Cardiovascular Autonomic Nervous System: a link between worker and occupational environment

Nicola Montano MD, PhD

IRCCS Ca' Granda Foundation,
Ospedale Maggiore Policlinico
University of Milan, Milan, Italy

Air Pollution Disasters

1930 Meuse River Valley, Belgium

A three-day episode of severe air pollution makes 6,000 ill and kills 63.

1948 Denora, PA

Oct. 26 to 31: air pollution episode leaves 20 dead out of 14,000 persons.

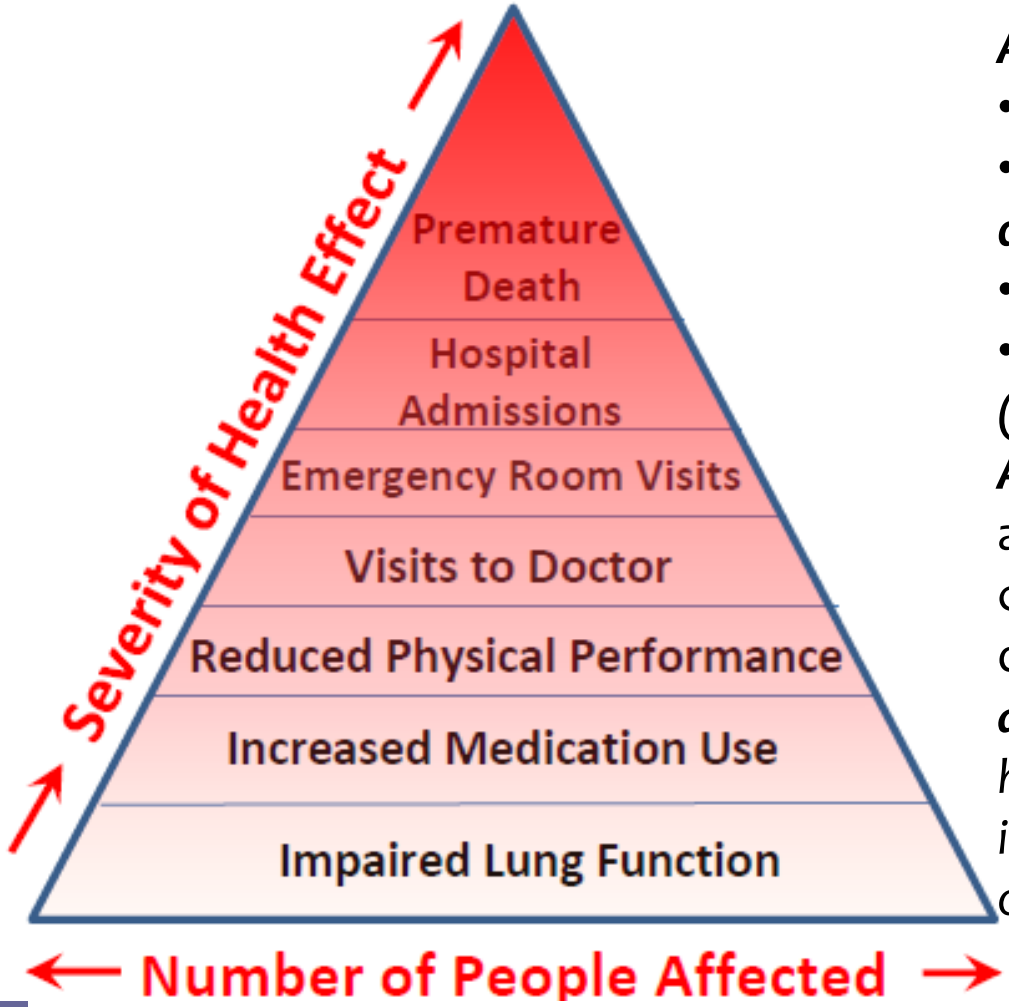
Donora, PA at noon on Oct. 29, 1948

1952 London, England

Dec. 4 to 9: "Killer Fog" leaves three to four thousand people dead.

