

Health effects of ambient combustion-related fine and ultrafine particulate air pollution: recent epidemiological evidence

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Outline of epidemiologic evidence that exposure to combustion-related fine PM is a risk factor for cardiopulmonary disease:

- I. **Episode studies**--Increases in both respiratory and cardiovascular morbidity and mortality during and immediately following pollution episodes.
- II. **Daily time-series studies**--Day-to-day changes in PM associated with cardiopulmonary disease, deaths, and hospitalizations.
- III. **Population and cohort studies of long-term exposure**--Increased risk of cardiopulmonary mortality associated with spatial differences in PM.
- IV. **Studies of specific physiologic endpoints**--suggestive of general pathophysiological mechanisms or pathways that link PM and cardio-respiratory morbidity and mortality.

Note: Daily time series studies have now been conducted in 100+ cities throughout the world.

Estimates of daily mortality effects of an increase in exposure to PM by broad cause-of-death categories.

Cause of Death	% of total deaths	Cause-specific percent increase per 50 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$	% of excess deaths due to PM exposure
All cause	100	7.0	100
Respiratory	8	25.0	28
Cardiovascular	45	11.0	69
Other	47	0.4	3

Source: Pope. Environmental Perspectives 108(suppl4):713-723(2000)

Lung Cancer, Cardiopulmonary Mortality, and Long-term Exposure to Fine Particulate Air Pollution

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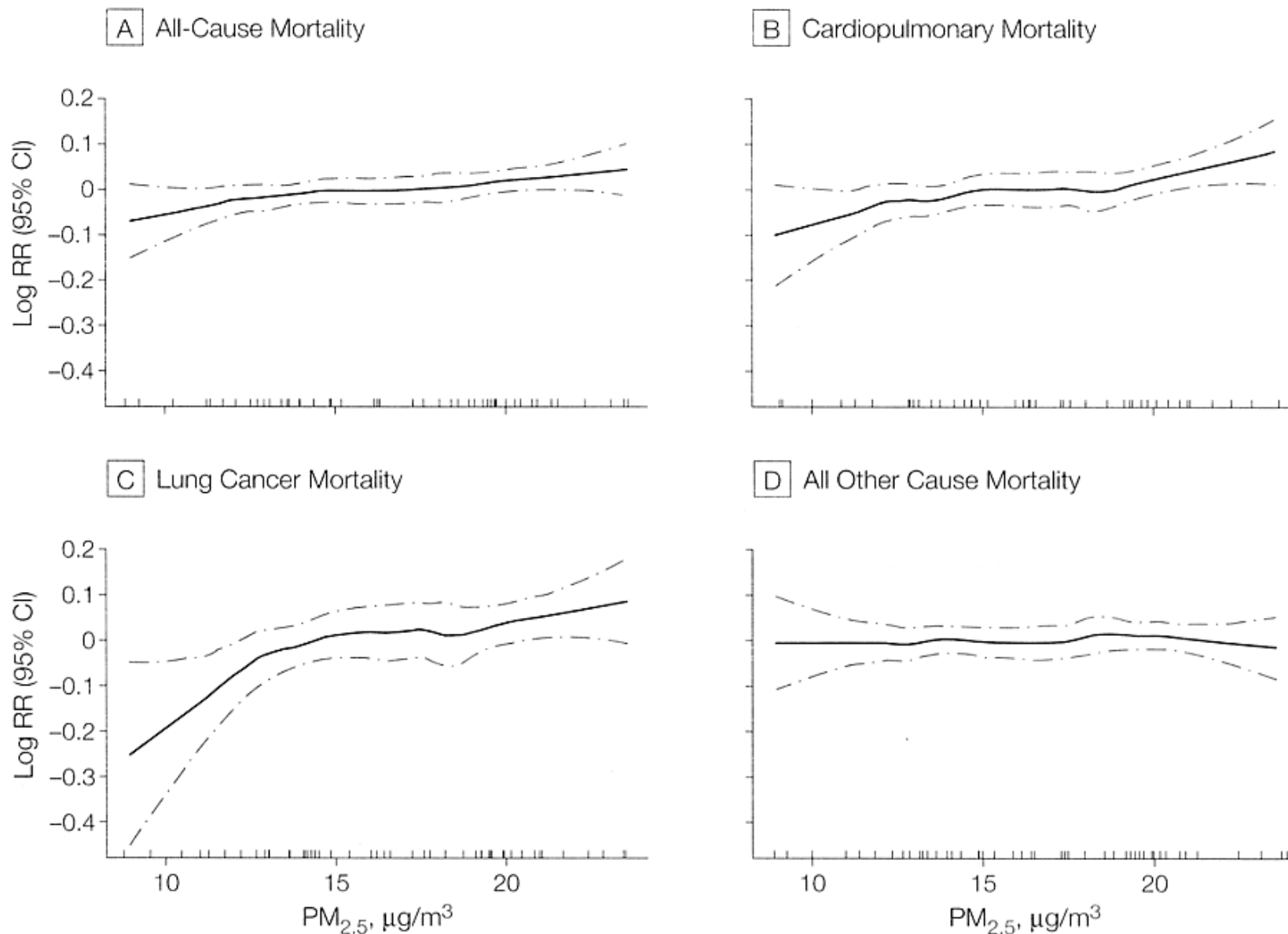
Kazuhiko Ito, PhD

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A large prospective cohort study of PM and mortality originally motivated by the Harvard Six-cities study (Dockery et al. NEJM 1993)

JAMA, 2002

Figure 2. Nonparametric Smoothed Exposure Response Relationship



IV. Studies exploring mechanistic pathways linking PM exposure and mortality

The epidemiological studies provide compelling evidence of a statistical association between combustion-related fine PM and cardiopulmonary disease and mortality but . . .

. . . what are the mechanistic pathways linking exposure, disease, and mortality?

Four Hypothesized General Pathophysiologic pathways:

1. Accelerated Progression of COPD and related disease
2. Altered Cardiac Autonomic Function
3. Pulmonary/Systemic Oxidative Stress
Inflammation/Accelerated Atherosclerosis
4. Modulated host defenses and immunity

1. Accelerated Progression of COPD

Supported by evidence that exposure to PM is associated with:

- Reduced lung function and lung function growth in children
(Note recent results from So. Cal. Children's Health Study, Gauderman et al. NEJM 2004).
- Increased symptoms of obstructive airway disease



2. Altered Cardiac Autonomic Function

Supported by evidence that exposure to PM is associated with:

➤ Changes in:

Heart Rate (Peters et al. 1999; Pope et al. 1999)

HRV (Liao et al 1999; Pope et al 1999, 2004; Gold et al. 2000)

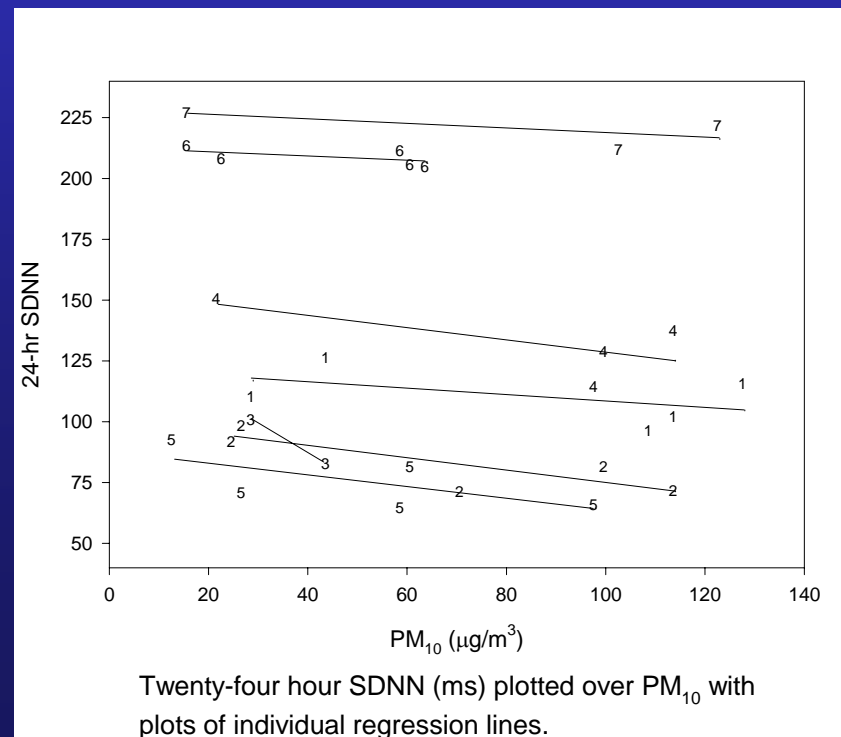
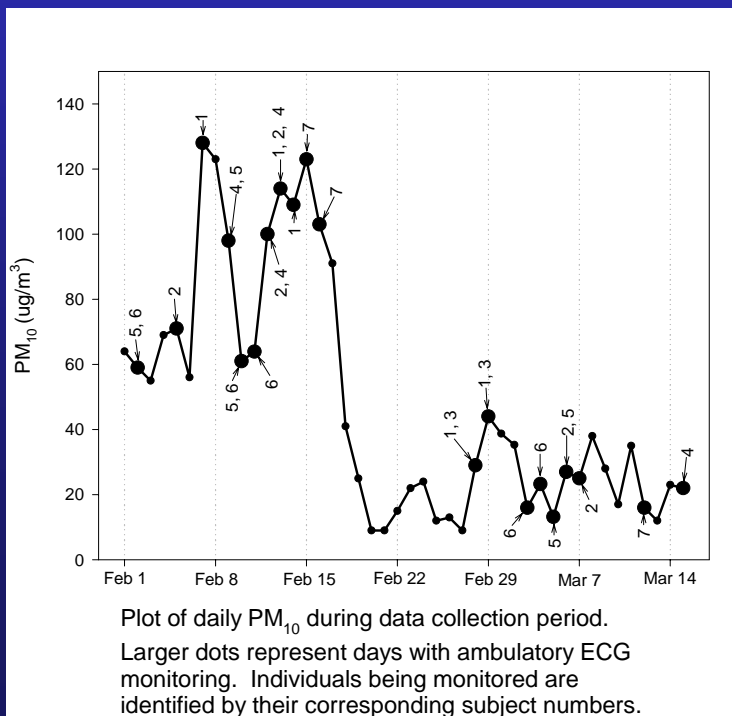
Blood pressure (Ibald-Muli et al. 2001, 2004)

