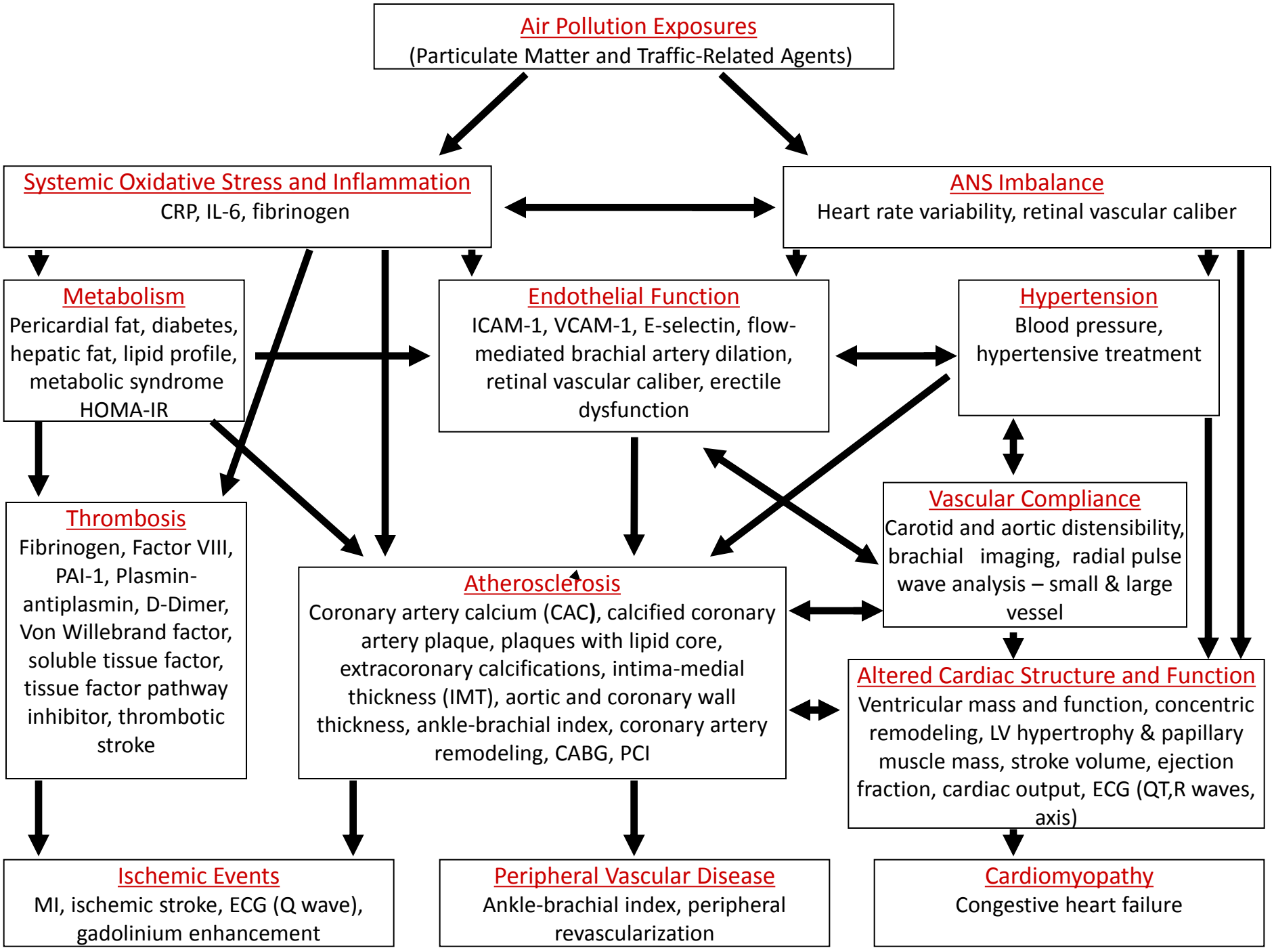
Figure 1 | A framework for the characterization of the effects of environmental factors in cardiovascular disease. A general framework can be constructed to follow the pathways by which the effects of agents are seen. Agents enter the body through established routes, interact with one or more organs and tissues, initiating signalling cascades and physiological responses, leading to subclinical and ultimately clinical pathological changes.

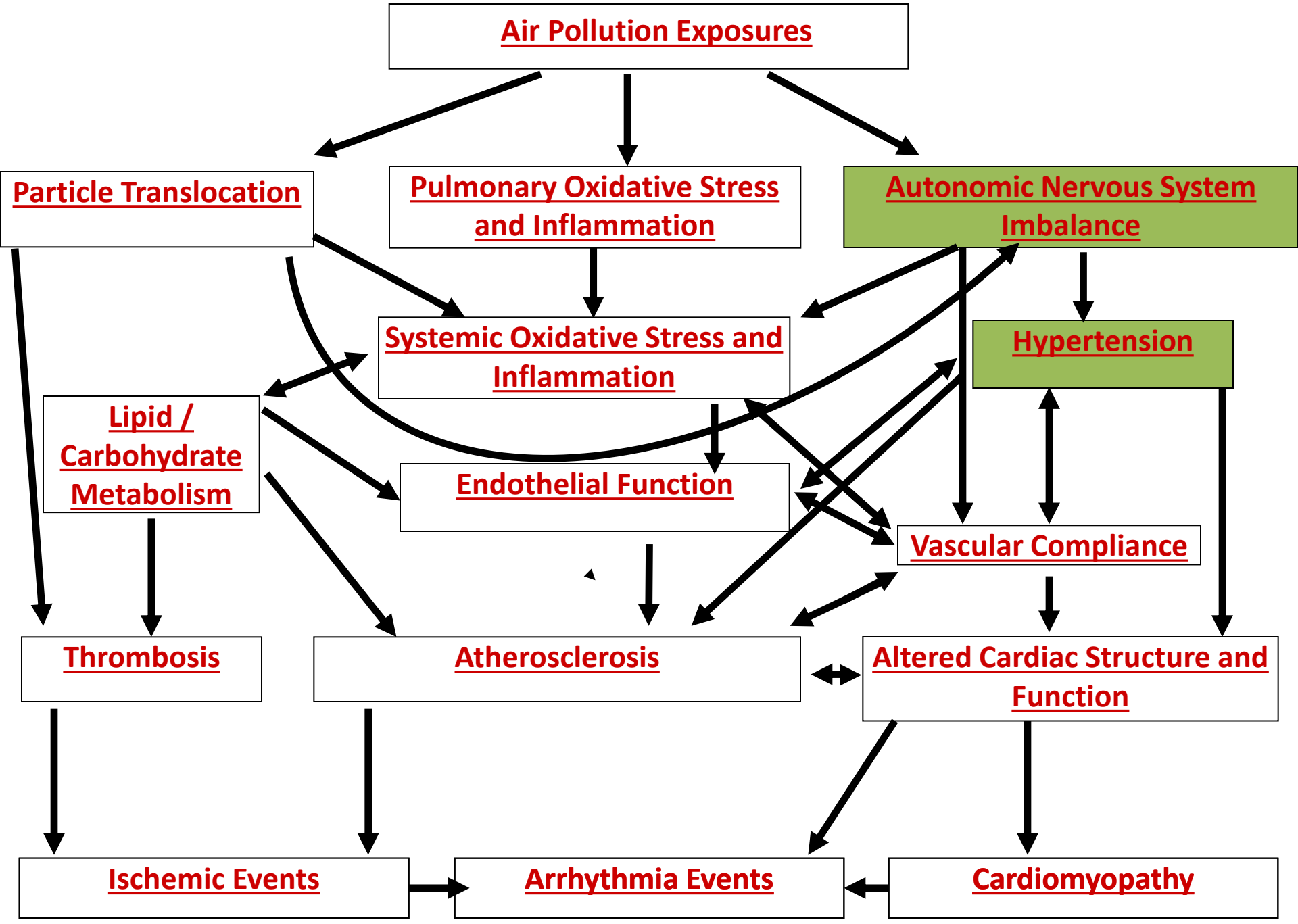

Air Pollution Exposures
Particle Translocation
Systemic Oxidative Stress and Inflammation
Autonomic Nervous System Imbalance
Ischemic Events
Arrhythmia Events
Cardiomyopathy