London buses are escorted by lantern at 10:30 in the morning.

Air Pollution and health



At greater risk from air pollution:

- ***Children (including teenagers)***
- ***People with asthma or another lung disease***
- ***Healthy adults who are active outdoors***
- ***People with cardiovascular disease (that's your heart and blood vessels).***

Air pollution can contribute to heart attacks, strokes, cardiac arrest, congestive heart failure – and premature death. ***People in middle age and older are also at risk.*** *In middle age, our risk for heart and lung diseases generally increases – and so does our risk from ozone and particle pollution*

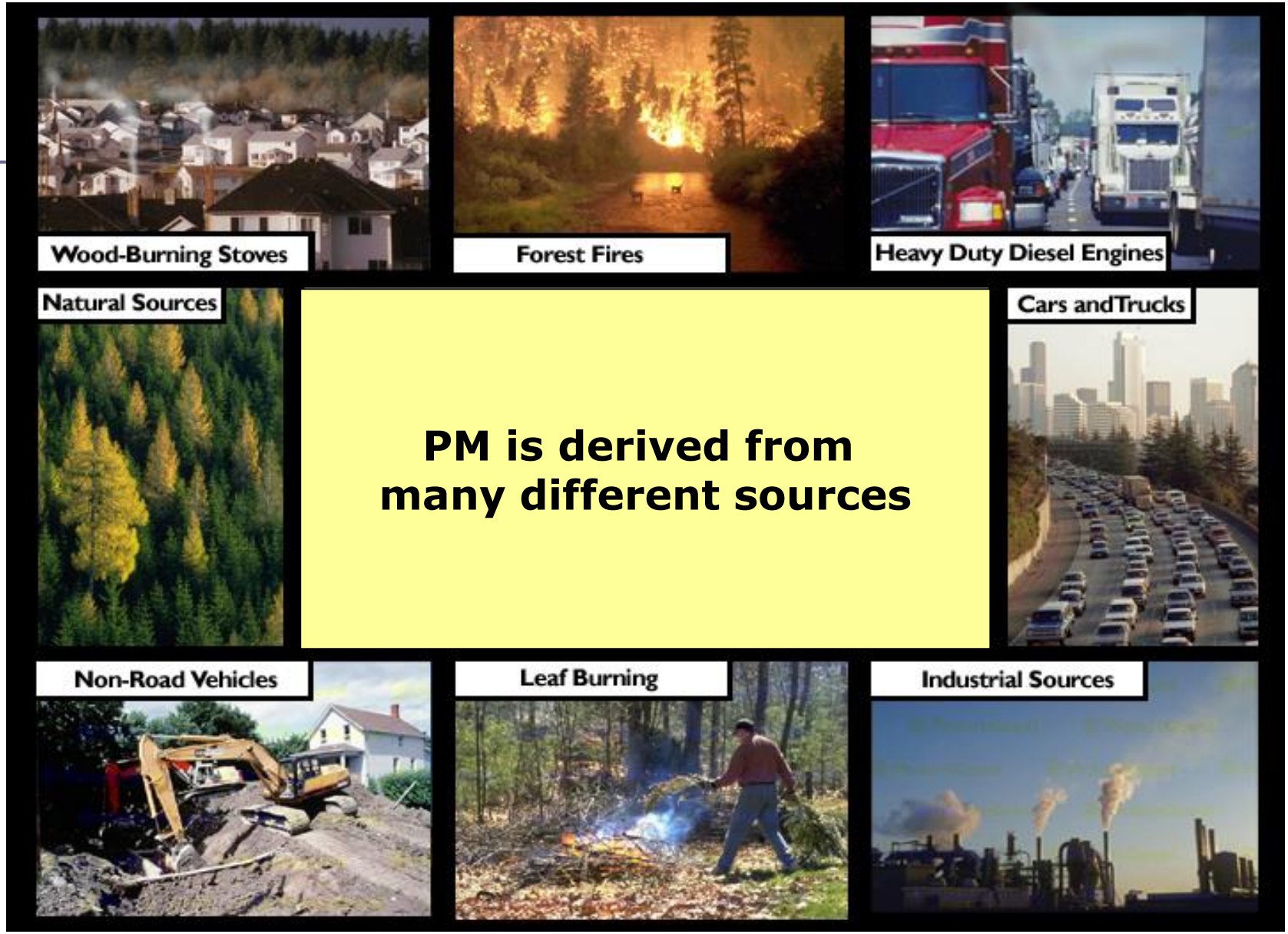
References: WHO Factsheet No. 313 Air quality and health; WHO Air Quality Guidelines - global update; US EPA factsheet **Air Quality: Important at Every Age** (www.airnow.gov) **2013**