➤ **Arrhythmias indicated by ICD discharges** (Peters, et al. 2001)



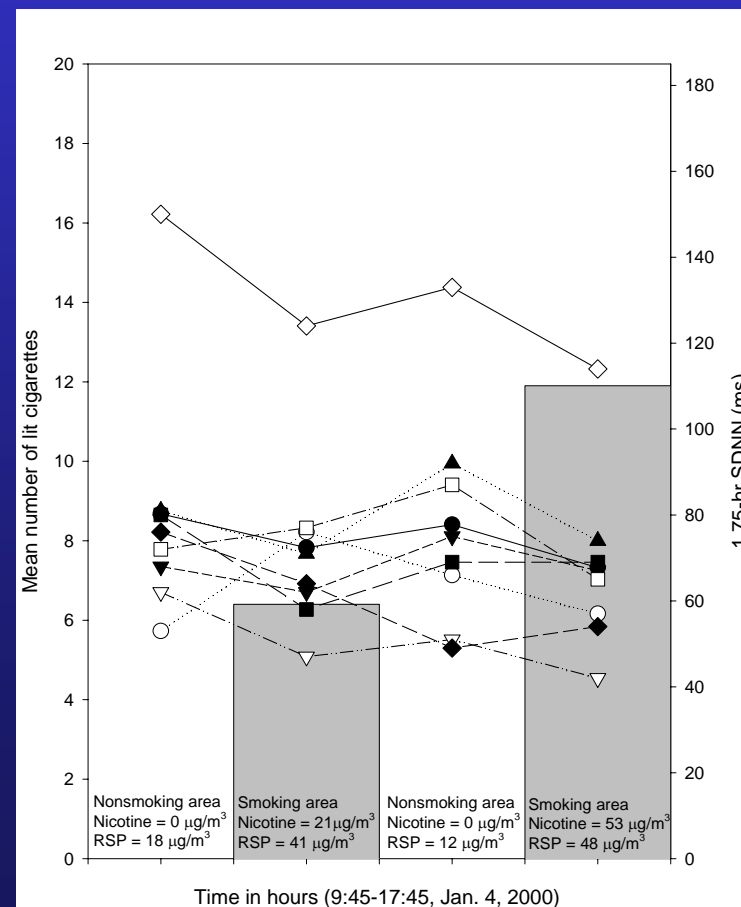
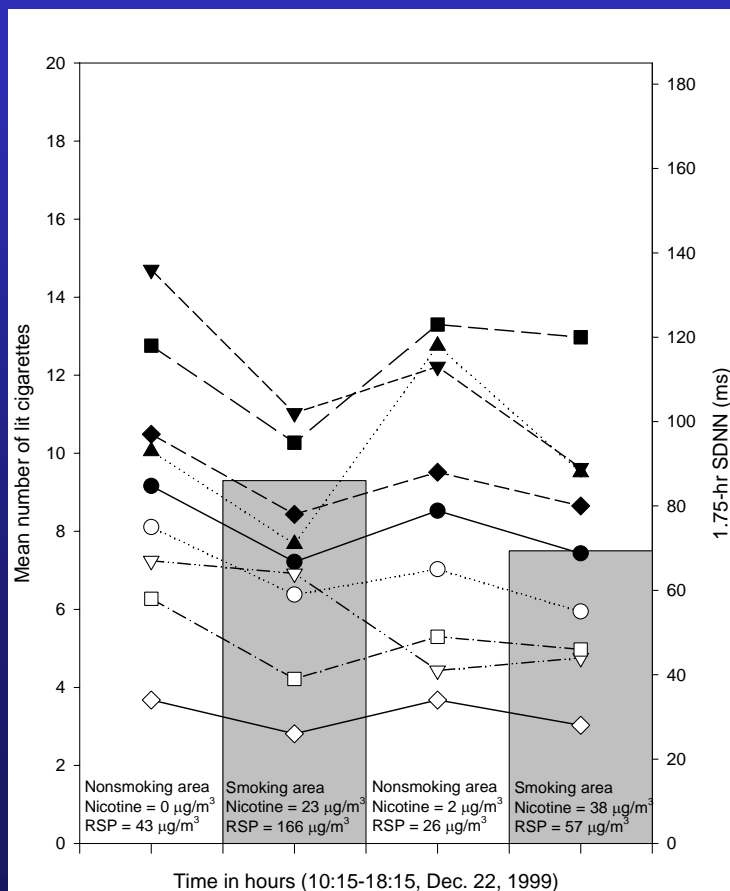
Example 2a: Pope, Verrier, Lovett et al. Am Heart J 1999

- Basic methods: Repeated 24-hr AECG monitoring was conducted on 7 subjects before, during, and after PM pollution episodes.
- Basic results: After controlling for individual fixed effects a 100 $\mu\text{g}/\text{m}^3$ increase in PM_{10} was associated with about an 18 ms decrease in SDNN (a measure of overall HRV).



Example 2b: Pope, Eatough, Gold et al. EHP 2001

- AECG monitoring over 8 hrs while subjects alternated 2 hrs in nonsmoking and smoking areas of the SLC airport.
- ETS-related PM exposure (being in the smoking lounge) was associated with an average 10 ms decrease in SDNN.



Example 2c: Pope, Hansen, Long, et al. EHP 2004

Methods: Multiple 24-hr
AECG monitoring and
collection of blood markers of
inflammation in a panel of 88
elderly subjects from three
communities along the
Wasatch Front in Utah.