Air Pollution Exposures
Particle Translocation
Pulmonary Oxidative Stress and Inflammation
Autonomic Nervous System Imbalance
Systemic Oxidative Stress and Inflammation
Ischemic Events
Arrhythmia Events
Cardiomyopathy

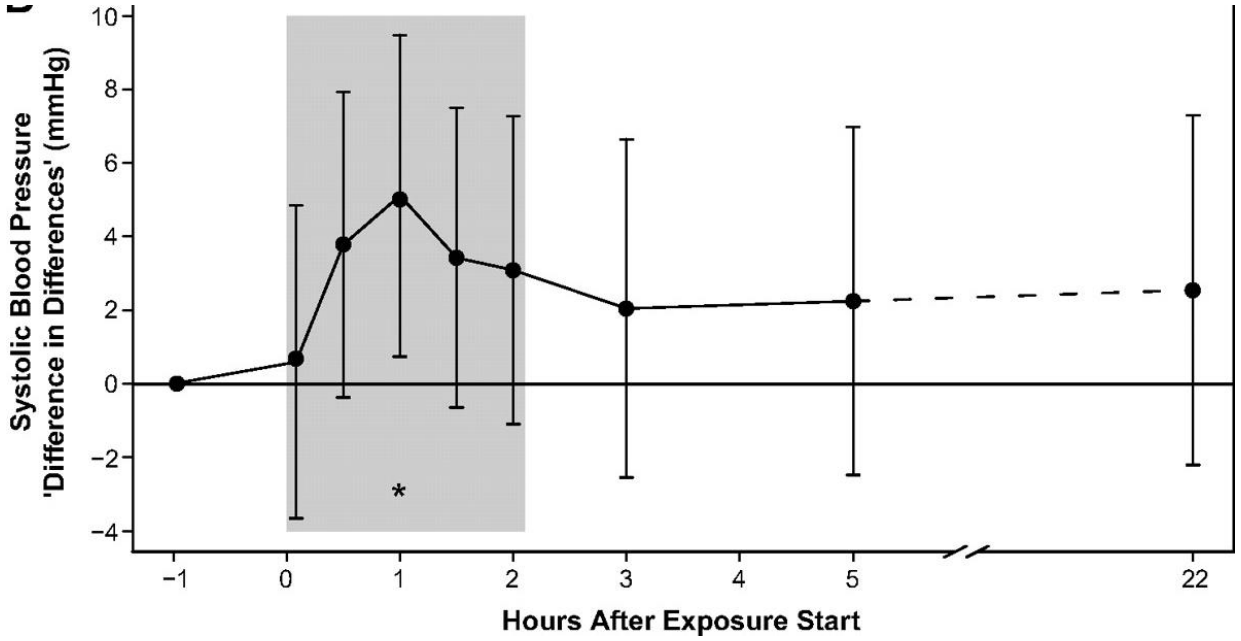

Air Pollution Exposures
Particle Translocation
Pulmonary Oxidative Stress and Inflammation
Autonomic Nervous System Imbalance
Systemic Oxidative Stress and Inflammation
Thrombosis
Atherosclerosis
Altered Cardiac Structure and Function
Ischemic Events
Arrhythmia Events
Cardiomyopathy


Air Pollution Exposures
Particle Translocation
Pulmonary Oxidative Stress and Inflammation
Autonomic Nervous System Imbalance
Systemic Oxidative Stress and Inflammation
Hypertension
Lipid / Carbohydrate Metabolism
Endothelial Function
Vascular Compliance
Thrombosis
Atherosclerosis
Altered Cardiac Structure and Function
Ischemic Events
Arrhythmia Events
Cardiomyopathy


Air Pollution Exposures
(Particulate Matter and Traffic-Related Agents)
Systemic Oxidative Stress and Inflammation
CRP, IL-6, fibrinogen
ANS Imbalance
Heart rate variability, retinal vascular caliber
Metabolism
Pericardial fat, diabetes, hepatic fat, lipid profile, metabolic syndrome HOMA-IR
Endothelial Function
ICAM-1, VCAM-1, E-selectin, flow-mediated brachial artery dilation, retinal vascular caliber, erectile dysfunction
Hypertension
Blood pressure, hypertensive treatment
Thrombosis
Fibrinogen, Factor VIII, PAI-1, Plasmin-antiplasmin, D-Dimer, Von Willebrand factor, soluble tissue factor, tissue factor pathway inhibitor, thrombotic stroke
Vascular Compliance
Carotid and aortic distensibility, brachial imaging, radial pulse wave analysis – small & large vessel
Atherosclerosis
Coronary artery calcium (CAC), calcified coronary artery plaque, plaques with lipid core, extracoronary calcifications, intima-medial thickness (IMT), aortic and coronary wall thickness, ankle-brachial index, coronary artery remodeling, CABG, PCI
Altered Cardiac Structure and Function
Ventricular mass and function, concentric remodeling, LV hypertrophy & papillary muscle mass, stroke volume, ejection fraction, cardiac output, ECG (QT,R waves, axis)
Ischemic Events
MI, ischemic stroke, ECG (Q wave), gadolinium enhancement
Peripheral Vascular Disease
Ankle-brachial index, peripheral revascularization
Cardiomyopathy
Congestive heart failure


Air Pollution Exposures
Particle Translocation
Pulmonary Oxidative Stress and Inflammation
Autonomic Nervous System Imbalance
Systemic Oxidative Stress and Inflammation
Hypertension
Lipid / Carbohydrate Metabolism
Endothelial Function
Vascular Compliance
Thrombosis
Atherosclerosis
Altered Cardiac Structure and Function
Ischemic Events
Arrhythmia Events
Cardiomyopathy

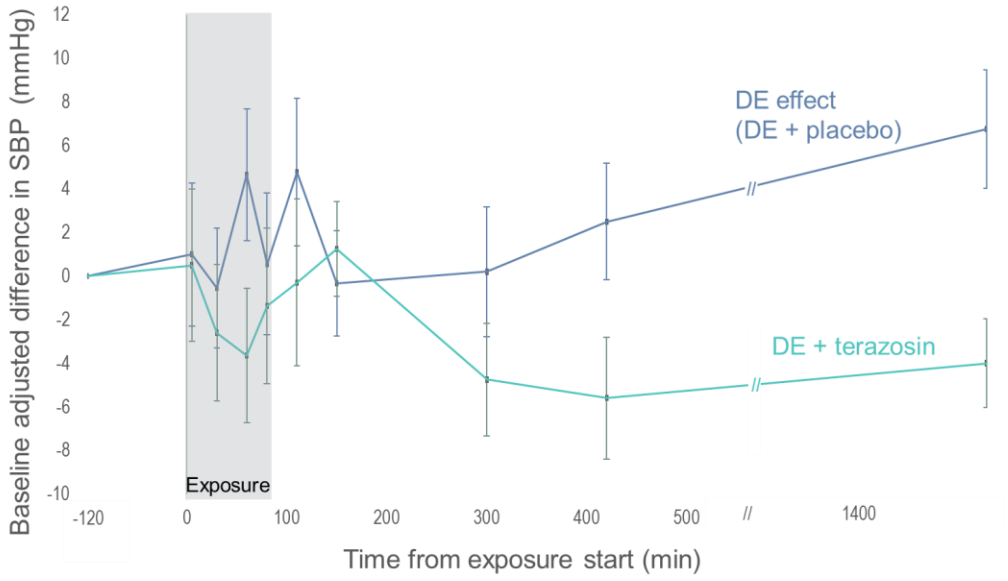
DE exposure: Mean change in systolic blood pressure from baseline



Mean diesel exhaust effect on SBP. Mean difference between change (from pre-exposure) in SBP with DE exposure and change in SBP with FA exposure: a measure of the DE effect on SBP. The mean effect is positive at all of the time points, with peak difference (5.1 mm Hg [95% CI: 0.7–9.5]; *P*=0.02) occurring ≈60 minutes after exposure start. Error bars represent 95% CIs for the paired *t* test.