Air pollution is the environmental factor with the greatest health impact in Europe!

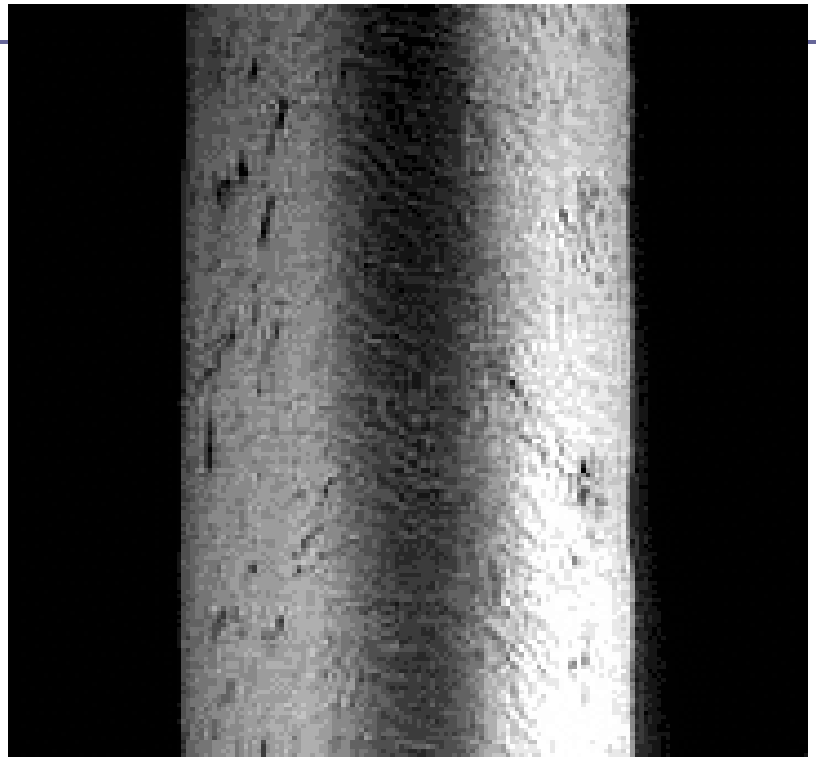
- WHO estimates for Europe (51 countries)
  - Children age 0-4 years: 1.8 – 6.4 % of deaths from all causes due to outdoor air pollution
  - Mild mental retardation due to lead exposure: 4.4 % of all DALYs
- In a selection of European cities each year:
  - **Air pollution** responsible for 100 000 deaths and
  - 725 000 years of lost life (DALYs)
- European Commission estimates in CAFÉ:
  - 350 000 premature deaths in 2000 due to outdoor air pollution of PM2.5 alone
  - Average loss of life expectancy of 9 months for each European citizen
- Ozone causes 20.000 premature deaths annually

American Cancer Society:
mortality increase for each > PM $_{2,5}$ 10 µg/m3

- All-cause mortality: **+4%**
- Cardiopulmonary diseases: **+ 6%**
- Lung cancer: **+8%**