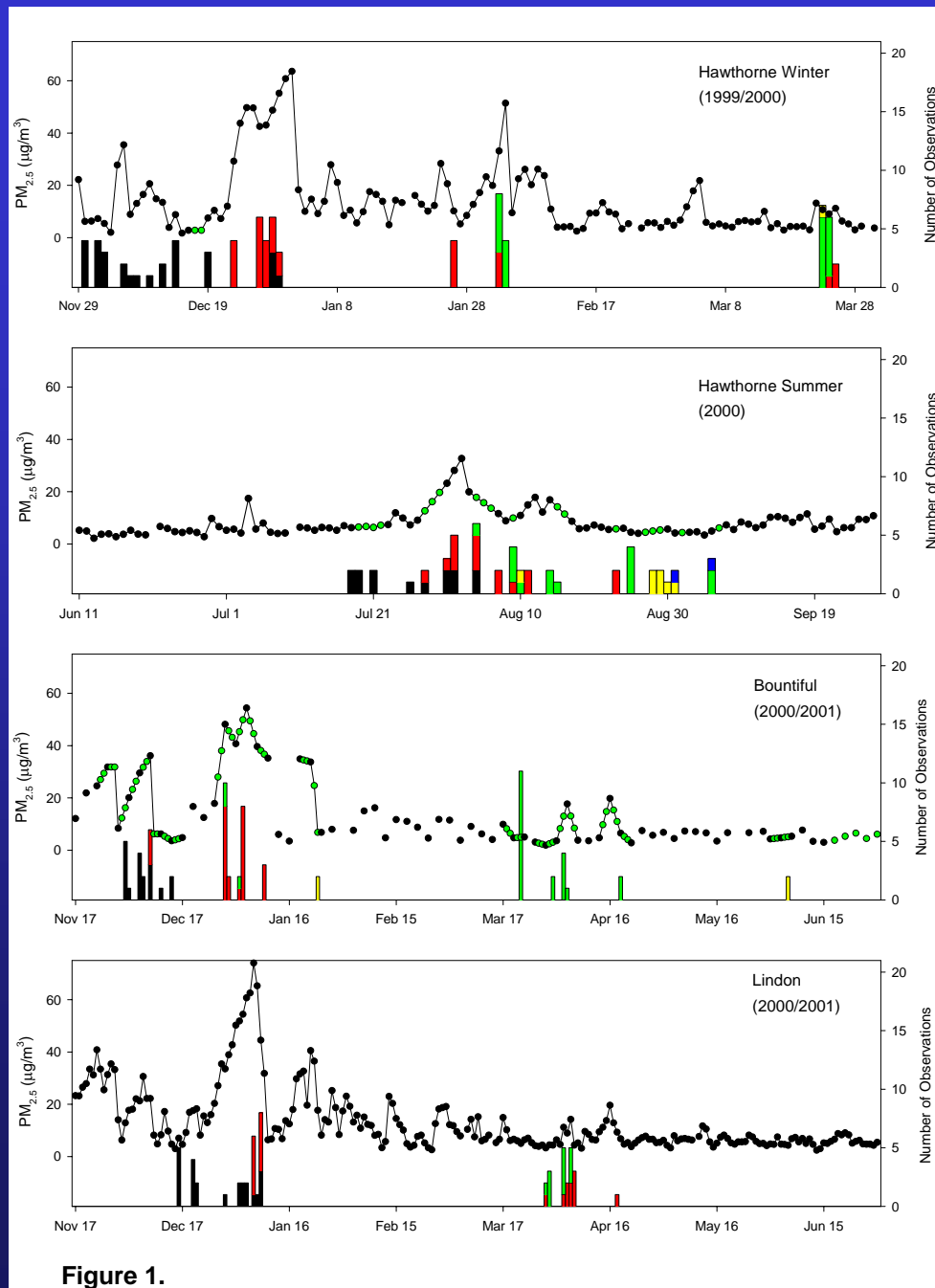


Figure 1.

Example 2c: Pope, Hansen, Long, et al. EHP 2004 --continued

Results: A 100- $\mu\text{g}/\text{m}^3$
increase in $\text{PM}_{2.5}$ was
associated with:

➤ 35 (SE=8) msec decline in
SDNN

➤ 0.81 (SE=0.17) mg/dl
increase in CRP

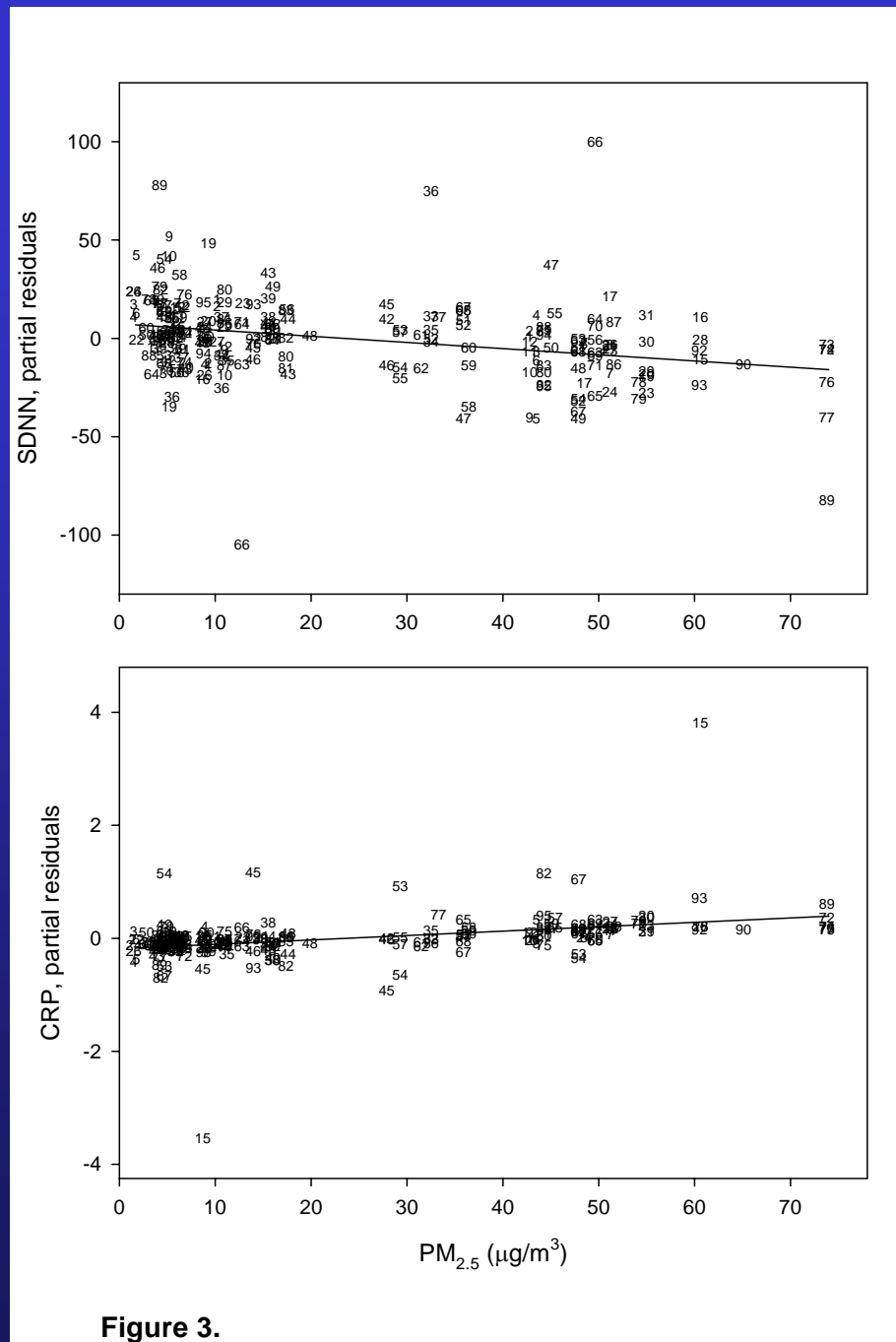
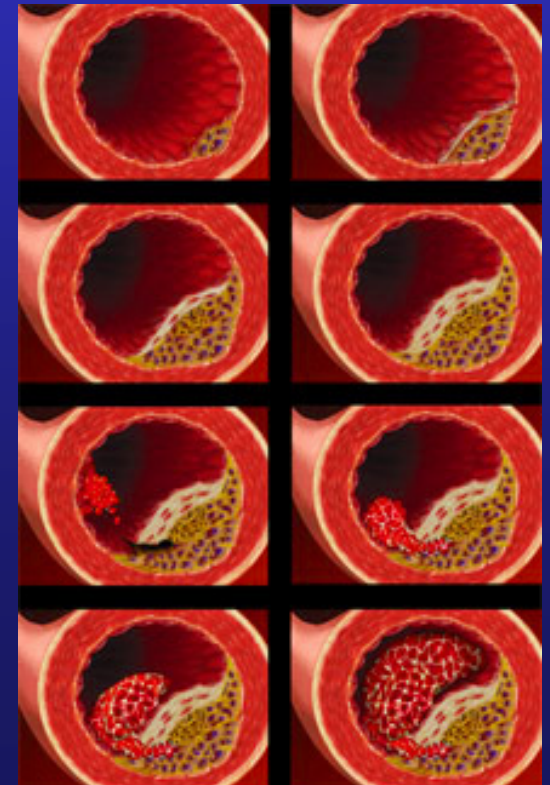
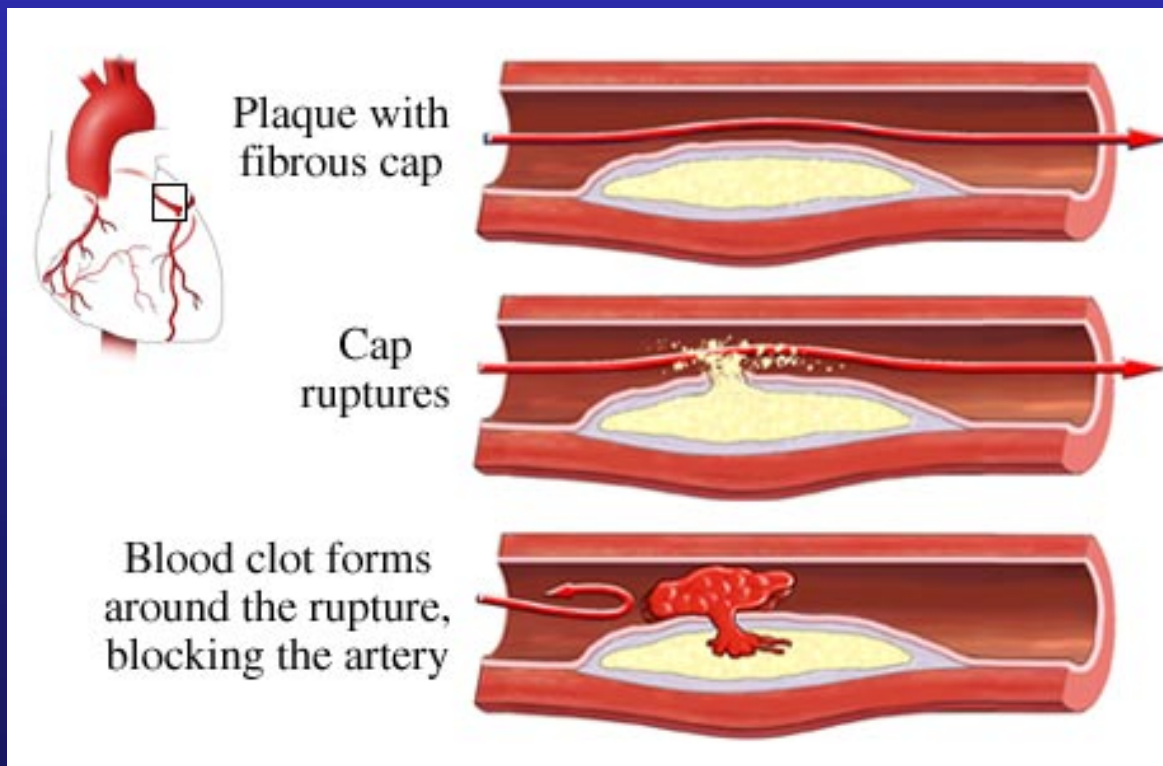