Cosselman K E et al. Hypertension 2012;59:943-948

DE, Blood Pressure, effect of alpha-adrenergic blockade



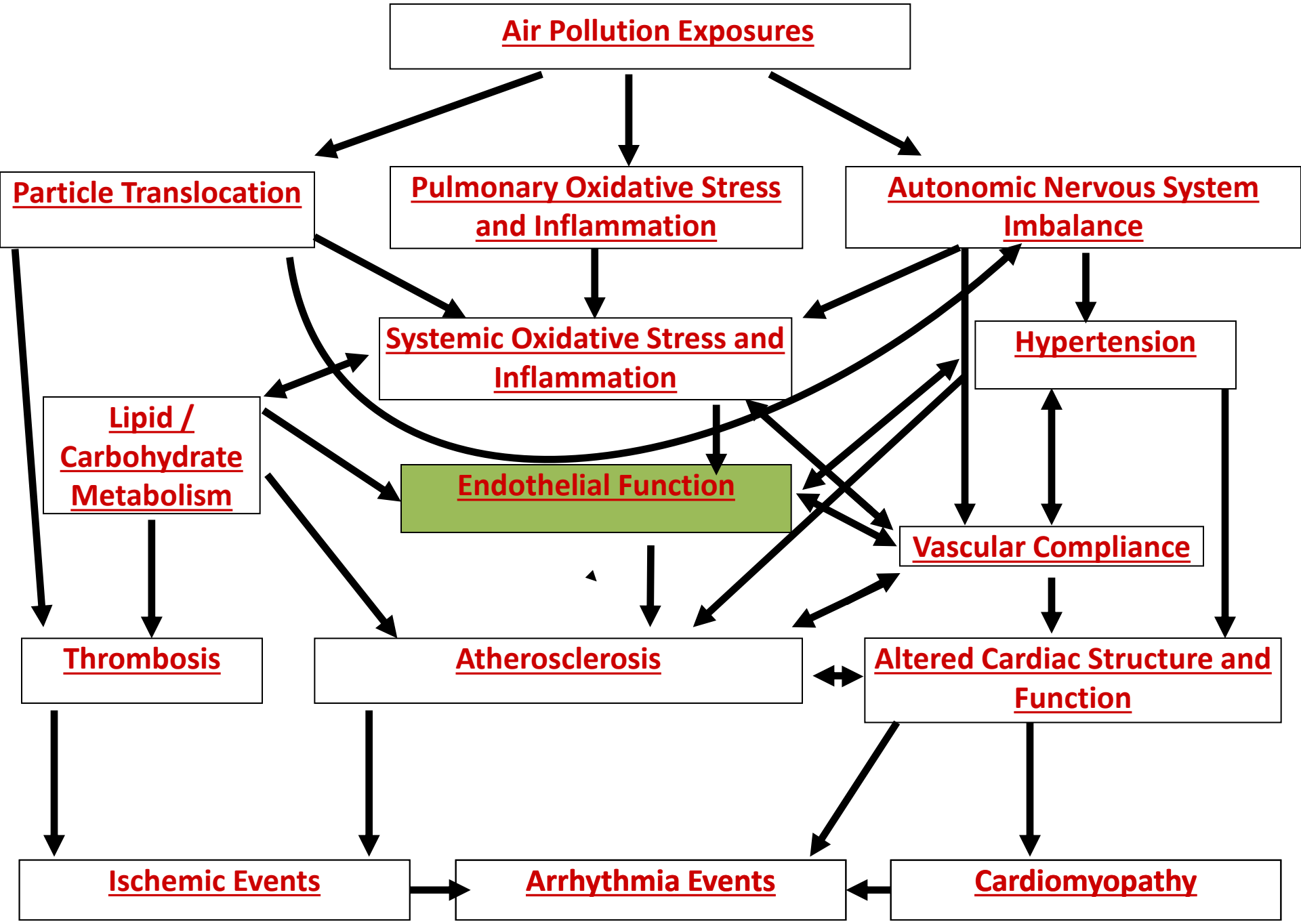
Mean effect of diesel exhaust exposure on systolic blood pressure with terazosin and placebo.

Each line reflects the mean difference between change (from pre-exposure) in SBP with DE exposure and change in SBP with FA exposure: a measure of the DE effect on SBP. Error bars represent 95% confidence intervals.

- Compared with filtered air, systolic blood pressure increased 2.4 mmHg overall (p=0.003 vs. the two-sided hypothesis of no DE effect), with the peak effect 24 hours post exposure (6.8 mmHg, p=0.01).
- Terazosin prophylaxis eliminated the DE effect at all time points, with a -4.8 mmHg (p<.001) and -10.8 mmHg (p=0.005) effect of the interaction overall and at 24 hours, respectively.
- Effects were independent of subjects' perception of exposure or pretreatment.
- Diastolic blood pressure and heart rate were not modified by DE exposure.

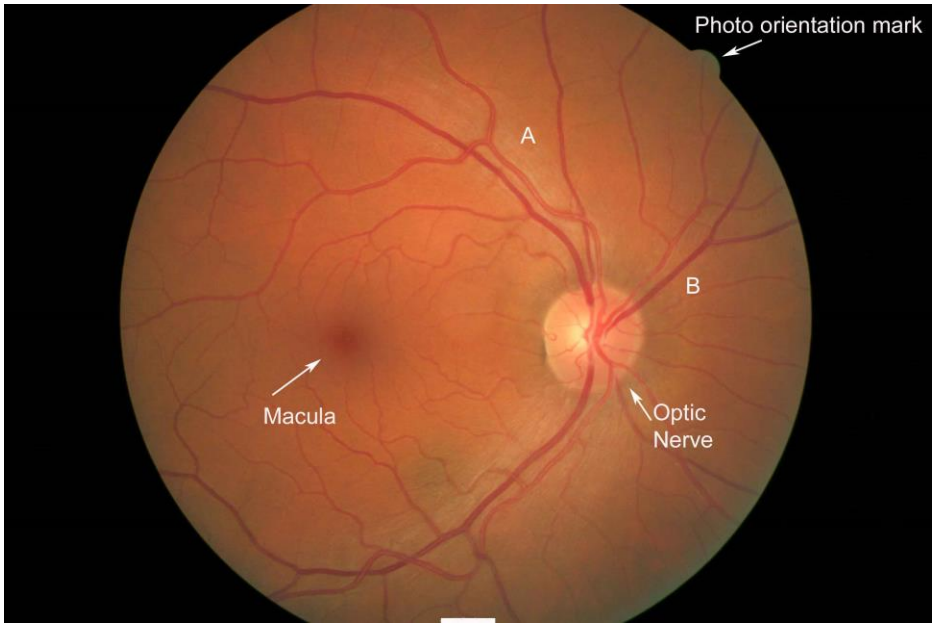
	mean (± SD)*
N	20
Age, yrs	28 ± 8
Male, n (%)	10 (50)
Caucasian, n (%)	13 (65)
Body mass index	24 ± 2.5
SBP, mmHg	106 ± 10
DBP, mmHg	72 ± 7
Heart Rate, bpm	63 ± 8
Total cholesterol, mg/dL	160 ± 28
LDL	95 ± 23
HDL	50 ± 10
Triglycerides	76 ± 40

*unless specified otherwise


Air Pollution Exposures
Particle Translocation
Pulmonary Oxidative Stress and Inflammation
Autonomic Nervous System Imbalance
Systemic Oxidative Stress and Inflammation
Hypertension
Lipid / Carbohydrate Metabolism
Endothelial Function
Vascular Compliance
Thrombosis
Atherosclerosis
Altered Cardiac Structure and Function
Ischemic Events
Arrhythmia Events
Cardiomyopathy

Retinal Photography

- Non-invasive, *in vivo,* method to characterize human microvasculature
- Observes retinal vessels 100-300 μm



Associations between retinal diameter and long- and short-term $PM_{2.5}$ exposures

Model	Retinal Arteriolar Diameter (CRAE)		Retinal Venular Diameter (CRVE)	
	Long-Term Effects	Short-Term Effects	Long-Term Effects	Short-Term Effects
1	−0.5 (−0.9 to −0.1)	−0.4 (−0.8 to −0.04)	0.3 (−0.3 to 0.9)	−0.1 (−0.7 to 0.5)
2	−0.5 (−0.9 to −0.1)	−0.6 (−1.0 to −0.2)	0.5 (−0.04 to 1.1)	−0.1 (−0.7 to 0.5)
3	−0.8 (−1.1 to −0.4)	−0.5 (−1.0 to 0.03)	0.3 (−0.2 to 0.9)	−0.1 (−0.9 to 0.7)
4	−0.9 (−1.2 to −0.6)	−0.4 (−0.8 to 0.1)	0.9 (0.4 to –1.4)	0.4 (−0.3 to 1.1)
Joint	−0.8 (−1.1 to −0.5)	−0.4 (−0.8 to 0.1)	0.9 (0.4 to –1.4)	0.4 (−0.3 to 1.1)