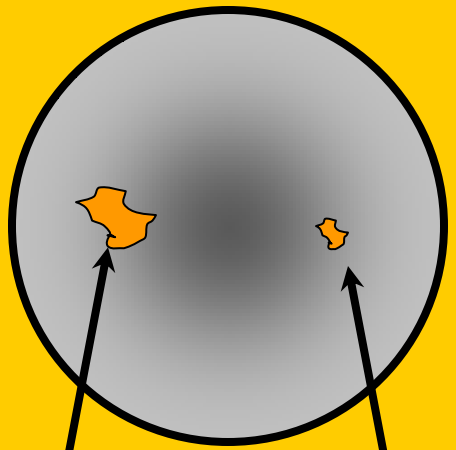

Wood-Burning Stoves
Forest Fires
Heavy Duty Diesel Engines
Natural Sources
PM is derived from many different sources
Cars andTrucks
Non-Road Vehicles
Leaf Burning
Industrial Sources

PM relative to hair cross section



Human Hair

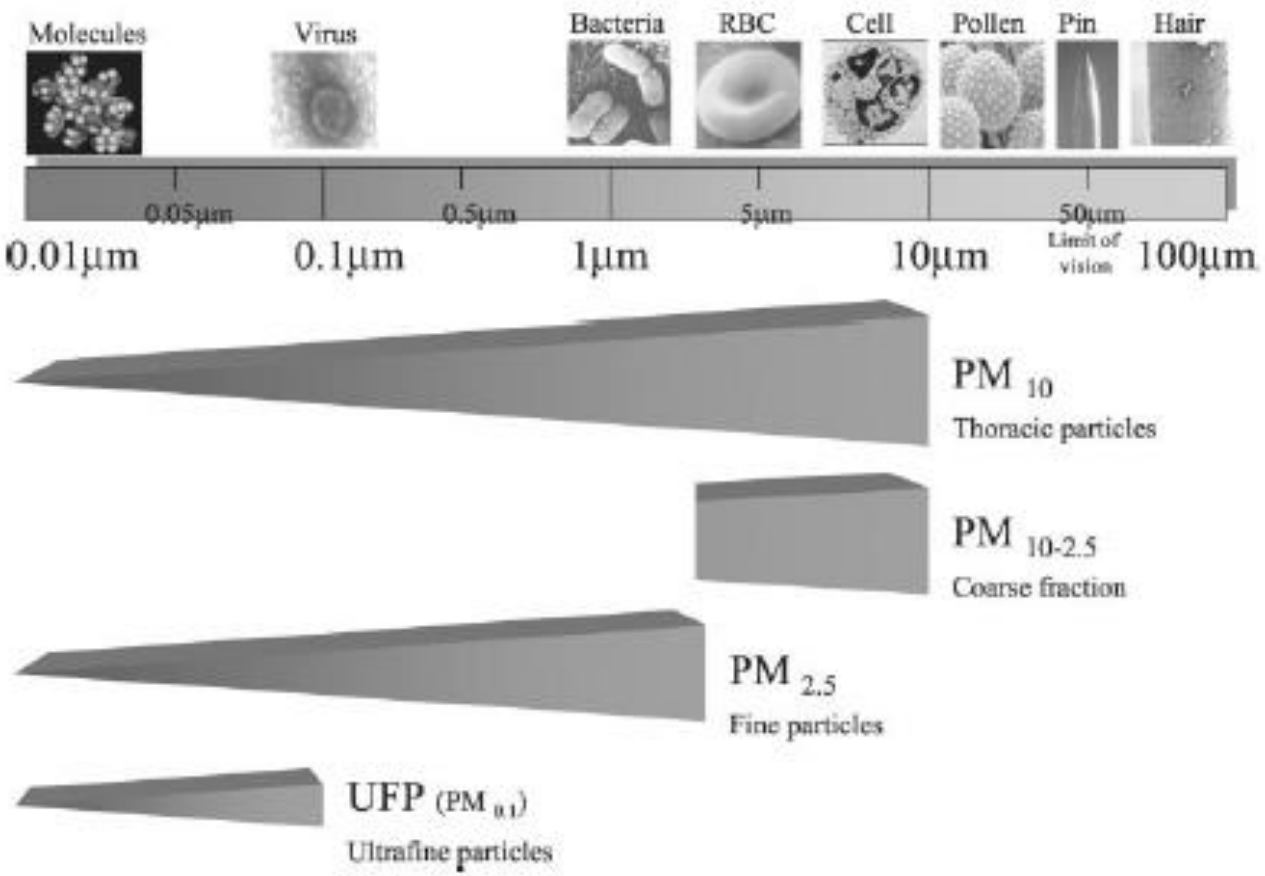
Hair cross section (60 μm)