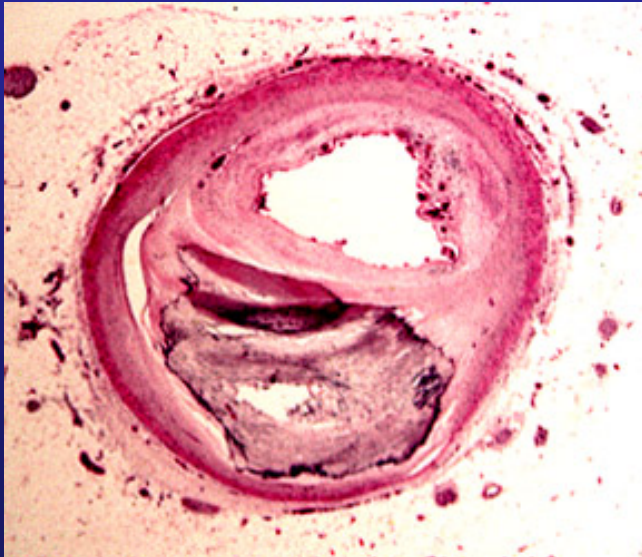
Figure 3.

3. Inflammation/Accelerated Atherosclerosis

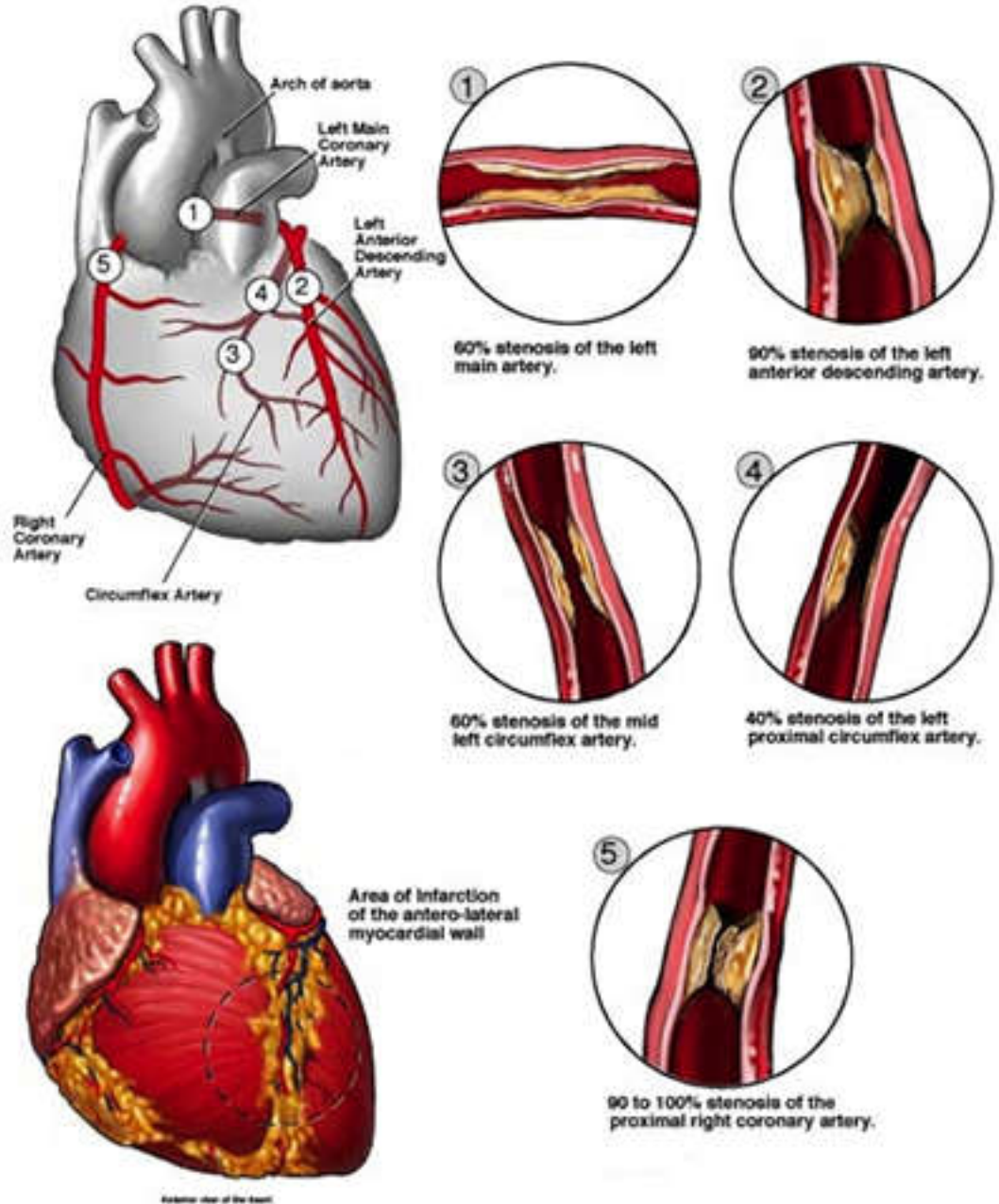
Atherosclerosis is a progressive disease characterized by the buildup of fatty plaques in artery walls. Atherosclerotic plaques are encased in a fibrous cap. They have different sizes, shapes and vulnerability to rupture and blood clots.



Atherosclerotic plaques in the coronary arteries result in coronary artery disease (CAD) and varying degrees of restricted flow of blood and oxygen (ischemia). This ischemia may cause chest pain (angina), change in cardiac function, and/or damage to the heart.