All associations reported as μm per interquartile range of 3 $\mu g/m^3$ (for long term) and 9 $\mu g/m^3$ (for short term). For both long- and short-term associations, model 1 controlled for age, sex, and race/ethnicity. In our long-term analyses, model 2 also included control for BMI, waist-to-hip ratio, income, education, smoking history, alcohol use, and family history of cardiovascular disease. Model 3 of our long-term analysis and Model 2 of our short-term analysis added control for LDL, HDL, blood pressure, diabetes, glucose, physical activity, emphysema, CRP, fibrinogen, and homocysteine. In our short-term analyses, model 2 controlled for all variables in model 3 of our long-term analysis while model 3 also included city-specific trends for day of week, time, temperature, and relative humidity. Model 4 added control for the fellow vessel diameter (e.g., CRAE or CRVE) to each models 3, and the joint model included long- and short-term concentrations simultaneously with control for covariates listed in the two respective models 4.

Adar et al, PLoS Medicine, 2010

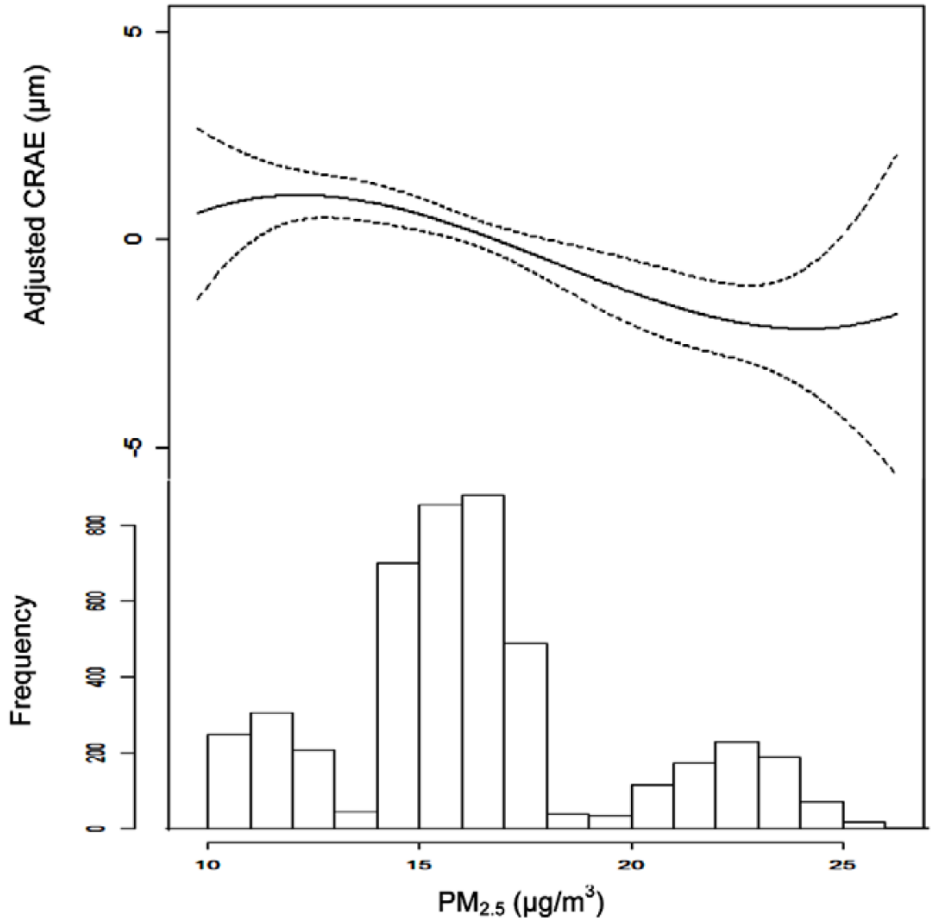


Figure 1. Associations between retinal arteriolar diameter (CRAE) and modeled long-term $PM_{2.5}$ concentrations after control for covariates. Note: CRAE values represent residuals from full joint model (i.e., model controlled for age, sex, race/ethnicity, BMI, waist-to-hip ratio, income, education, smoking history, alcohol use, family history of cardiovascular disease, LDL, HDL, blood pressure, diabetes, glucose, physical activity, emphysema, CRP, fibrinogen, homocysteine, CRVE, and previous day $PM_{2.5}$ concentration). Data are plotted as a cubic polynomial with 3 df.

Adar et al, PLoS Medicine, 2010

Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 60, No. 21, 2012
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.08.973

