Particulate Matter Air Pollution Health Effects

AQI 32
PM$_{2.5}$ 10

AQI 45
PM$_{2.5}$ 14

AQI 72
PM$_{2.5}$ 26
PM Air Pollution Health Effects

- What is air pollution?
- What makes us think it could be related to cardiovascular disease?
  - Epidemiologic evidence
    - Acute cardiovascular effects related to air pollutants
    - Cardiovascular effects related to long-term air pollution exposure
- What could the mechanism be?
- Diesel Exhaust Health Effects

AHA Scientific Statement

Air Pollution and Cardiovascular Disease
A Statement for Healthcare Professionals From the Expert Panel on Population and Prevention Science of the American Heart Association

Robert D. Brook, MD; Barry Franklin, PhD, Chair; Wayne Cascio, MD; Yiying Hong, MD, PhD; George Howard, PhD; Michael Lipsitt, MD; Russell Luepker, MD; Murray Mittleman, MD, ScD; Jonathan Samet, MD; Sidney C. Siegel, Jr, MD; Ira Tager, MD

Abstract—Air pollution is a heterogeneous, complex mixture of gases, liquids, and particulate matter. Epidemiological studies have demonstrated a consistent increased risk for cardiovascular events in relation to both short- and long-term exposure to present-day concentrations of ambient particulate matter. Several plausible mechanistic pathways have been described, including enhanced coagulation/thrombosis, a propensity for arrhythmias, acute arterial vasoconstriction, systemic inflammatory responses, and the chronic promotion of atherosclerosis. The purpose of this statement is to provide healthcare professionals and regulatory agencies with a comprehensive review of the literature on air pollution and cardiovascular disease. In addition, the implications of these findings in relation to public health and regulatory policies are addressed. Practical recommendations for healthcare providers and their patients are outlined. In the final section, suggestions for future research are made to address a number of remaining scientific questions. (Circulation. 2004;109:2655-2671.)
Air Pollution and Cardiovascular Disease

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- What makes us think it could be related to cardiovascular disease?
  - Epidemiologic evidence
    - Acute cardiovascular effects related to air pollutants
    - Cardiovascular effects related to long-term air pollution exposure
  - What could the mechanism be?
  - Research at UW on air pollution and cardiovascular disease

PM is a “Criteria” Air Pollutant

Air Quality Criteria for Particulate Matter

www.epa.gov/ncea

NAS/NRC Panel on PM

- Four Reports on the State of the Science and Research Priorities, published between 1998 and 2004

Particulate Matter

- Aggravation of asthma
- Respiratory symptoms
- Chronic Bronchitis
- Decreased lung function
- Premature mortality

- Coarse PM, Fine PM, Ultra-fine PM
respiratory tract from a deposition perspective:

extrathoracic (nasopharyngeal)
- nose
- mouth
- oropharynx
- larynx

tracheo-bronchial
- trachea
- bronchi
- terminal bronchioles

alveolar (pulmonary)
- respiratory bronchioles
- alveolar ducts
- alveoli

The site and amount of deposition depend on particle size.
The two particle size modes differ by composition and source.

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 µg/m³
    - 12,000 Excess Deaths Attributed to Event

Research and Public Policies Concerning Particulate-Matter Air Pollution

Key Air Pollution Disasters of the 20th Century

The Fog Disaster in the Meuse Valley, 1930...led to the first scientific proof of the potential for atmospheric pollution to cause deaths and disease, and it clearly identified the most likely causes.

- 60 deaths that were attributed to the fog occurred on Dec 4 and 5.

Beginning on October 26, 1948, sparse air movement contributed to a temperature inversion in the atmosphere over western Pennsylvania, Ohio, and areas of neighboring states. A fog laden with particulates and other industrial contaminants enveloped the city of Donora, a small industrial town on the banks of the Monongahela River, some 30 miles south of Pittsburgh. Visibility was so poor that even locals lost their sense of direction. An estimated 5000 to 7000 persons in a town of 14,000 residents became ill, 400 required hospitalization, and 20 died before rain dispersed the killing smog on October 30 and 31, 1948.
  - Helfand et al. AJPH 2001

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Daytime in London, 1952

Particle levels – 3,000 µg/m³
Source: National Archives

From crisis to questions

- We began with crisis—Meuse Valley 1932, Donora 1948, London 1952 and have moved to questions:
  - Are there adverse effects of today’s air pollution?
  - How large are these risks?
  - Who is susceptible?
  - What is the cost-benefit ratio for control?