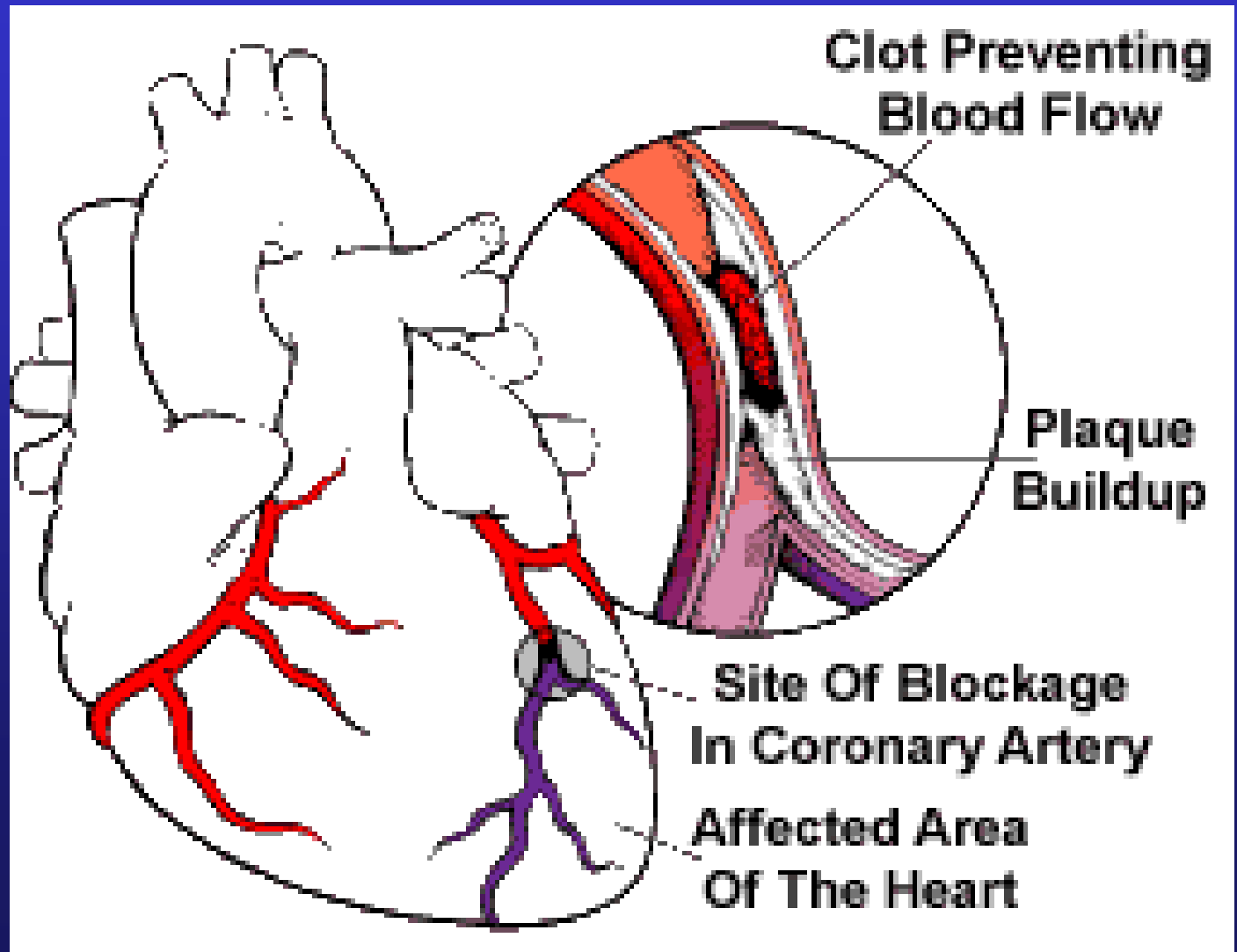


Atherosclerotic Coronary Artery Disease



Histopathological view of artery

Plaque rupture and clot formation can often completely block an already narrowed artery. This is what happens in most heart attacks (myocardial infarctions) and strokes.



So, what is the hypothesized link between PM air pollution and atherosclerosis?

- Much evidence suggests that inhaling PM can provoke low-grade pulmonary/systemic inflammation.
- Over the last few decades research has linked inflammation along with blood lipid levels to atherosclerosis (Libby, Ridker, Maseri. *Circulation* 2002).
- Inflammation contributes to the initiation and progression of atherosclerosis.
- Inflammation also contributes to acute thrombotic complications, making plaques more vulnerable to rupture, clotting, and precipitating acute cardiovascular or cerebrovascular events (heart attacks and strokes).
- C-reactive protein (CRP), a marker of low-grade chronic inflammation, has been shown to serve as a predictor of risk of atherosclerosis related cardiovascular disease.

Example 3a: Souza, Saldiva, Pope, Luiza. *Chest* 1998

- Basic methods: Lung tissue samples were collected during necropsies of individuals who died due to violent causes and who lived in relatively clean and polluted areas near Sao Paulo, Brazil.
- Basic results: Those who lived in more polluted areas had histopathologic evidence of sub-clinical chronic inflammatory lung injury.

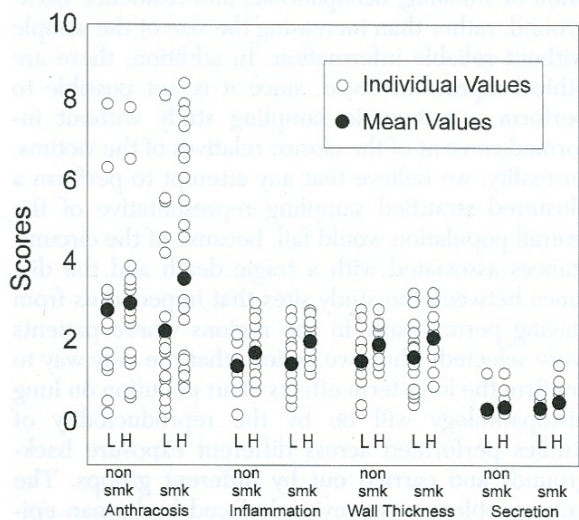


FIGURE 1. Mean and individual values of the morphologic parameter scores for smokers (smk) and nonsmokers (non smk) who lived in low (L) and high (H) air pollution levels.

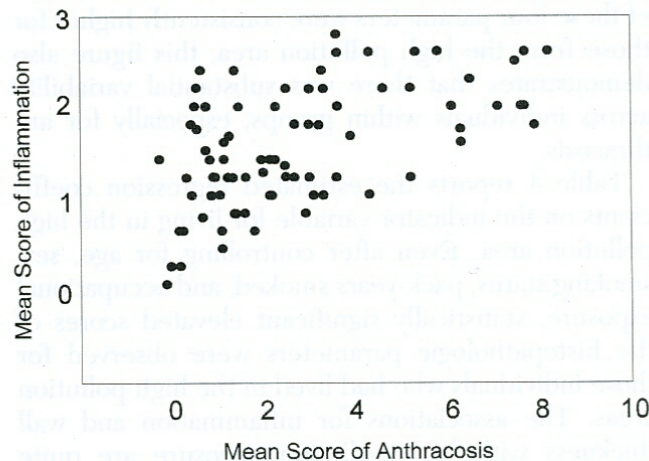


FIGURE 2. Scatter plot for inflammation mean scores over anthracosis mean scores.

Inflammation/Accelerated Atherosclerosis is supported by evidence that PM exposure is associated with:

- C-reactive protein (CRP) (Peters et al. 1997; Pope et al 2004)
- Blood plasma viscosity (Peters et al 1997)
- Bone marrow and blood cell responses (Tan et al. 2000)
- Proinflammatory cytokines (Van Eeden et al. 2001)
- Inflammatory lung injury (Ghio, Devlin 2001; Souza et al 1998)
- Endothelial dysfunction and brachial artery vasoconstriction (Brook et al. 2002)
- Triggering of Myocardial Infarction (Peters et al. 2001)
- Increased CIMT (carotid intima-media thickness) (Kunzli et al)
- Accelerated atherosclerosis (in rabbits) (Suwa et al. 2002)



Circulation. 2004;109:71-77.

Cardiovascular Mortality and Long-Term Exposure to Particulate Air Pollution

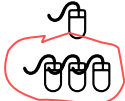









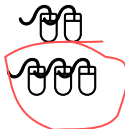
Epidemiological Evidence of General Pathophysiological Pathways of Disease

C. Arden Pope III, PhD; Richard T. Burnett, PhD; George D. Thurston, ScD; Michael J. Thun, MD; Eugenia E. Calle, PhD; Daniel Krewski, PhD; John J. Godleski, MD

Methods:

- General pathophysiological pathways linking long-term PM exposure with mortality and expected patterns of PM-mortality with specific causes of death were proposed *a priori*.
- Vital status, risk factor, and cause-of-death data from ACS CPS-II were linked with pollution data.
- Estimate PM-mortality associations for specific causes of deaths controlling for other risk factors (using similar statistical modeling described in the previous ACS analysis)

Table 1. Expected patterns of PM-mortality associations for specific causes of cardiopulmonary deaths based on three hypothesized general pathophysiological pathways.