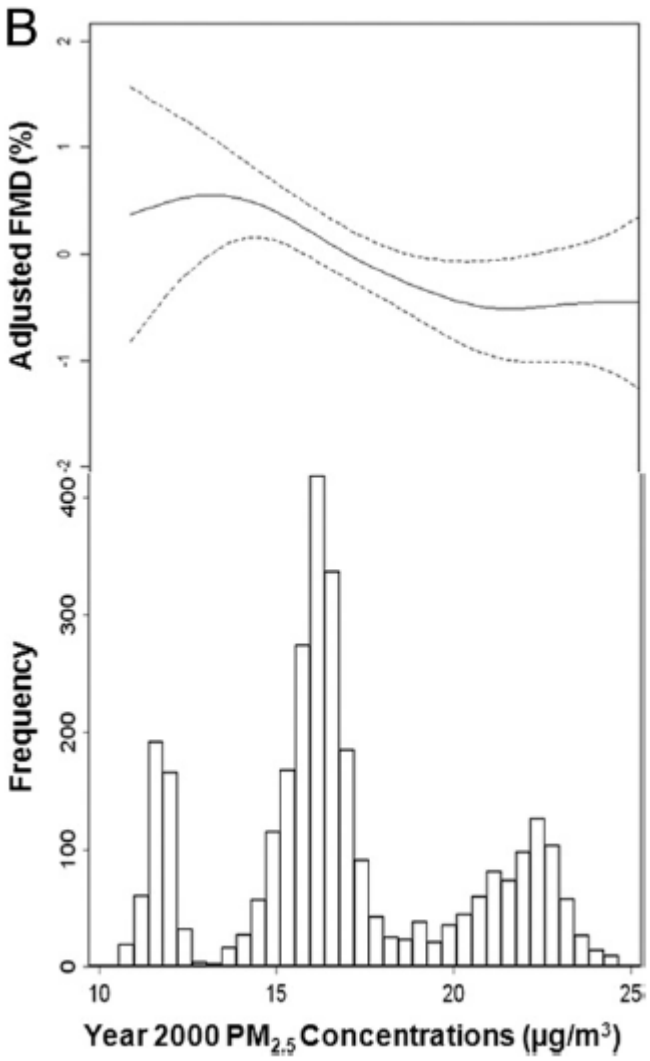
Cardiometabolic Risk

Vascular Responses to Long- and Short-Term Exposure to Fine Particulate Matter

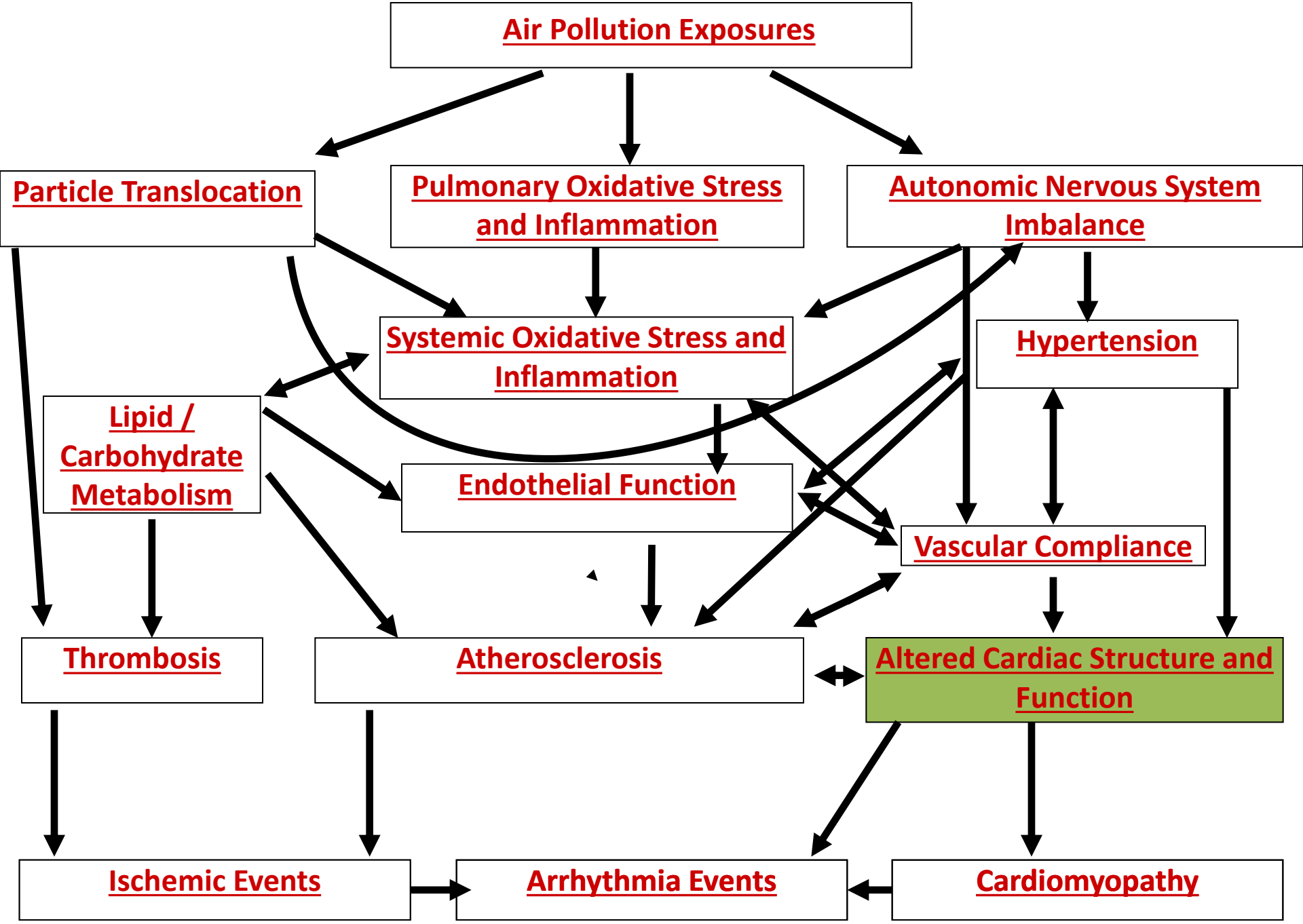
MESA Air (Multi-Ethnic Study of Atherosclerosis and Air Pollution)

Ranjini M. Krishnan, MD, MS,*† Sara D. Adar, ScD,†‡ Adam A. Szpiro, PhD,§ Neal W. Jorgensen, MS,§ Victor C. Van Hee, MD, MPH,*† R. Graham Barr, MD, DrPH,‖ Marie S. O'Neill, PhD,‡¶ David M. Herrington, MD,#** Joseph F. Polak, MD, MPH,†† Joel D. Kaufman, MD, MPH*†#

Results An interquartile increase in long-term $PM_{2.5}$ concentration (3 $\mu g/m^3$) was associated with a 0.3% decrease in FMD (95% confidence interval [CI] of difference: −0.6 to −0.03; p = 0.03), adjusting for demographic characteristics, traditional risk factors, sonographers, and 1/BAD. Women, nonsmokers, younger participants, and those with hypertension seemed to show a greater association of $PM_{2.5}$ with FMD. FMD was not significantly associated with short-term variation in $PM_{2.5}$ (−0.1% per 12 $\mu g/m^3$ daily increase [95% CI: −0.2 to 0.04] on the day before examination).



The values for **(A)** baseline arterial diameter (BAD) and **(B)** flow-mediated dilation (FMD) represent partial residuals from a final model controlled for age, gender, ethnicity, body surface area, sonographer, income, education, smoking, alcohol use, dietary fat intake, emotional distress, physical activity, waist to hip ratio, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein, C-reactive protein, fibrinogen, homocysteine, fasting blood glucose, anti-inflammatory agents, antihypertensive agents, lipid-lowering drugs, and vitamin C. FMD% includes adjustment for 1/BAD. Data are plotted as penalized thin-plate regression splines with smoothness parameter selected by generalized cross-validation for BAD and FMD%.


Air Pollution Exposures
Particle Translocation
Pulmonary Oxidative Stress and Inflammation
Autonomic Nervous System Imbalance
Systemic Oxidative Stress and Inflammation
Hypertension
Lipid / Carbohydrate Metabolism
Endothelial Function
Vascular Compliance
Thrombosis
Atherosclerosis
Altered Cardiac Structure and Function
Ischemic Events
Arrhythmia Events
Cardiomyopathy

Exposure to Traffic and Left Ventricular Mass and Function

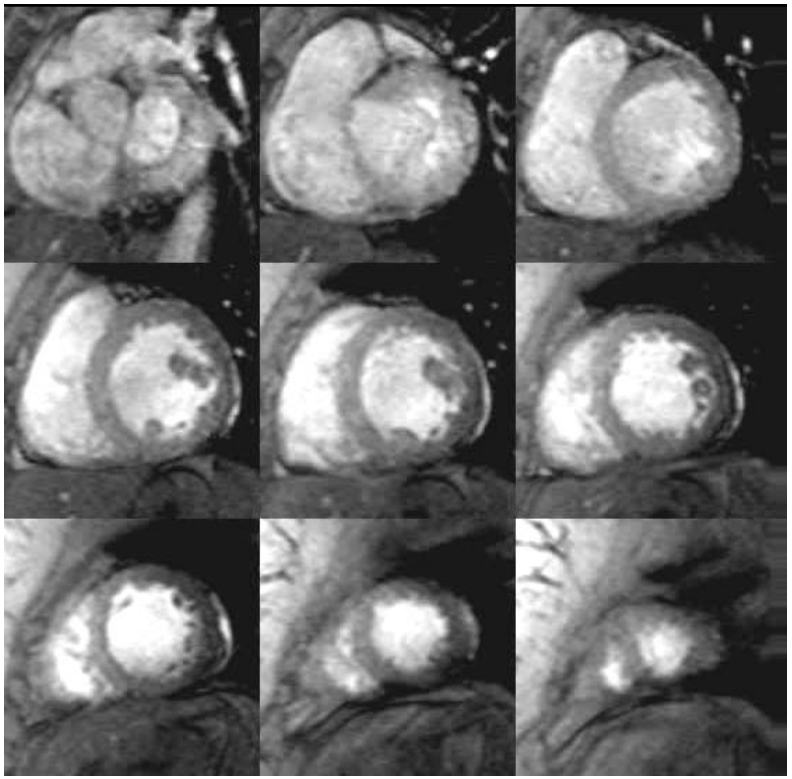
The Multi-Ethnic Study of Atherosclerosis

Victor C. Van Hee[1,2], Sara D. Adar[1], Adam A. Szpiro[3], R. Graham Barr[4], David A. Bluemke[5], Ana V. Diez Roux[6], Edward A. Gill[2], Lianne Sheppard[1,3], and Joel D. Kaufman[1,2]

Methods: A total of 3,827 eligible participants (aged 45–84 yr) underwent cardiac magnetic resonance imaging between 2000 and 2002. We estimated air pollution exposures using residential proximity to major roadways and interpolated concentrations of fine particulate matter (less than 2.5 microns in diameter). We examined adjusted associations between these exposures and left ventricular mass and function.

Measurements and Main Results: Relative to participants living more than 150 m from a major roadway, participants living within 50 m of a major roadway showed an adjusted 1.4 g/m² (95% CI, 0.3–2.5) higher LVMI, a difference in mass corresponding to a 5.6 mm Hg greater systolic blood pressure. Ejection fraction was not associated with proximity to major roadways. Limited variability in estimates of fine particulate matter was observed within cities, and no associations with particulate matter were found for either outcome after adjustment for center.