1952 London Fog

~10,000 excess deaths
What is Epidemiology?

“Epidemiology is the study of how disease is distributed in populations and of the factors that influence or determine this distribution”

(Leon Gordis, 2000)

“I hate definitions”

Benjamin Disraeli (1804 – 1881)

50 Years of Air Pollution Research

<table>
<thead>
<tr>
<th>Year</th>
<th>Study/Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>London Fog Surveys</td>
</tr>
<tr>
<td>1960</td>
<td>Ecological studies</td>
</tr>
<tr>
<td></td>
<td>Early time-series studies</td>
</tr>
<tr>
<td>1970</td>
<td>Six Cities Study</td>
</tr>
<tr>
<td>1980</td>
<td>Exposure Assessment</td>
</tr>
<tr>
<td>1990</td>
<td>Modern time-series studies</td>
</tr>
<tr>
<td>2000</td>
<td>Multi-site studies</td>
</tr>
<tr>
<td>2005</td>
<td></td>
</tr>
</tbody>
</table>

1952 London Fog

- ~10,000 excess deaths

Date: December 1952

Deaths vs. Sulfur dioxide vs. Smoke
Daily time series of air pollution mortality and weather in Baltimore 1987-1994

Air pollution signal order of magnitude smaller than confounders


Epidemiology and PM in the 1990s

1990

1
2
3
4
5
6
7
8
9

1 2

Initial mortality time-series studies 6 cities

ACS Morbidity Studies PM 2.5 standard Multicity studies

Issues

Validity of findings

Harvesting

Confounding

PM effect?

Measurement error

Toxic particles

National Morbidity Mortality Air Pollution Study

Deaths

Temp

PM10
Cardiovascular Disease and PM: Epidemiologic Observations

- Increased cardiac mortality
- Increased hospitalizations for CVD
- Increased hospitalizations for CHF
- Increased arrhythmia (AICD)
- Changes in heart rate and heart rate variability

Table 3: Hospital admissions for cardiovascular disease

<table>
<thead>
<tr>
<th>Time series study</th>
<th>Geographical area</th>
<th>Pollutants</th>
<th>Effect on CV admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balmes 1993**</td>
<td>Barcelona, Spain</td>
<td>SO2, NO2, O3</td>
<td>Increased hospitalizations</td>
</tr>
</tbody>
</table>
Air pollution can cause death.

Fig. 1: The mean concentration of airborne particulate (μg/m³) from the four inner monitoring stations in London, and the count of daily deaths in the London Administrative County during the beginning of December 1932.

Short-term increases in low concentrations of PM are associated with increased deaths.

Daily Mortality and PM_{10} Pollution in Utah Valley

C. ARDEN POPE III
Brigham Young University
Provo, Utah

JOEL SCHWARTZ
U.S. Environmental Protection Agency
Washington, DC

MICHAEL B. KANOM
Brigham Young University
Provo, Utah

Fig. 1. Relative risk of death, by quartile of PM_{10} concentration.

1. Old people are at more risk.
2. Deaths are due to cardio-pulmonary causes.

Hypothesized mechanisms of cardiovascular death due to short-term exposure to PM:

AHA Scientific Statement

Air Pollution and Cardiovascular Disease: A Statement for Healthcare Professionals From the Expert Panel on Population and Prevention Sciences of the American Heart Association

Robert J. Brook, MD, John B. Prineas, MD, MSc, Robert G. Coultas, MD, Tribby P. Egan, MD, George Rewcastle, MD, Robert C. Cole, MD, Robert L. Koh, MD, Michael M. Abruzzese, MD, MSc, Steven Y. Snipes, MD, William J. Detre, MD, and David J. Lipton, MD

Abstract: Recent evidence has demonstrated increased cardiovascular disease risk in association with particulate air pollution, including exposure to fine particles (PM_{2.5}) and 10-year-old studies. This article presents the current evidence on the association between ambient PM_{2.5} exposure and its cardiovascular effects, as well as recommendations for healthcare professionals. It also includes recommendations for healthcare professionals on how to prevent and treat cardiovascular disease associated with PM_{2.5} exposure.
Daily Mortality effects, by broad cause-of-death categories