Cause of Death	Accelerated Progression of COPD	Inflammation/ Accelerated Atherosclerosis	Altered Cardiac Autonomic Function
All cardiovascular diseases plus diabetes			
Ischemic heart disease	→		
Dysrhythmias, heart failure, cardiac arrest	→		
Hypertensive disease			
Other atherosclerosis, aortic aneurysms			
Cerebrovascular disease			
Diabetes			
All other cardiovascular diseases			
Diseases of the respiratory system			
COPD and allied conditions	→		
Pneumonia and influenza			
All other respiratory			

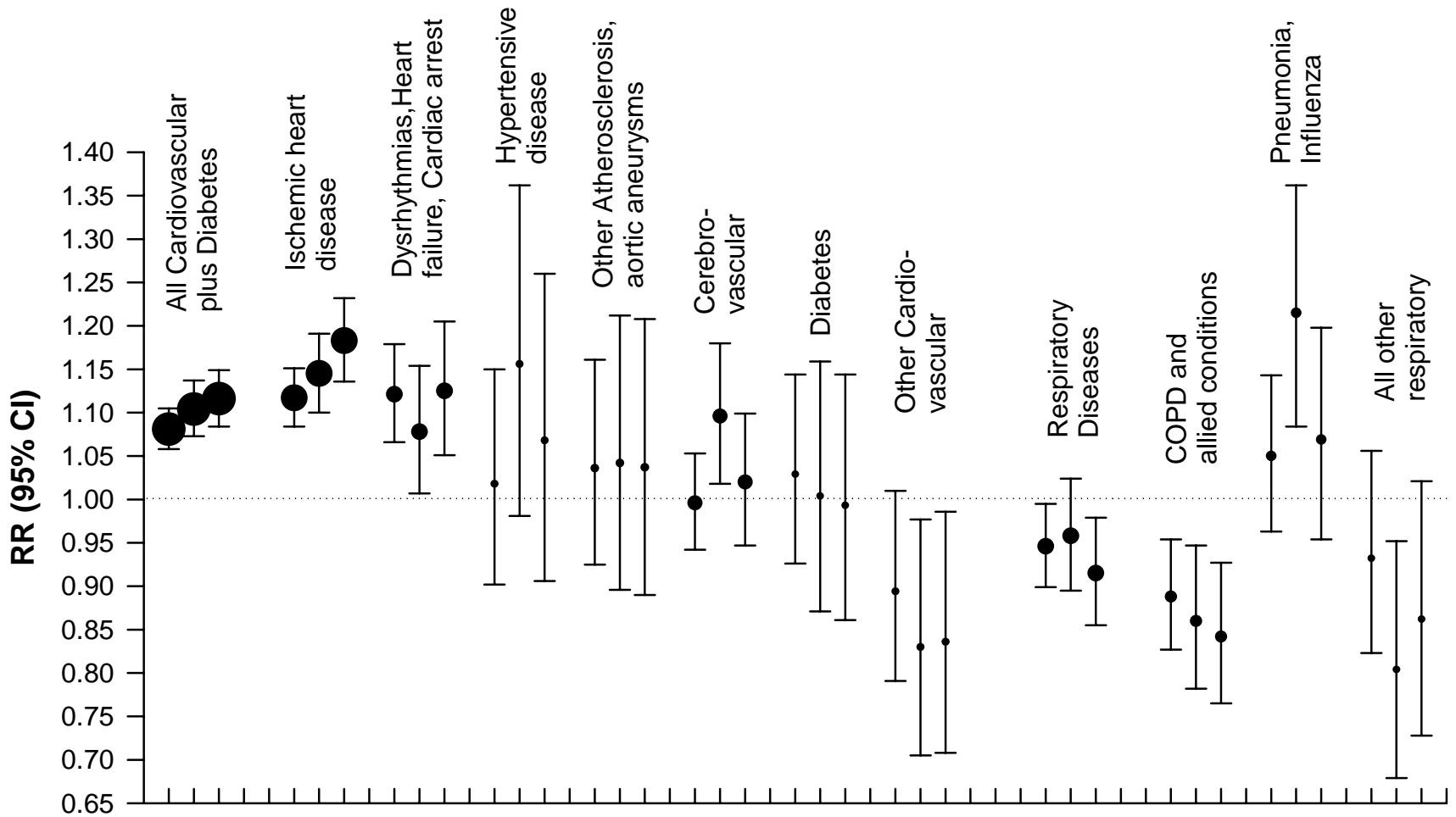
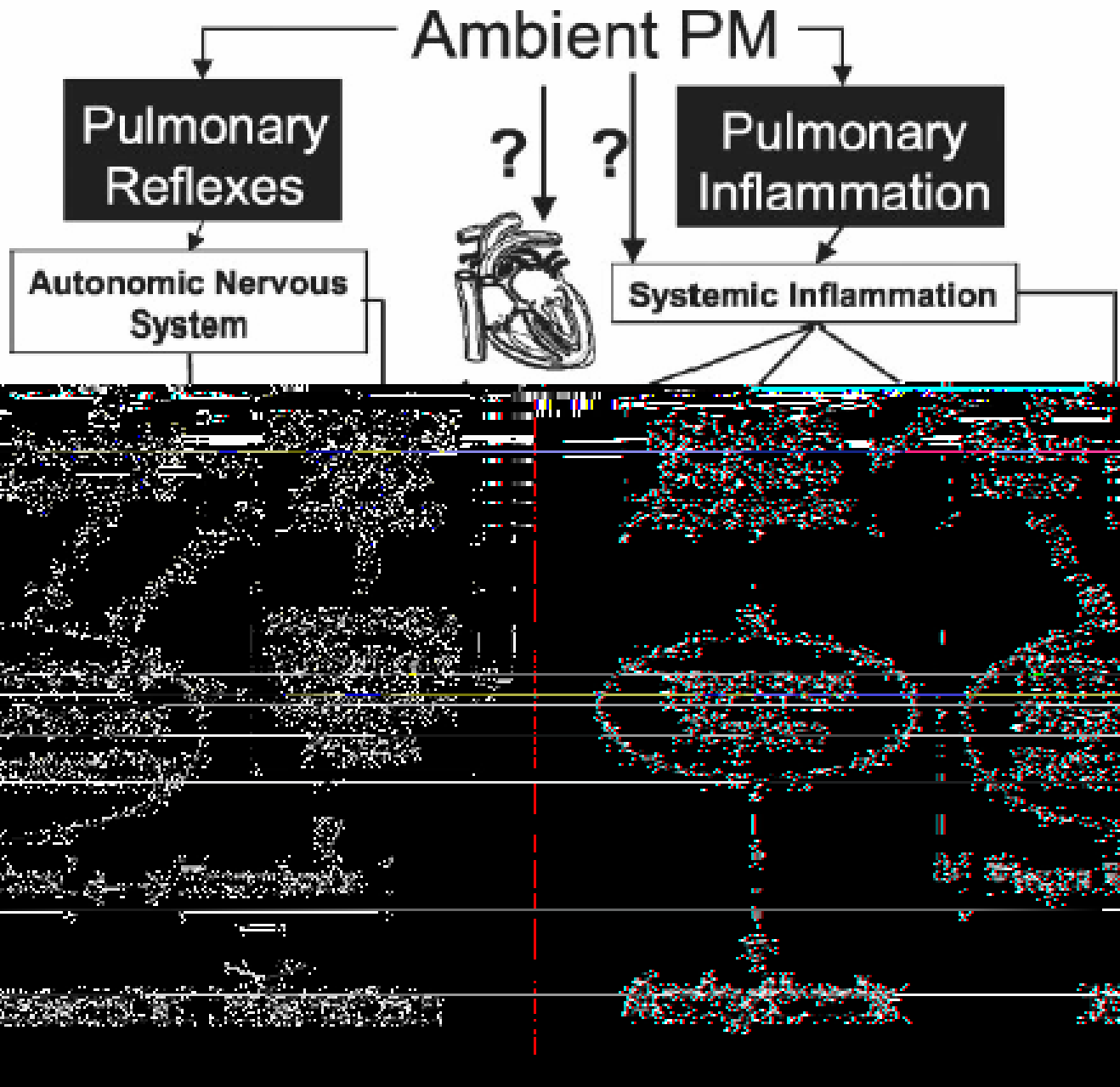


Figure 1. Adjusted relative risk ratios for cardiovascular and respiratory mortality associated with a $10 \mu\text{g}/\text{m}^3$ change in $\text{PM}_{2.5}$ for 1979-1983, 1999-2000, and the average of the two periods. (Relative size of the dots correspond to the relative number of deaths for each cause.)

➤ **Modulation of host defenses and immunity** is suggested by the increase in pneumonia and influenza deaths, but not COPD deaths, associated with long-term PM exposure. Other reports of pollution associations with pediatric respiratory hospitalizations and bronchitis and pneumonia related symptoms are also suggestive .