Conclusions: Living in close proximity to major roadways is associated with higher LVMI, suggesting chronic vascular end-organ damage from a traffic-related environmental exposure. Air pollutants or another component of roadway proximity, such as noise, could be responsible.



Am J Respir Crit Care Med Vol 179. pp 827–834, 2009

Association of Long-term Air Pollution With Ventricular Conduction and Repolarization Abnormalities

Victor C. Van Hee,[a,b] *Adam A. Szpiro,*[c] *Ronald Prineas,*[d] *Jonathan Neyer,*[e] *Karol Watson,*[e] *David Siscovick,*[a,f] *Sung Kyun Park,*[g] *and Joel D. Kaufman*[a,b,f]

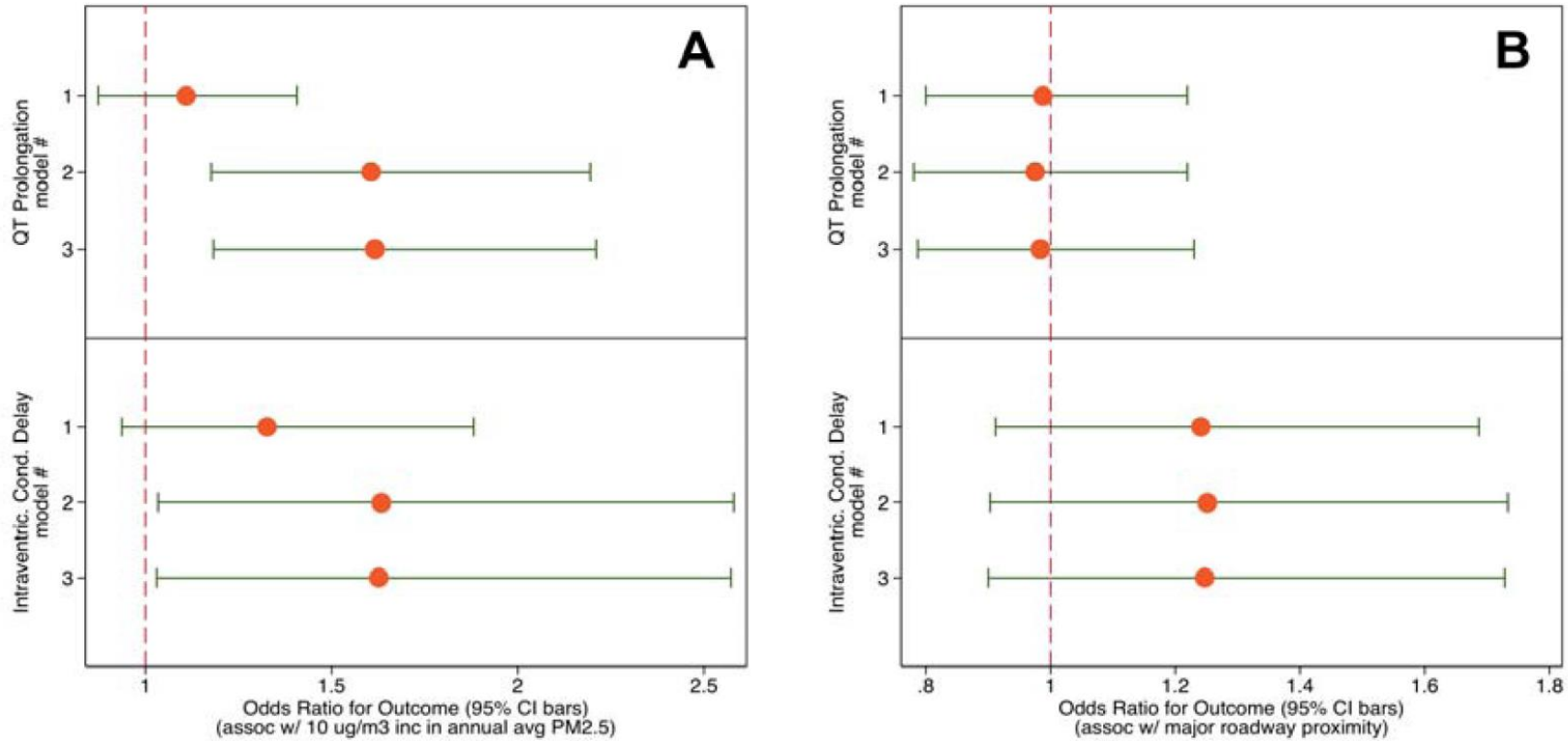
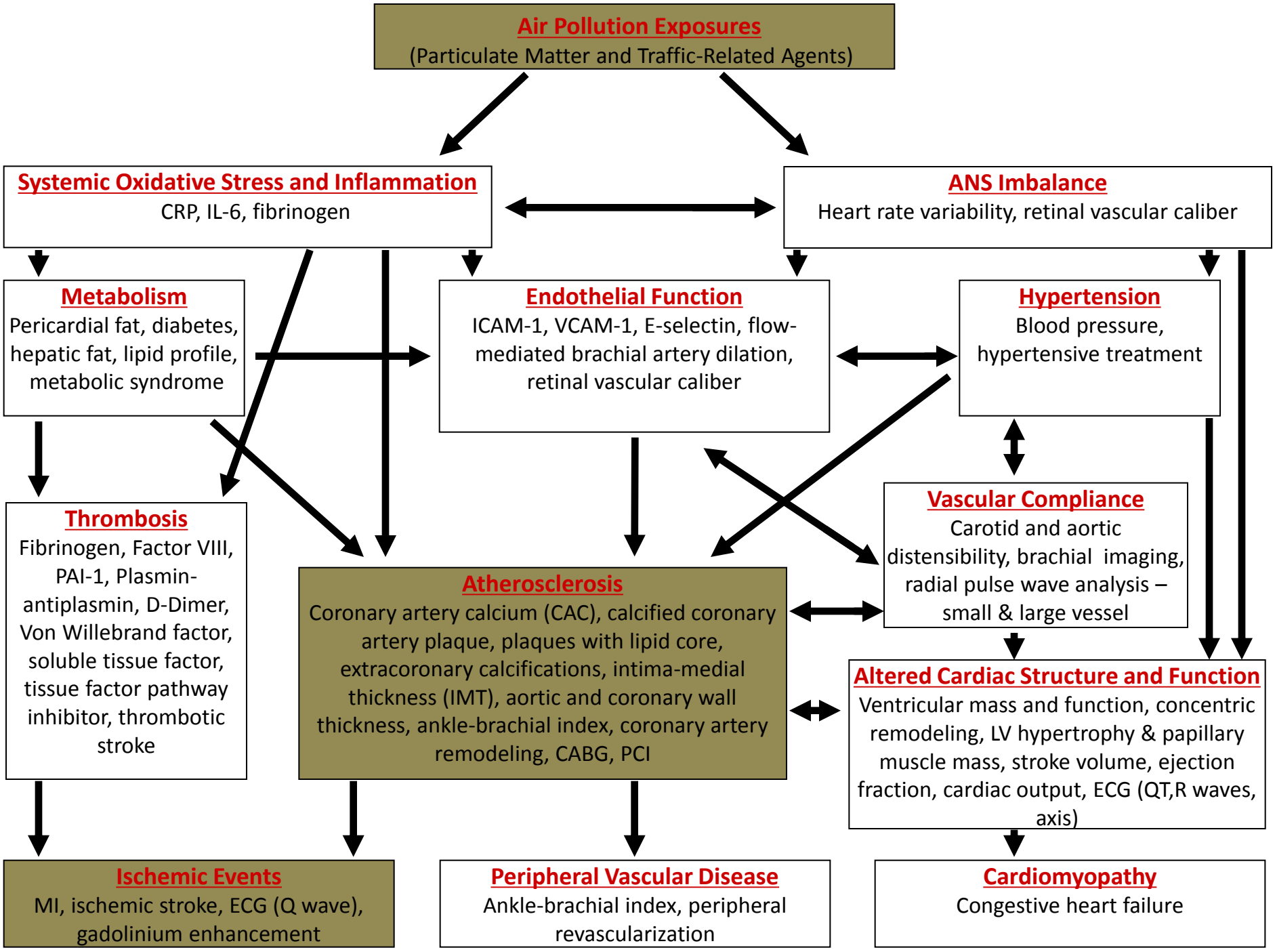


Figure 2: Associations between ventricular conduction abnormalities and A) fine particulate matter ($PM_{2.5}$) exposure and B) residential major roadway proximity. Model 1 includes race, gender, age, and body mass index, income, education, cigarette smoking, systolic and diastolic blood pressure, hypertensive status by JNC VI criteria, diabetes status by 2003 American Diabetes Association fasting blood glucose criteria, LDL and HDL cholesterol, and alcohol use. Model 2 additionally includes study site. Model 3 additionally includes medications known to impact ventricular conduction.