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Percent of total deaths</th>
<th>Cause-specific percent increase per 10 μg/m^3 increase in PM_{2.5}</th>
<th>Percent of excess deaths due to PM exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>100</td>
<td>7.0</td>
<td>108</td>
</tr>
<tr>
<td>Respiratory</td>
<td>8</td>
<td>25.0</td>
<td>28</td>
</tr>
<tr>
<td>Other disease</td>
<td>47</td>
<td>0.4</td>
<td>3</td>
</tr>
</tbody>
</table>

Based on adjusted summary estimates prev. results (p<0.05) for smoking, cooking, housing, etc.

Pope, 2000

Air Pollution and Cardiovascular Disease

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  - Epidemiologic evidence
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- What could the mechanism be?

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

Harvard Six Cities Study

- Mortality Analyses
  - Comparing mean annual pollutant levels in each city for years near start of follow-up
- Key Assumptions
  - Subjects did not move during follow-up
  - Rank ordering of cities by level of pollutants invariant of follow-up time
- Stratified Cox proportional hazards models to estimate cause-specific relative risks
Mortality Rate Ratios: Most Polluted vs Least Polluted of Six Cities

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Percentage of Total</th>
<th>Current Smokers</th>
<th>Former Smokers</th>
<th>Most vs Least Polluted City</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted RR (95% CI)</td>
</tr>
<tr>
<td>All</td>
<td>100</td>
<td>2.00 (1.51–2.65)</td>
<td>1.39 (1.10–1.75)</td>
<td>1.26 (1.09–1.47)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>8.4</td>
<td>8.00 (2.97–21.6)</td>
<td>2.54 (0.90–7.18)</td>
<td>1.37 (0.81–2.31)</td>
</tr>
<tr>
<td>Cardiopulmonary disease</td>
<td>53.1</td>
<td>2.30 (1.56–3.41)</td>
<td>1.52 (1.10–2.10)</td>
<td>1.37 (1.11–1.68)</td>
</tr>
<tr>
<td>All others</td>
<td>38.5</td>
<td>1.46 (0.89–2.39)</td>
<td>1.17 (0.80–1.73)</td>
<td>1.01 (0.79–1.30)</td>
</tr>
</tbody>
</table>

*The city with the highest level of air pollution (indicated by the level of fine particles) was Seattle, Washington. The city with the lowest was Portage, Wisconsin. CI denotes confidence interval. Rates have been adjusted for age, sex, smoking, education, marital status, body mass index, alcohol consumption, occupational exposure, and diet.

The risk of death for a current smoker with approximately the average number of pack-years of smoking at enrollment (25 pack-years), as compared with that for a non-smoker.

The risk of death for a former smoker with approximately the average number of pack-years of smoking at enrollment (20 pack-years), as compared with that for a non-smoker.

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

Pope, *JAMA*, 2002; *Circulation* 2004; 109: 71

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>Cardiovascular</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>1.06 (1.01-1.10)</td>
<td>1.15 (1.04-1.22)</td>
<td>1.14 (1.04-1.22)</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 status, body mass index, alcohol consumption, occupational exposure, and diet. CI denotes confidence interval.

Pope, *JAMA*, 2002
Women’s Health Initiative O.S.
Time to First of Selected Cardiovascular Events, Deaths, per 10 µg/m³ PM$_{2.5}$

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
<th>Between Cities</th>
<th>HR</th>
<th>95% CI</th>
<th>Within Cities</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident Events</td>
<td>1706</td>
<td>1.21</td>
<td>1.06, 1.38</td>
<td>1.14</td>
<td>0.96</td>
<td>1.32</td>
<td>1.54</td>
<td>1.15</td>
<td>2.07</td>
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<td>MI</td>
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<td>Revascularization</td>
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<td></td>
<td></td>
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<tr>
<td>Stroke</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>273</td>
<td>1.70</td>
<td>1.22, 2.38</td>
<td>1.63</td>
<td>1.11</td>
<td>2.36</td>
<td>1.98</td>
<td>0.96</td>
<td>4.10</td>
</tr>
<tr>
<td>CVD death</td>
<td></td>
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<tr>
<td>Cardiovascular death</td>
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</tbody>
</table>