PM10 (10 μm)

PM2.5 (2.5 μm)

Brook et al Air Pollution



Public Health Risks Are Significant

- Particles are linked to:
- Premature death from heart and lung diseases
- Aggravation of heart and lung diseases, with increased:
  - Hospital admissions
  - Doctor and ER visits
  - Medication use
  - School and work absences

BMJ

BMJ 2013;348:f7412 doi: 10.1136/bmj.f7412 (Published 21 January 2014)

RESEARCH

Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project

Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study

Luke Clancy, Pat Goodman, Hamish Sinclair, Douglas W Dockery

Summary

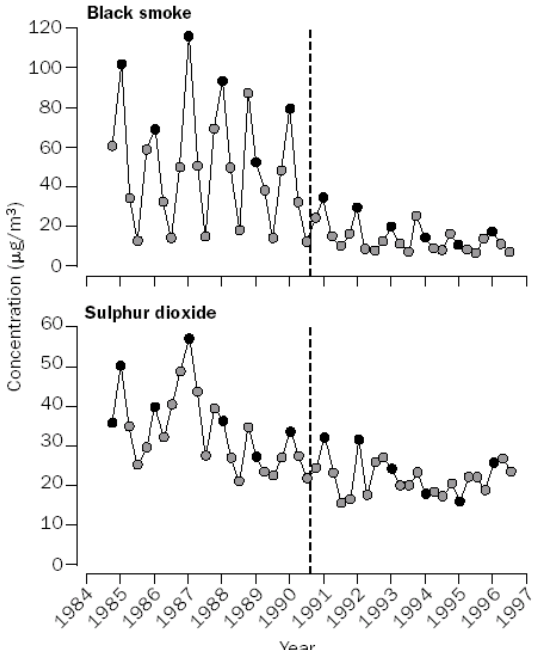
Background Particulate air pollution episodes have been associated with increased daily death. However, there is little direct evidence that diminished particulate air pollution concentrations would lead to reductions in death rates. We assessed the effect of air pollution controls—ie, the ban on coal sales—on particulate air pollution and death rates in Dublin.

Methods Concentrations of air pollution and directly-standardised non-trauma, respiratory, and cardiovascular death rates were compared for 72 months before and after the ban of coal sales in Dublin. The effect of the ban on age-standardised death rates was estimated with an interrupted time-series analysis, adjusting for weather, respiratory epidemics, and death rates in the rest of Ireland.

Findings Average black smoke concentrations in Dublin declined by 35·6 μg/m³ (70%) after the ban on coal sales. Adjusted non-trauma death rates decreased by 5·7% (95% CI 4–7, p<0·0001), respiratory deaths by 15·5% (12–19, p<0·0001), and cardiovascular deaths by 10·3% (8–13, p<0·0001). Respiratory and cardiovascular standardised death rates fell coincident with the ban on coal sales. About 116 fewer respiratory deaths and 243 fewer cardiovascular deaths were seen per year in Dublin after the ban.

Interpretation Reductions in respiratory and cardiovascular death rates in Dublin suggest that control of particulate air pollution could substantially diminish daily death. The net benefit of the reduced death rate was greater than predicted from results of previous time-series studies.