(*Epidemiology* 2011;22: 773–780)


Air Pollution Exposures
(Particulate Matter and Traffic-Related Agents)
Systemic Oxidative Stress and Inflammation
CRP, IL-6, fibrinogen
ANS Imbalance
Heart rate variability, retinal vascular caliber
Metabolism
Pericardial fat, diabetes, hepatic fat, lipid profile, metabolic syndrome
Endothelial Function
ICAM-1, VCAM-1, E-selectin, flow-mediated brachial artery dilation, retinal vascular caliber
Hypertension
Blood pressure, hypertensive treatment
Thrombosis
Fibrinogen, Factor VIII, PAI-1, Plasmin-antiplasmin, D-Dimer, Von Willebrand factor, soluble tissue factor, tissue factor pathway inhibitor, thrombotic stroke
Vascular Compliance
Carotid and aortic distensibility, brachial imaging, radial pulse wave analysis – small & large vessel
Atherosclerosis
Coronary artery calcium (CAC), calcified coronary artery plaque, plaques with lipid core, extracoronary calcifications, intima-medial thickness (IMT), aortic and coronary wall thickness, ankle-brachial index, coronary artery remodeling, CABG, PCI
Altered Cardiac Structure and Function
Ventricular mass and function, concentric remodeling, LV hypertrophy & papillary muscle mass, stroke volume, ejection fraction, cardiac output, ECG (QT,R waves, axis)
Ischemic Events
MI, ischemic stroke, ECG (Q wave), gadolinium enhancement
Peripheral Vascular Disease
Ankle-brachial index, peripheral revascularization
Cardiomyopathy
Congestive heart failure

Environmental factors in cardiovascular disease

Kristen E. Cosselman, Ana Navas-Acien and Joel D. Kaufman

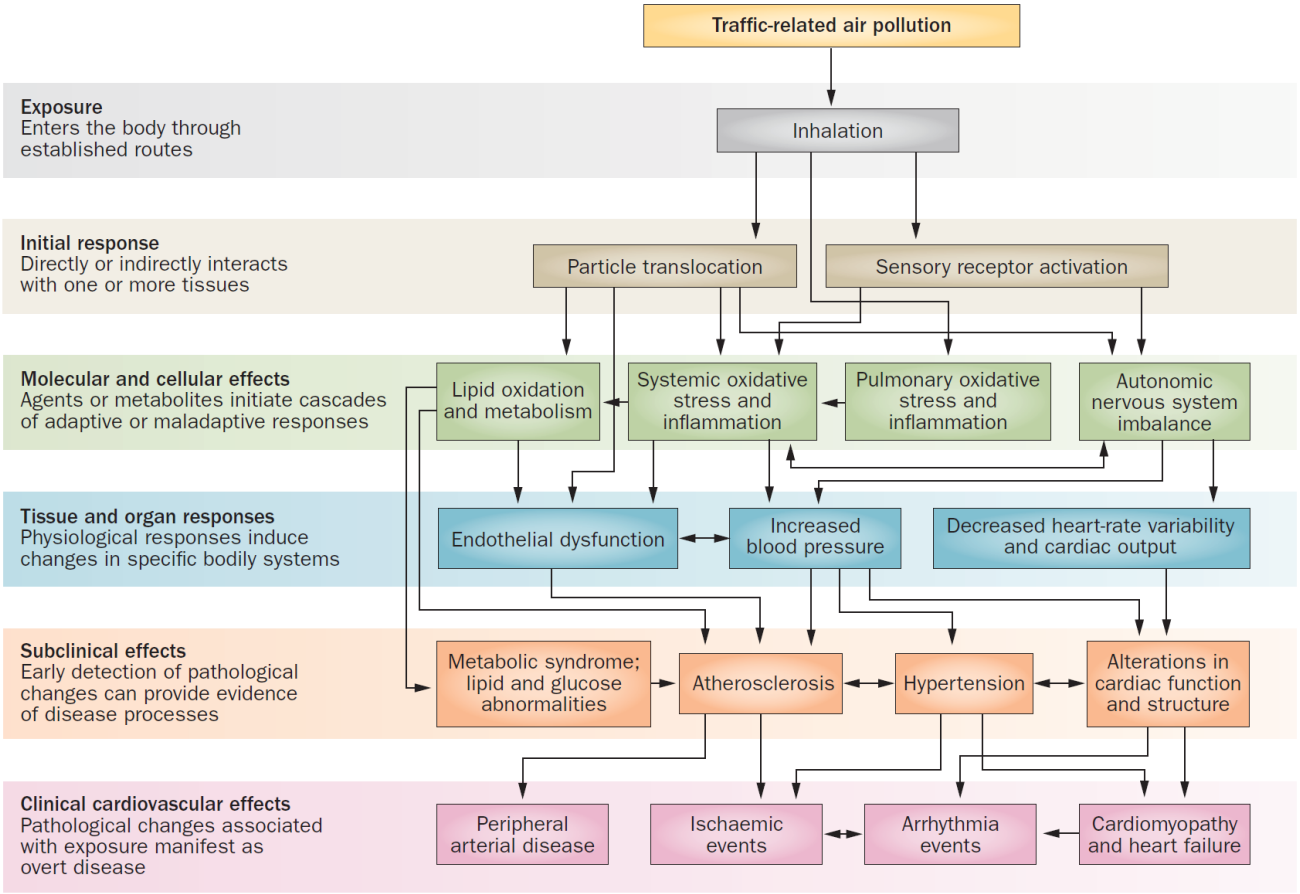


Figure 3 | Cardiovascular effects and proposed mechanisms of chronic exposure to traffic-related air pollution. Inhaled pollutants can activate receptors in the lung, or potentially cross at the alveolar level to enter the systemic circulation. Molecular and cellular effects lead to responses in various tissues and organs, to subclinical effects, and eventually to clinical cardiovascular effects.

