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

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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)

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

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

**THE TOP 12 RISK FACTORS**

Factors Causing the Greatest "Loss of Health"

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

Lancet, 2012

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).
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
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
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/m³ Change in Fine Particles Measuring Less Than 2.5 μm in Diameter

<table>
<thead>
<tr>
<th>Cause of Mortality</th>
<th>1979-1983</th>
<th>1999-2000</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>1.04 (1.01-1.08)</td>
<td>1.06 (1.02-1.10)</td>
<td>1.06 (1.02-1.11)</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>1.06 (1.02-1.10)</td>
<td>1.08 (1.02-1.14)</td>
<td>1.09 (1.03-1.16)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.08 (1.01-1.16)</td>
<td>1.13 (1.04-1.22)</td>
<td>1.14 (1.04-1.23)</td>
</tr>
<tr>
<td>All other cause</td>
<td>1.01 (0.97-1.05)</td>
<td>1.01 (0.97-1.06)</td>
<td>1.01 (0.95-1.06)</td>
</tr>
</tbody>
</table>

*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
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 them.
WHI-OS Participant Residences

Subjects per zip code: 6 - 12, 13 - 32, 33 - 65, 66 - 134, 135 - 297
Exposure Data

- EPA AIRS database
- Annual Average Concentrations, year 2000
- Pollutants:
  - $\text{PM}_{2.5}$ (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>
<thead>
<tr>
<th>PM$_{2.5}$ Exposure</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Individual exposure</td>
<td>13.5±3.7</td>
</tr>
<tr>
<td>Citywide average exposure</td>
<td>13.5±3.3</td>
</tr>
<tr>
<td>Difference between individual exposure and citywide average exposure</td>
<td>0±1.6</td>
</tr>
</tbody>
</table>

* 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.
Estimated Hazard Ratios for the Time to the First Cardiovascular Event or Death Associated with an Exposure Increase of 10 \(\mu g\) per Cubic Meter in the Level of Fine Particulate Matter (PM\(_{2.5}\))

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Events</th>
<th>Hazard Ratio (95% CI)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Overall</td>
<td>Between Cities</td>
<td>Within Cities</td>
</tr>
<tr>
<td>First cardiovascular event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cardiovascular event†</td>
<td>1816</td>
<td>1.24 (1.09–1.41)</td>
<td>1.15 (0.99–1.32)</td>
<td>1.64 (1.24–2.18)</td>
</tr>
<tr>
<td>Coronary heart disease‡</td>
<td>1268</td>
<td>1.21 (1.04–1.42)</td>
<td>1.13 (0.95–1.35)</td>
<td>1.56 (1.11–2.19)</td>
</tr>
<tr>
<td>Cerebrovascular disease§</td>
<td>600</td>
<td>1.35 (1.08–1.68)</td>
<td>1.20 (0.94–1.54)</td>
<td>2.08 (1.28–3.40)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>584</td>
<td>1.06 (0.85–1.34)</td>
<td>0.97 (0.75–1.25)</td>
<td>1.52 (0.91–2.51)</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>949</td>
<td>1.20 (1.00–1.43)</td>
<td>1.14 (0.93–1.39)</td>
<td>1.45 (0.98–2.16)</td>
</tr>
<tr>
<td>Stroke</td>
<td>554</td>
<td>1.28 (1.02–1.61)</td>
<td>1.12 (0.87–1.45)</td>
<td>2.08 (1.25–3.48)</td>
</tr>
<tr>
<td>Death from cardiovascular cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any death from cardiovascular cause</td>
<td>261</td>
<td>1.76 (1.25–2.47)</td>
<td>1.63 (1.10–2.40)</td>
<td>2.28 (1.10–4.75)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite diagnosis</td>
<td>80</td>
<td>2.21 (1.17–4.15)</td>
<td>2.22 (1.06–4.62)</td>
<td>2.17 (0.60–7.89)</td>
</tr>
<tr>
<td>Possible diagnosis</td>
<td>59</td>
<td>1.26 (0.62–2.56)</td>
<td>1.20 (0.54–2.63)</td>
<td>1.57 (0.29–8.51)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>122</td>
<td>1.83 (1.11–3.00)</td>
<td>1.58 (0.90–2.78)</td>
<td>2.93 (1.03–8.38)</td>
</tr>
</tbody>
</table>

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

Deterministic Models

Outdoor Pollutant Measurements

Indoor Pollutant Measurements

Reported Housing Characteristics

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

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
- \( \text{PM}_{2.5}, \text{NO}_2, \text{NO}_X, \text{BC} \)
- 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 (\( \text{NO}_X \) and \( \text{NO}_2 \) only)
  - Clusters around roadways
Fixed Sites & Home Outdoor
“Snapshot” Set Up
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.
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