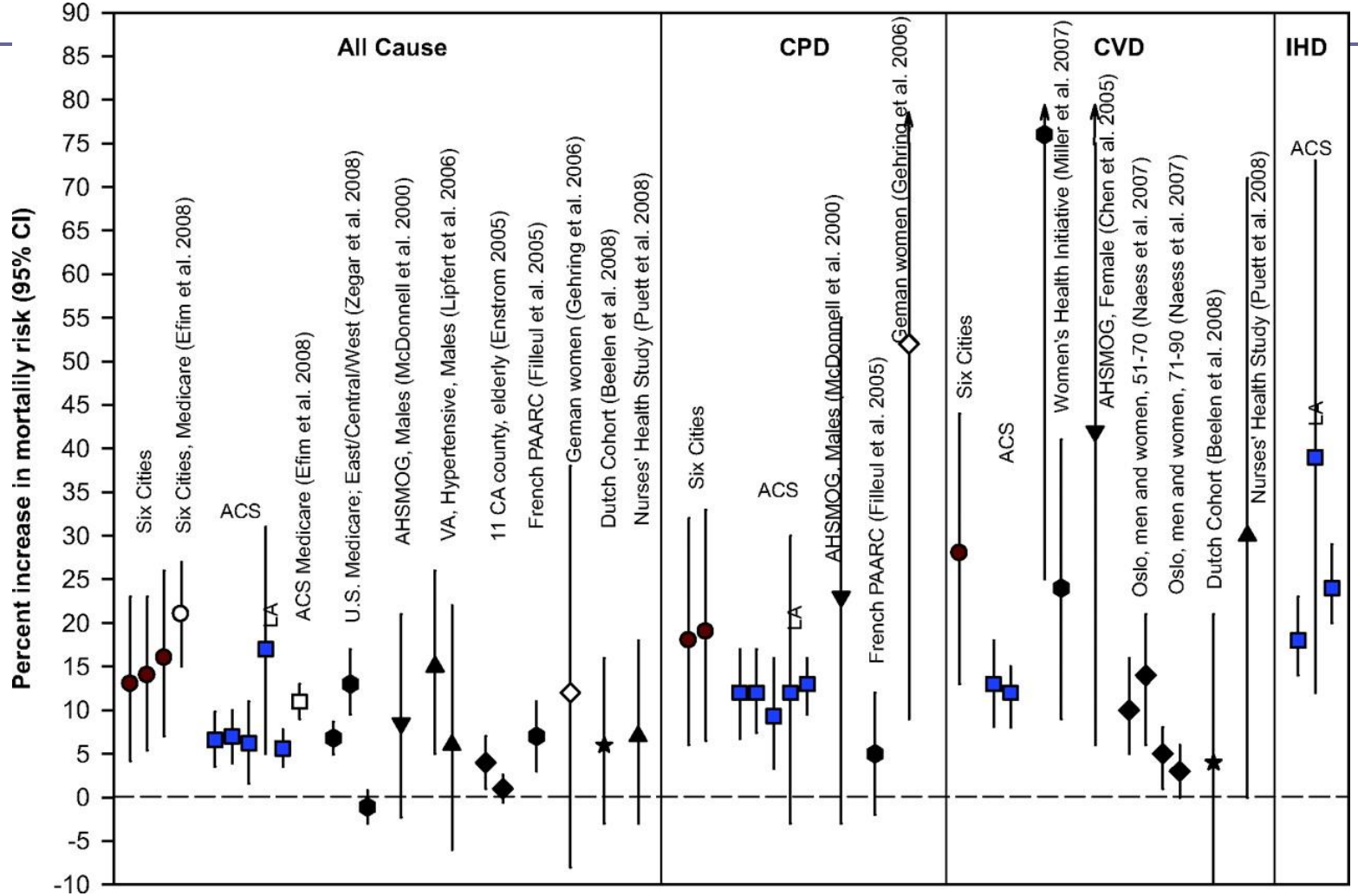
Lancet 2002; **360:** 1210–14



Unusual Opportunity:

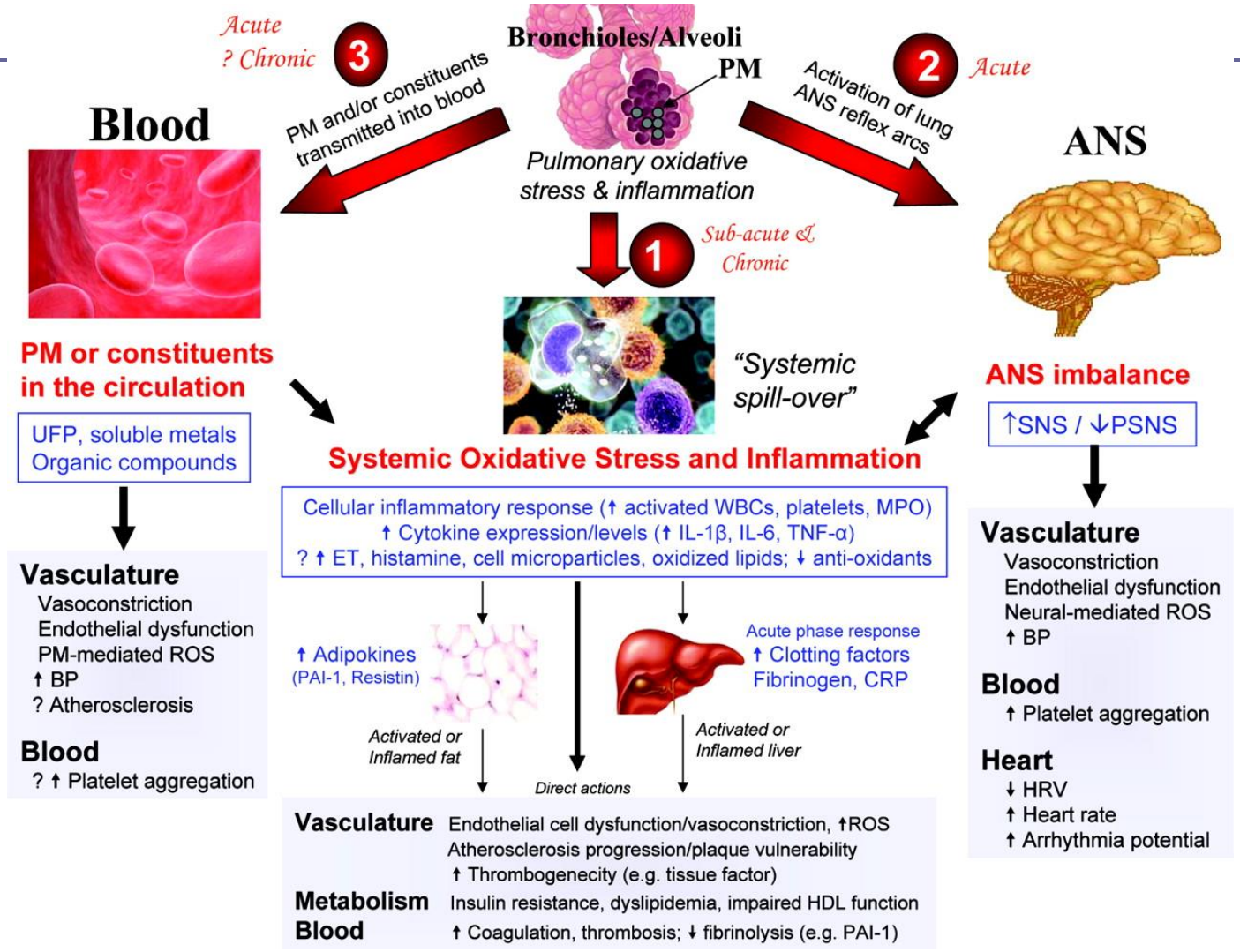
- Natural experiment
- Dramatic (70%) reduction in pollutant concentration over short period
- Control communities readily available
- Death rates decreased measurably – by 15.5% in case of deaths from respiratory causes

Figure 1. Risk estimates provided by several cohort studies per increment of 10 µg/m3 in PM2.5 or PM10.