KA Miller, et al, 2004

Summary of epidemiologic evidence of chronic effects of PM air pollution

<table>
<thead>
<tr>
<th>Health endpoint</th>
<th>Route of study design</th>
<th>Observed associations with particulate pollution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality rates</td>
<td>Population based cross-sectional analyses of mortality rates across communities with different levels of pollution</td>
<td>Higher mortality rates with higher fine particle air pollution and for blackpollution exposure. Mortality effect increased with model specifications and choices of covariates included in the analysis.</td>
</tr>
<tr>
<td>Survival/Life expectancy</td>
<td>Cohort based cross-sectional studies that link community based air pollution data with individual risk factors and survival data</td>
<td>Increased risk of respiratory and cardiovascular mortality in adults, and respiratory and maternal infant death syndrome mortality in infants, even after controlling for individual differences in age, gender, smoking, and various other risk factors.</td>
</tr>
<tr>
<td>Disease</td>
<td>Based on large studies of community air pollution with individual symptom/ disease data from survey or controlled cohorts</td>
<td>Increased chronic cough, bronchitis, and chest illness that are attributable.</td>
</tr>
<tr>
<td>Lung function</td>
<td>Based on large studies of community air pollution data with individual lung function data from review of surveys or controlled cohorts</td>
<td>Pulmonary air pollution associated with small but often statistically significant declines in various measures of lung function in both children and adults.</td>
</tr>
</tbody>
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Pope, 2000

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Mechanistic Speculation
Mechanistic Speculation

Endothelial Function

Diesel Exhaust may be especially potent source of PM

Endothelial function’s central role in atherosclerotic lesion development and events

Schiffrin et al, Am J Hypertension 2002

Diesel Exhaust: The Risk of the Risk Factors

Janssen et al EHP 2002; 110:43-9

- DE particles dominated by ultrafines
- DE particles rich in biologically active agents, especially agents exerting redox activity
Early Diesel Research

- Diesel exhaust is classified as “likely to be carcinogenic”
- Epidemiological studies suggest occupational exposure to diesel exhaust particulates causes increase in the risk of lung cancer
- No specific cancer unit risk estimate for diesel exhaust is adopted or recommended in the EPA assessment.
  - Animal (rat) cancer studies are not clear for human hazard prediction and unsuitable for environmental exposure risk estimate. Quantitative statements on human risk cancer should be based on human epidemiological studies. Currently available data, due to a number of uncertainties, is deemed unsuitable for quantitative risk assessment.

2002

- Non-cancer health effects from diesel emissions may include short-term (i.e., acute) exposure effects such as transient irritation and inflammatory reaction, as well as exacerbation of existing allergies and asthma symptoms. The nature and extent of these symptoms, however, are highly variable across the population.
- Diesel emissions, as a mixture of many constituents, also contribute to ambient concentrations of several criteria air pollutants including nitrogen oxides, sulfur oxides, fine particles, as well as other hazardous air pollutants.

Typical Diesel Particle Size Distribution - Log Scale

Typical Engine Exhaust Size Distribution
Both Mass and Number Weightings are Shown

- Normalized Concentration, [C(x)/C(Ref)]
- Diameter (μm)
- Mass Weighting
- Number Weighting

- Ultrafine Particles: Dp < 100 nm
- Accumulation Mode
- Coarse Mode
- Fine Particles: Dp < 2.5 μm
- PM10: Dp < 10 μm
- Nuclear Mode
- Nanoparticles: Dp < 50 nm
DE and Cancer

Animal Data

- DE is lung carcinogen in rat, but dose-effect relationship similar to those from organic-free black carbon
- DE contains procarcinogens and mutagens, and agents which generate reactive oxygen species

DE and Cancer

Epidemiologic Data

- 22 studies, most with substantial limitations, primarily from occupational settings
- Railroad workers, Truck drivers, heavy equipment operators,
- Relative risk estimates generally about 1.2-1.5

PM and DE

- Diesel Exhaust is major contributor to fine PM in urban setting, especially of PM from combustion sources
- DE is majority of ultrafine particles (<100 nm)