Average PM$_{2.5}$ Predictions at Subject Locations
PM$_{2.5}$ Predictions

Average PM$_{2.5}$ Predictions at Los Angeles Subject Locations
NO\textsubscript{X} Predictions: 2000 Average
\( \text{NO}_x \) Predictions: 2000 Average
Coronary Artery Calcium (CAC)

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

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

- 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

<table>
<thead>
<tr>
<th>Site</th>
<th>PM$_{2.5}$ (µg/m$^3$)</th>
<th>NO$_X$ (ppb)</th>
<th>NO$_2$ (ppb)</th>
<th>BC (µg/m$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St. Paul</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baltimore</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chicago</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winston-Salem</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall IQR</td>
<td>(12.9, 15.7)</td>
<td>(21.4, 57.3)</td>
<td>(11.8, 26.4)</td>
<td>(0.5, 1.2)</td>
</tr>
</tbody>
</table>
Number of CT Scans by Exam

- Eligible: 7067
  - Score at E1: 7057
    - No Follow-Up
      - 1 Score: 814
        - 1 Score Used for Cross-Sectional Piece of Model: 887
          - Coronary Revascularization: 166
            - Before E2 or E3: 61
            - Before E4: 32
            - Before E5: 73

- Have Follow-Up Scores: 6243
  - 2 Scores: 2660
    - Last Score E2 or E3: 2335
    - E4 Score: 123
    - E5 Score: 202
      - 2 Scores Used: 2712
        - Last Score E2 or E3: 2394
        - Last Score E4: 118
        - Last Score E5: 200

  - 3 Scores: 2823
    - Last Score E4: 301
    - Last Score E5: 2522
      - 3 Scores Used: 2719
        - Last Score E4: 292
        - Last Score E5: 2427

  - 4 Scores: 760
    - Last Score E5
      - 4 Scores Used: 739
        - Last Score E5
## Baseline Participant Characteristics by Exposure

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


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

PM or constituents in the circulation
- UFP, soluble metals
- Organic compounds

Blood
- PM or constituents in the circulation
- Blood
  - Vasoconstriction
  - Endothelial dysfunction
  - PM-mediated ROS
  - ↑ BP
  - ↑ Platelet aggregation

Blood
- ↑ Platelet aggregation

Vasculature
- Endothelial cell dysfunction/vasoconstriction, ↑ ROS
- Atherosclerosis progression/plaque vulnerability
- ↑ Thrombogenicity (e.g. tissue factor)

Metabolism
- Insulin resistance, dyslipidemia, impaired HDL function
- ↑ Coagulation, thrombosis; ↓ fibrinolysis (e.g. PAI-1)

Cellular inflammatory response (↑ activated WBCs, platelets, MPO)
- ↑ Cytokine expression/levels (↑ IL-1β, IL-6, TNF-α)
- ↑ ET, histamine, cell microparticles, oxidized lipids; ↓ anti-oxidants

Acute phase response
- ↑ Clotting factors
- Fibrinogen, CRP

Activated or Inflamed fat
- Direct actions
- Activated or Inflamed liver

Acute
- Activation of lung ANS reflex arcs

Sub-acute & Chronic
- Systemic spill-over

Blood
- Activation of lung ANS reflex arcs

Blood
- Activation of lung ANS reflex arcs

ANS imbalance
- ↑ SNS / ↓ PSNS

Vasculature
- Vasoconstriction
- Endothelial dysfunction
- Neural-mediated ROS
- ↑ BP

Blood
- ↑ Platelet aggregation

Heart
- ↓ HRV
- ↑ Heart rate
- ↑ Arrhythmia potential

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

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

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 inSBP 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.
DE, Blood Pressure, effect of alpha-adrenergic blockade

- 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 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.

<table>
<thead>
<tr>
<th></th>
<th>mean (± SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>28 ± 8</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24 ± 2.5</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>106 ± 10</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>72 ± 7</td>
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<tr>
<td>Heart Rate, bpm</td>
<td>63 ± 8</td>
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<tr>
<td>Total cholesterol, mg/dL</td>
<td>160 ± 28</td>
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<tr>
<td>LDL</td>
<td>95 ± 23</td>
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<tr>
<td>HDL</td>
<td>50 ± 10</td>
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<tr>
<td>Triglycerides</td>
<td>76 ± 40</td>
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</table>
Pulmonary Oxidative Stress and Inflammation