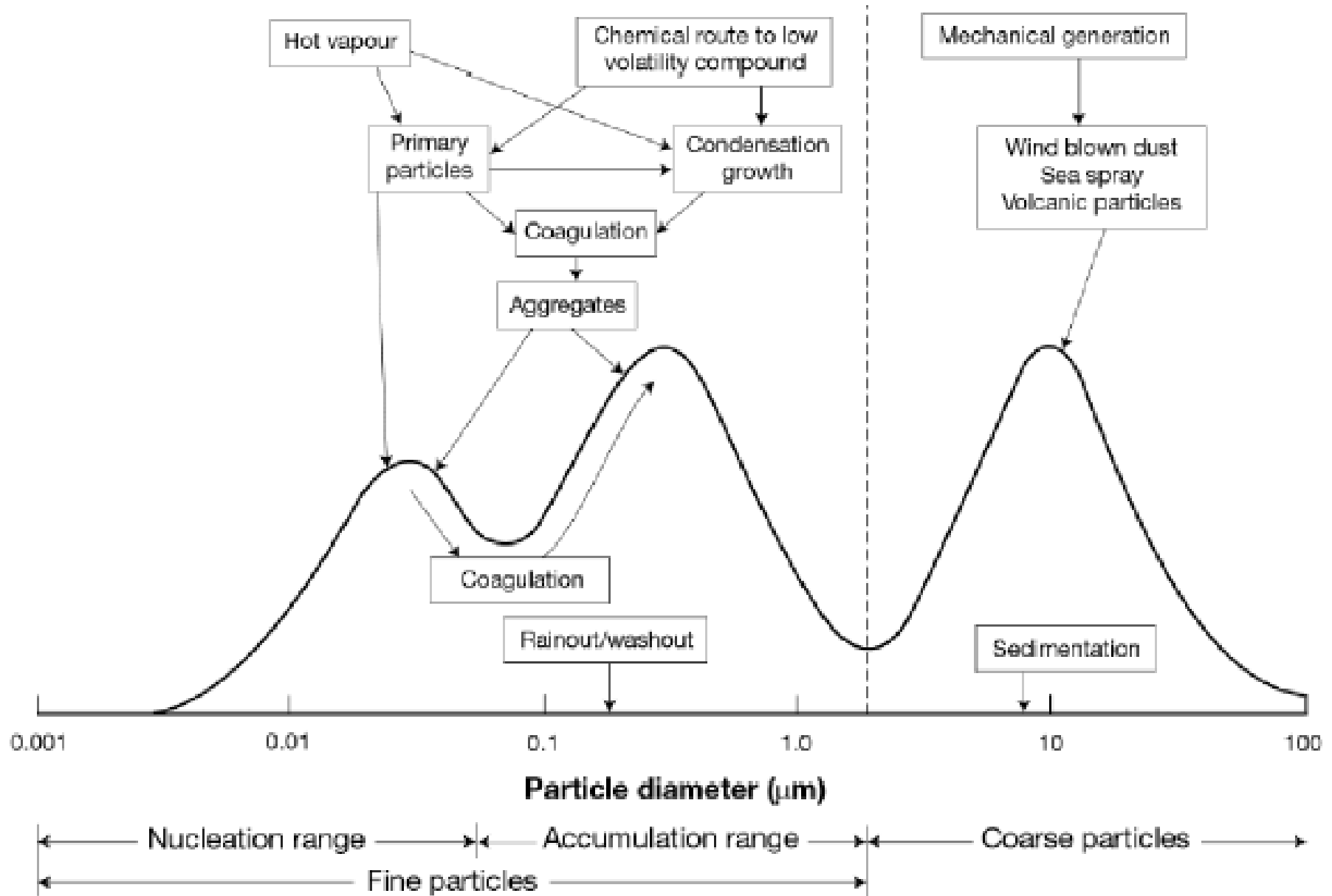


General scheme illustrating potential mechanistic pathways.

From:
 AHA Scientific Statement--
 Brook RD, et al.
Circulation 2004

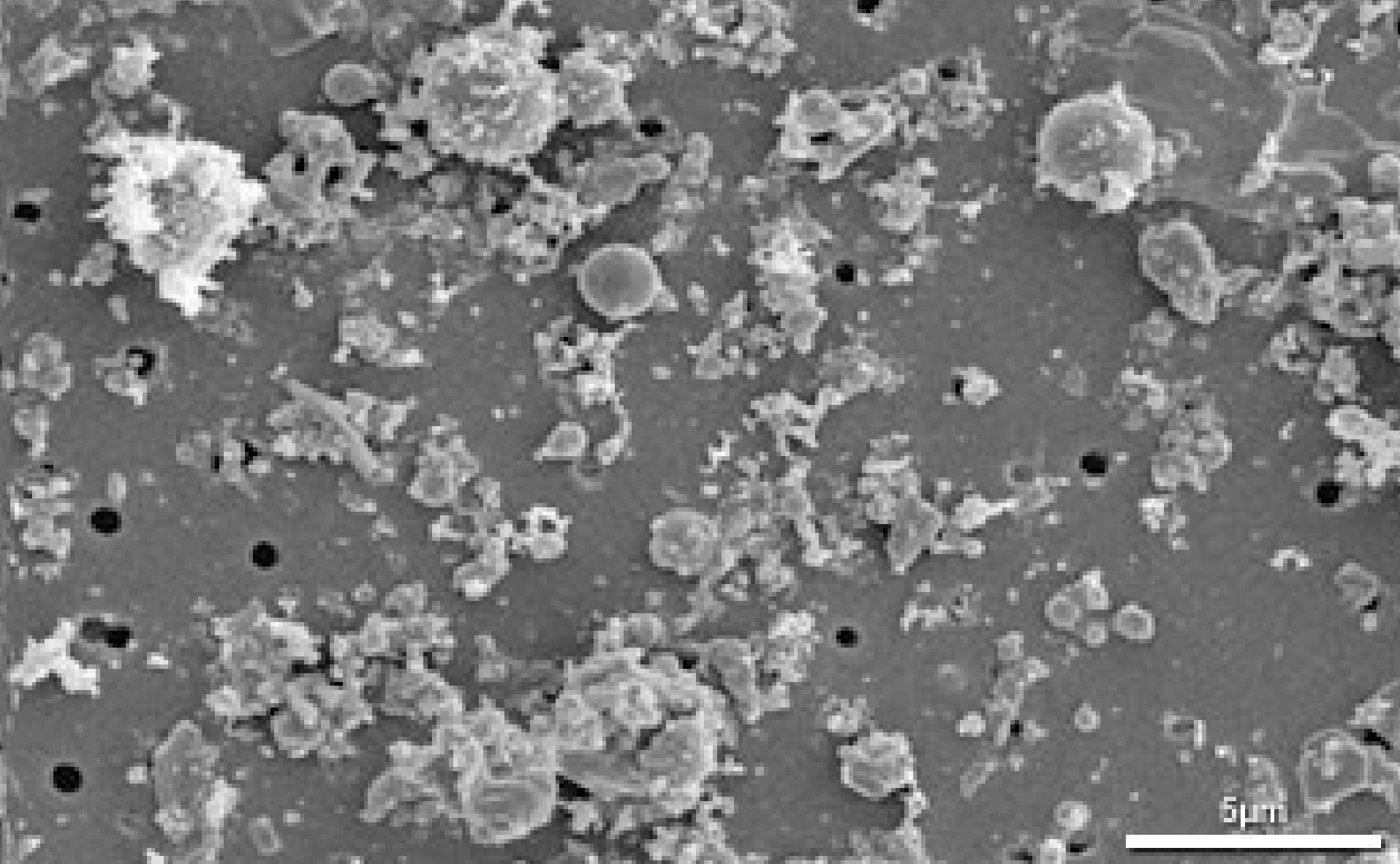
What is the role of ultrafine (or nanoparticles) versus other combustion-related fine particles?