Increasing Worldwide Prevalence of Asthma

- Clear evidence of worldwide increase in asthma prevalence, especially in urban populations
- Likely "environmental" (broadly defined)
- Leading Hypotheses
  - \( T_{H1} \) \( T_{H2} \) priming
  - "hygiene hypothesis"
    - Less infections, less animal exposures early in life
  - Changes in diet
  - Could it be something in the air?
**DE and Allergies**

- DEPs enhance IgE production by B-lymphocytes
- DEPs stimulate eosinophils
- DEPs influence key cytokines and chemokines
- DEPs exert direct inflammatory effect via redox activity
- DEPs act as adjuvant in allergic response

**Adjuvant Properties of DE**

- DE effect on responses consistently synergistic with allergen
- Numerous animal and in vitro studies
- Human nasal exposure model
  - Challenge of subjects allergic to ragweed with DEPs plus ragweed allergen resulted in a 16-fold increase in ragweed-specific IgE compared to ragweed alone (Diaz-Sanchez 1997)
- Human neo-antigen study
- Stockholm road tunnel study

**Adjuvant Properties of DE**

[Chart showing adjuvant properties of DE]

**DE augments sensitization to neo-antigen**

[Graphs showing sensitization with and without DE]

Diaz-Sanchez J Allergy Clin Immunol 1999;1185-8
DE Exposures

- Typical Ambient Exposures
  - Average estimates for DPM in general population: 1.4 µg/m³
  - 4-20 µg/m³ in urban outdoor environments
  - Worst cases (downtown bus stop) near 50 µg/m³
- Occupational Exposures range up to
  - approximately 1,280 µg/m³ (miners), lower for railroad workers (39-191 µg/m³), firefighters (4-748 µg/m³), public transit personnel who work with diesel equipment (7-98 µg/m³), mechanics and dockworkers (5-65 µg/m³), truck drivers (2-7 µg/m³), and bus drivers (1-3 µg/m³).

The Northlake Laboratory

Current Issues with DE and Policy

- Changes in Fuels
- Changes in Truck Requirements and evolving non-highway regulations
- California declares DE a carcinogenic hazardous air toxic
- Increased concern regarding children’s exposures on school buses
- Diesel and Global Climate Change
MESA Air Pollution Study

A New Prospective Cohort Study of Air Pollution and Cardiovascular Disease

A New Prospective Cohort Study of Air Pollution and Cardiovascular Disease

• Prior studies compelling but had limitations
• Importance of long-term exposures on effects
• Hypothesis that ambient fine particulates accelerate atherosclerosis
• New developments in exposure assessment
• Newly validated measures of subclinical atherosclerosis

Applying Recent Lessons to a New Cohort Study

• NHLBI Multi-Ethnic Study of Atherosclerosis (MESA): Cohort Creation
  – Exposure heterogeneity: Population-based cohort recruited from areas near Los Angeles, Chicago, St. Paul, New York City, Baltimore, Winston-Salem
  – At risk: 45-84 yrs old, without clinical CV dz
  – Sampling strategy to include populations with varying ethnicity (African-American, Hispanic, Asian)

Multi-Ethnic Study of Atherosclerosis (MESA)

• Designed to assess risk factors for progression of atherosclerosis as measured by:
  – Coronary Artery Calcification by CT
  – Carotid Artery Intima Medial Thickness by Ultrasound
  – Clinical Events
Coronary Artery Calcification by EBCT

Carotid intima-medial thickness (IMT)

MESA and Air Pollution: Exposure Heterogeneity

<table>
<thead>
<tr>
<th></th>
<th>Alhambra</th>
<th>Santa Monica*</th>
<th>Rubidoux/Riverside*</th>
<th>St. Paul</th>
<th>Chicago*</th>
<th>Manhattan/Brine</th>
<th>Rockland</th>
<th>Burke</th>
<th>West Nile</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM2.5</td>
<td>L M M H M M L M M</td>
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L=Low, M=Medium, H=High, VH=Very High
e.g., for PM2.5: L= (~10 µg/m³), M= (~15 µg/m³), H= (~22 µg/m³), VH= (~30 µg/m³) annual averages

Scientific Opportunities

*Principal Study Objectives*

- Air Pollution and Subclinical Atherosclerosis
  - CAC and IMT
- Air Pollution and Clinical Cardiovascular Disease
- Individual-level Exposure Assessment for Air Pollutants