Autonomic Nervous System Imbalance

Ischemic Events

Cardiomyopathy

Arrhythmia Events

Air Pollution Exposures

Particle Translocation

Lipid / Carbohydrate Metabolism

Thrombosis

Atherosclerosis

Systemic Oxidative Stress and Inflammation

Endothelial Function

Hypertension

Vascular Compliance

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

<table>
<thead>
<tr>
<th>Model</th>
<th>Retinal Arteriolar Diameter (CRAE)</th>
<th>Retinal Venular Diameter (CRVE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Long-Term Effects</td>
<td>Short-Term Effects</td>
</tr>
<tr>
<td>1</td>
<td>$-0.5 (-0.9$ to $-0.1)$</td>
<td>$-0.4 (-0.8$ to $-0.04)$</td>
</tr>
<tr>
<td>2</td>
<td>$-0.5 (-0.9$ to $-0.1)$</td>
<td>$-0.6 (-1.0$ to $-0.2)$</td>
</tr>
<tr>
<td>3</td>
<td>$-0.8 (-1.1$ to $-0.4)$</td>
<td>$-0.5 (-1.0$ to $0.03)$</td>
</tr>
<tr>
<td>4</td>
<td>$-0.9 (-1.2$ to $-0.6)$</td>
<td>$-0.4 (-0.8$ to $0.1)$</td>
</tr>
<tr>
<td>Joint</td>
<td>$-0.8 (-1.1$ to $-0.5)$</td>
<td>$-0.4 (-0.8$ to $0.1)$</td>
</tr>
</tbody>
</table>

All associations reported as μm per interquartile range of 3 μg/m$^3$ (for long term) and 9 μg/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
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, Ph.D,§
Neal W. Jorgensen, MS,§ Victor C. Van Hee, MD, MPH,‡ R. Graham Barr, MD, DrPH,||
Marie S. O’Neill, Ph.D,‡¶ 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 μg/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 μg/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 thinned 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

Systemic Oxidative Stress and Inflammation

Endothelial Function

Lipid / Carbohydrate Metabolism

Thrombosis

Atherosclerosis

Hypertension

Vascular Compliance

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\textsuperscript{1,2}, Sara D. Adar\textsuperscript{1}, Adam A. Szpiro\textsuperscript{3}, R. Graham Barr\textsuperscript{4}, David A. Bluemke\textsuperscript{5}, Ana V. Diez Roux\textsuperscript{6}, Edward A. Gill\textsuperscript{2}, Lianne Sheppard\textsuperscript{1,3}, and Joel D. Kaufman\textsuperscript{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/m\textsuperscript{2} (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.
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 Siscovich,$^{a,f}$ 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)
**Systemic Oxidative Stress and Inflammation**
CRP, IL-6, fibrinogen

**Metabolism**
Pericardial fat, diabetes, hepatic fat, lipid profile, metabolic syndrome

**Thrombosis**
Fibrinogen, Factor VIII, PAI-1, Plasmin-antiplasmin, D-Dimer, Von Willebrand factor, soluble tissue factor, tissue factor pathway inhibitor, thrombotic stroke

**Endothelial Function**
ICAM-1, VCAM-1, E-selectin, flow-mediated brachial artery dilation, retinal vascular caliber

**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

**Hypertension**
Blood pressure, hypertensive treatment

**Vascular Compliance**
Carotid and aortic distensibility, brachial imaging, radial pulse wave analysis – small & large vessel

**Ischemic Events**
MI, ischemic stroke, ECG (Q wave), gadolinium enhancement

**Peripheral Vascular Disease**
Ankle-brachial index, peripheral revascularization

**Cardiomyopathy**
Congestive heart failure

**ANS Imbalance**
Heart rate variability, retinal vascular caliber

**Air Pollution Exposures**
(Particulate Matter and Traffic-Related Agents)
Environmental factors in cardiovascular disease

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

Traffic-related air pollution

Exposure
Enters the body through established routes

Inhalation

Initial response
Directly or indirectly interacts with one or more tissues

Particle translocation
Sensory receptor activation

Molecular and cellular effects
Agents or metabolites initiate cascades of adaptive or maladaptive responses

Lipid oxidation and metabolism
Systemic oxidative stress and inflammation
Pulmonary oxidative stress and inflammation
Autonomic nervous system imbalance

Tissue and organ responses
Physiological responses induce changes in specific bodily systems

Endothelial dysfunction
Increased blood pressure
Decreased heart-rate variability and cardiac output

Subclinical effects
Early detection of pathological changes can provide evidence of disease processes

Metabolic syndrome; lipid and glucose abnormalities
Atherosclerosis
Hypertension
Alterations in cardiac function and structure

Clinical cardiovascular effects
Pathological changes associated with exposure manifest as overt disease

Peripheral arterial disease
Ischaemic events
Arrhythmia events
Cardiomyopathy and heart failure

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

**Exposure**
Enters the body through established routes

**Initial response**
Directly or indirectly interacts with one or more tissues

**Molecular and cellular effects**
Agents or metabolites initiate cascades of adaptive or maladaptive responses

**Tissue and organ responses**
Physiological responses induce changes in specific bodily systems

**Subclinical effects**
Early detection of pathological changes can provide evidence of disease processes

**Clinical cardiovascular effects**
Pathological changes associated with exposure manifest as overt disease

**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