Ambient air is constantly being polluted by fresh emissions of ultrafine particles that have short lives (minutes to hours) and rapidly grow (through coagulation and/or condensation) to form complex aggregates



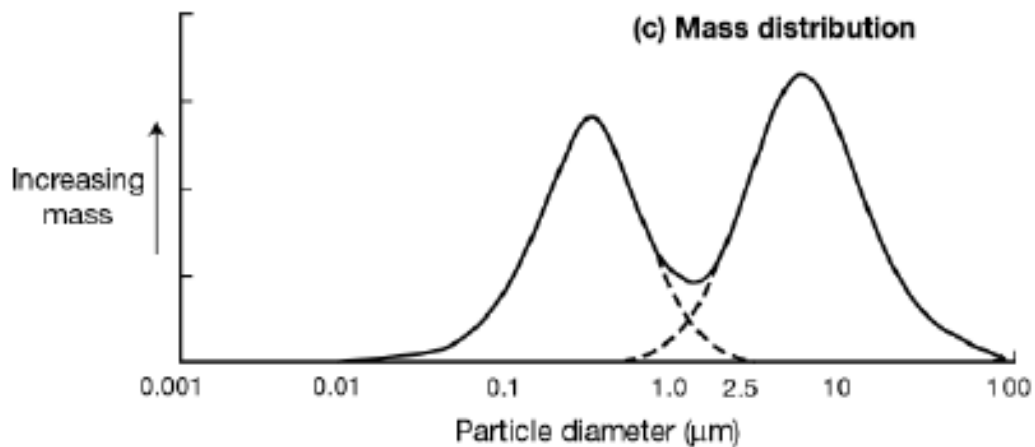
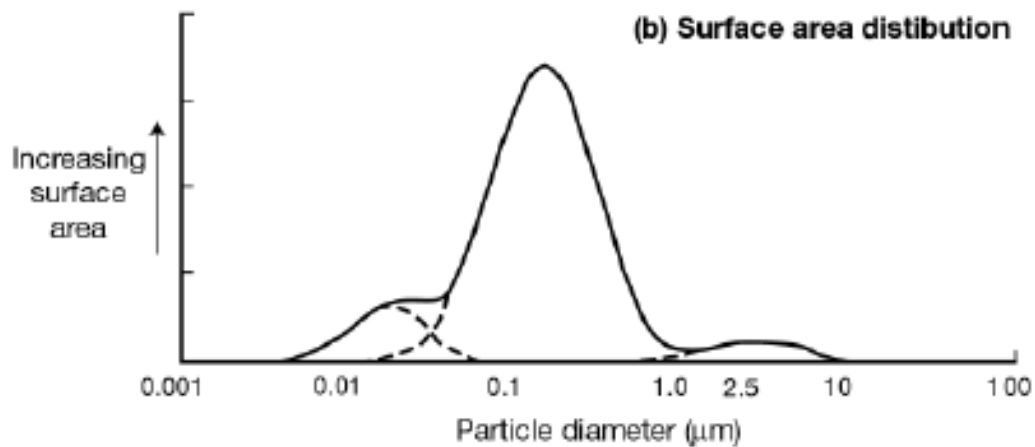
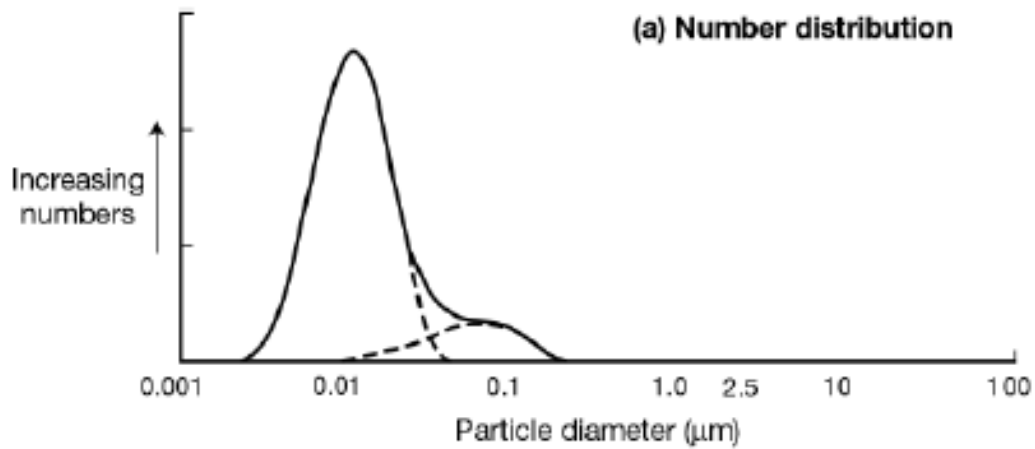


Magnification of urban soot depicting aggregates of individual particles
(www.defra.gov.uk/environment/airquality/aqs/air_measure/03.htm)



Magnified ambient particles from the industrial city of Port Talbot, England.
(www.nasa.gov/vision/earth/environment)

- Epidemiology is limited in its ability to elucidate the role of ultrafine (or nanoparticles) versus other combustion-related fine particles (in the accumulation mode because of the complex and ever changing nature of these particles).
- Nevertheless, there is clear evidence that both fine and ultrafine particles can have adverse effects on cardiorespiratory health.



Idealized particle size distribution of urban aerosols.

From: Whitby K.
Atmospheric
Environment 1978

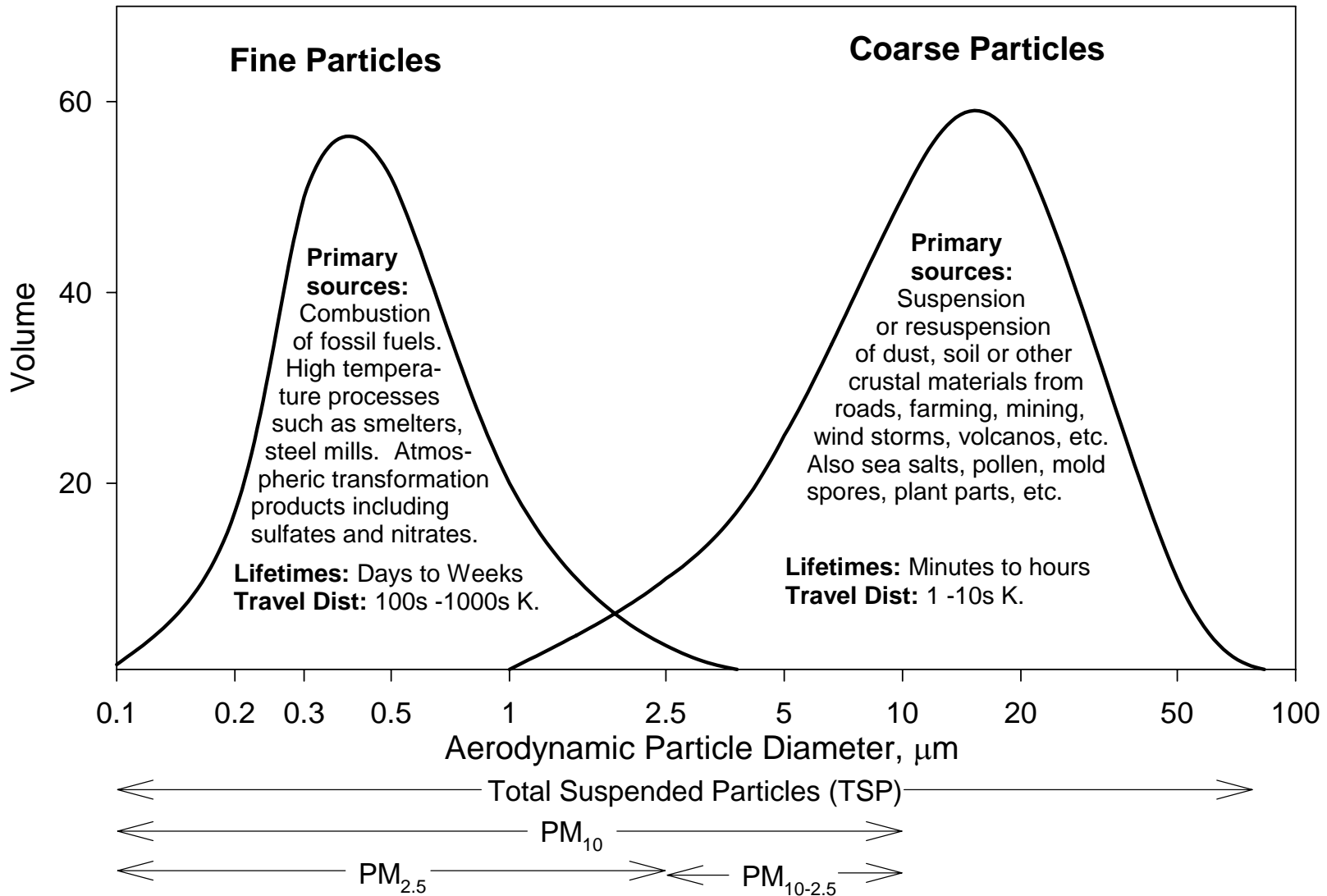


Figure 1. Stylized distributions of fine and coarse ambient particulate matter. The distribution is truncated at $0.1 \mu\text{m}$, excluding the ultrafine fraction. Source: Adapted from Wilson and Suh (1997).