Environmental factors in cardiovascular disease

Kristen E. Cosselman, Ana Navas-Acien and Joel D. Kaufman

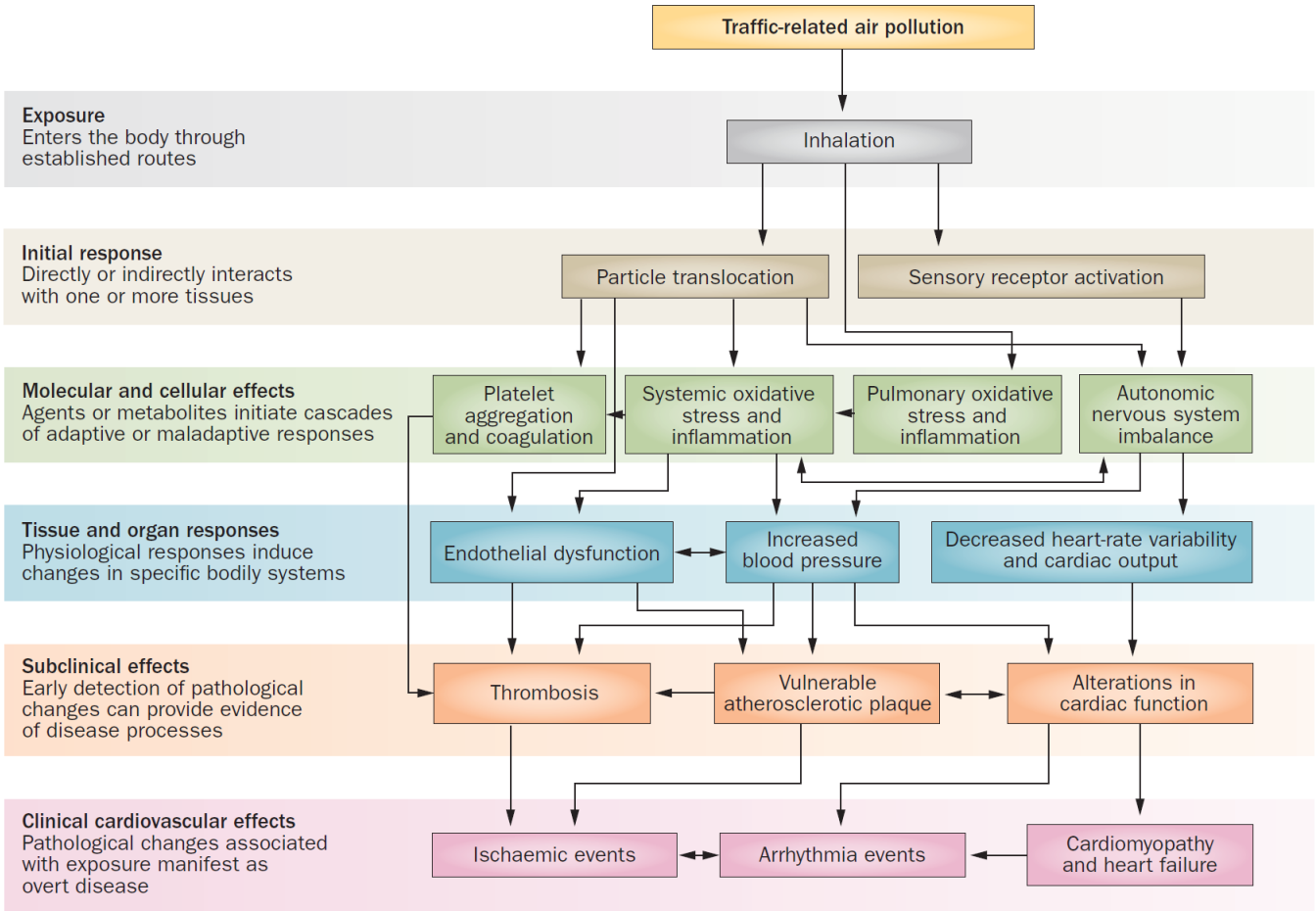


Figure 4 | Cardiovascular effects and proposed mechanisms of acute exposure to traffic-related air pollution. Inhaled pollutants can initiate biological effects at the local or systemic level. Increases in pollutant exposure can trigger acute cardiovascular effects in susceptible individuals.

Environmental factors in cardiovascular disease

Kristen E. Cosselman, Ana Navas-Acien and Joel D. Kaufman

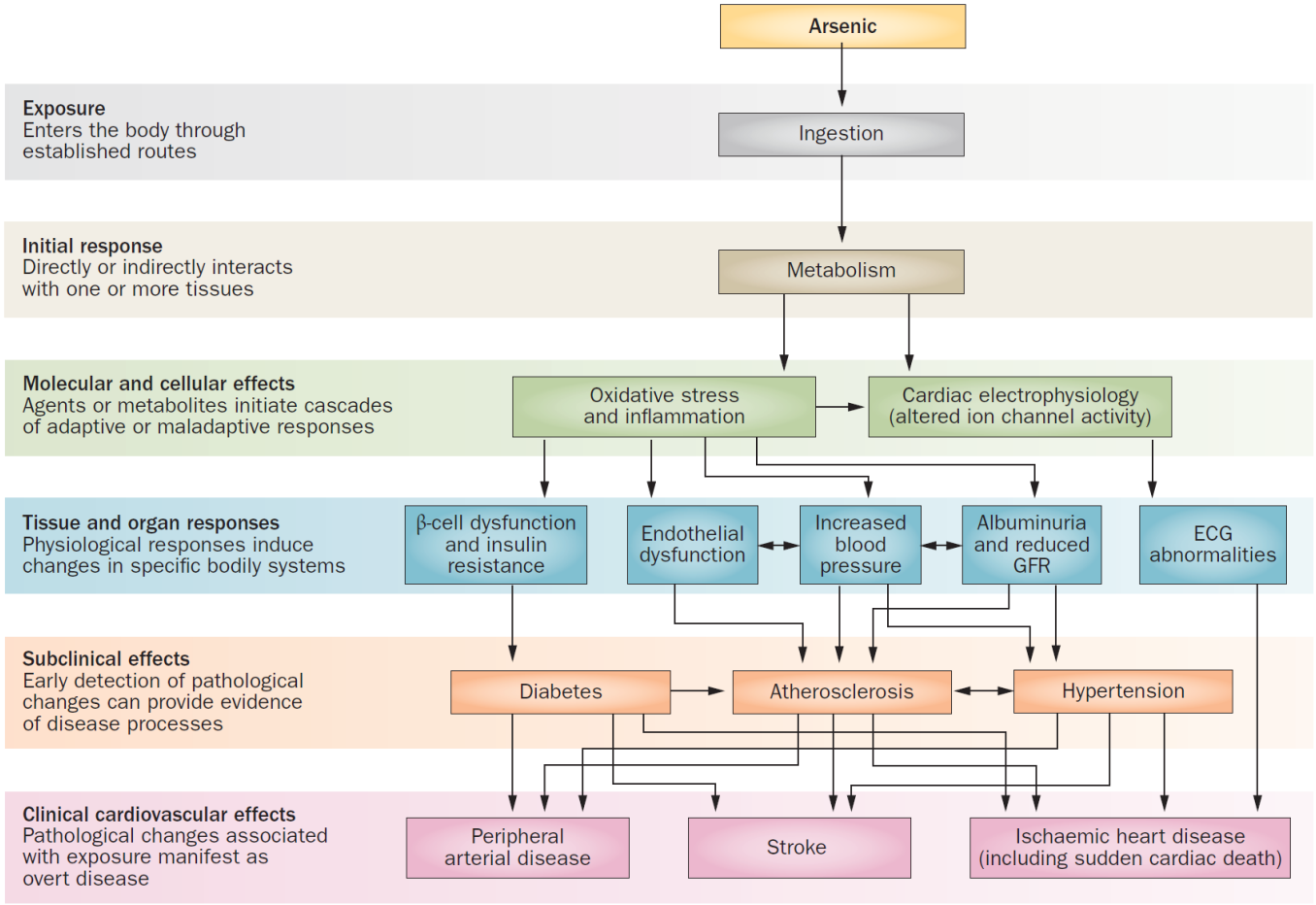


Figure 5 | Possible mechanisms for the cardiovascular effects of exposure to arsenic. Ingestion of food and water containing arsenic constitutes the main source of exposure to arsenic in most populations, although occupational exposure and inhalation are also routes. Abbreviations: ECG, electrocardiograph; GFR, glomerular filtration rate.

Environmental Factors in Cardiovascular Disease

- Disease Expression Can Usually Be Conceived of as Genes + Environment
- Environmental Factors
  - Some well-evaluated and often-considered
  - Some less-thoroughly understood
  - "Lifestyle" factors vs. factors to which exposure is not a personal choice

Air Pollution and the Cardiovascular System

- Epidemiological Studies
  - Increasingly sophisticated and mostly consistent observations
    - From “cardiopulmonary” mortality in cohort studies and overall mortality in time-series studies
    - To verified cardiovascular events in cohort studies and case-crossover studies
    - To clinically (or pathophysiologically) relevant subclinical measures in panel or cohort studies
- Experimental Approaches
  - Animal Studies Using Relevant Models
  - Human Controlled Exposure Inhalation Studies
    - CAPS and DE

Cardiovascular Events with Short-Term Air Pollutant Exposures

- More Consistent
  - Myocardial Infarction
  - Stroke
    - Mostly ischemic?
- Some Observations
  - Arrhythmias
  - Heart Failure

Mechanisms Sought to Explain Epidemiological Observations

- Short-term Increases in Pollutant Concentration Associated with *Triggering* of Acute Cardiovascular Events
- Long-term Concentration Gradients Associated with Increased Risk of Cardiovascular Events

- Appealing to consider common mechanisms, though common mechanism not necessary

Research Needs

- Understand biological mechanisms underlying effects
- Understanding of most toxic components of the air pollution mix
  - Enable more cost-effective prevention measures
- Understanding of most susceptible populations
  - Target prevention resources
- Testing of interventions to reduce exposures and effects
  - Translate research into action