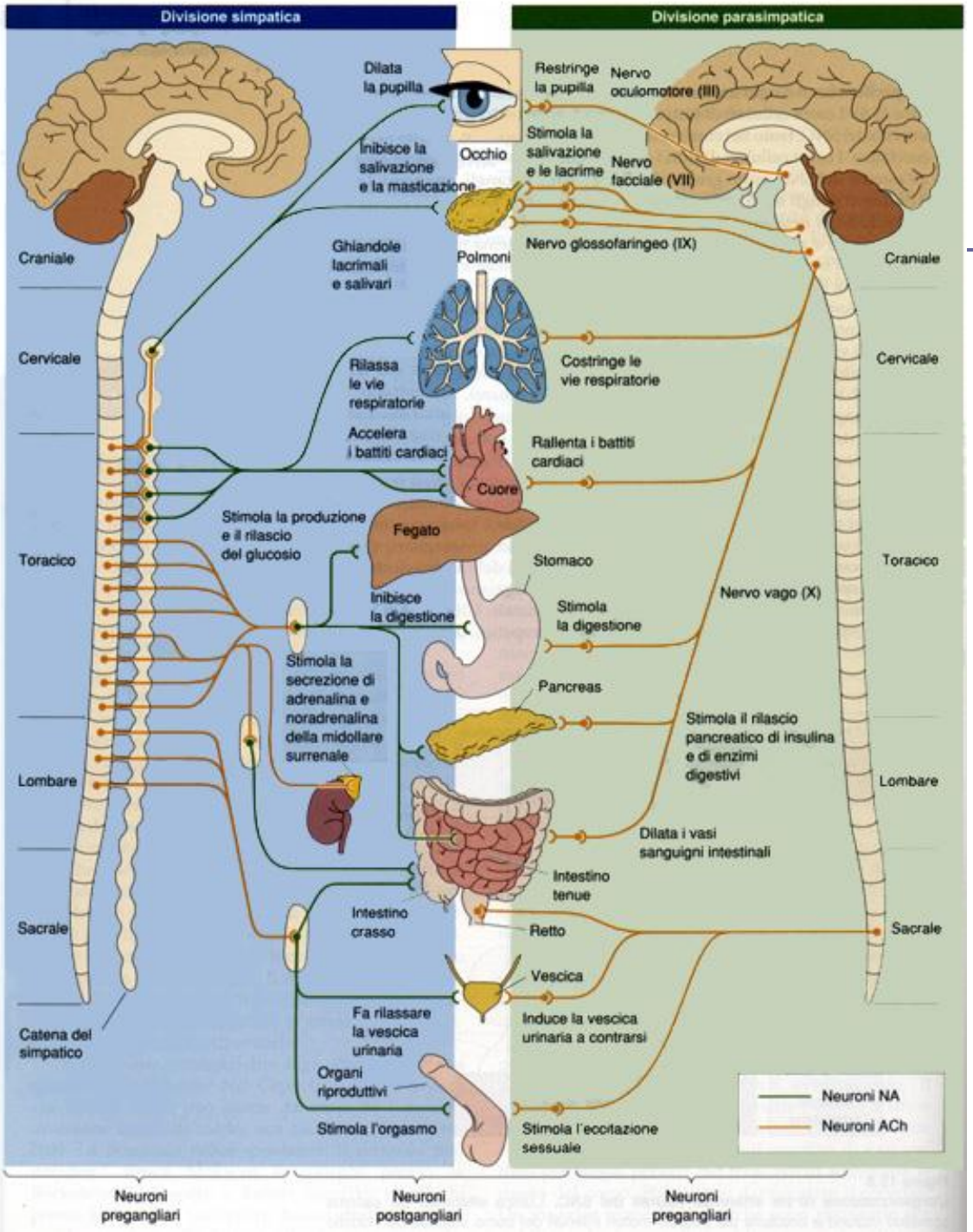


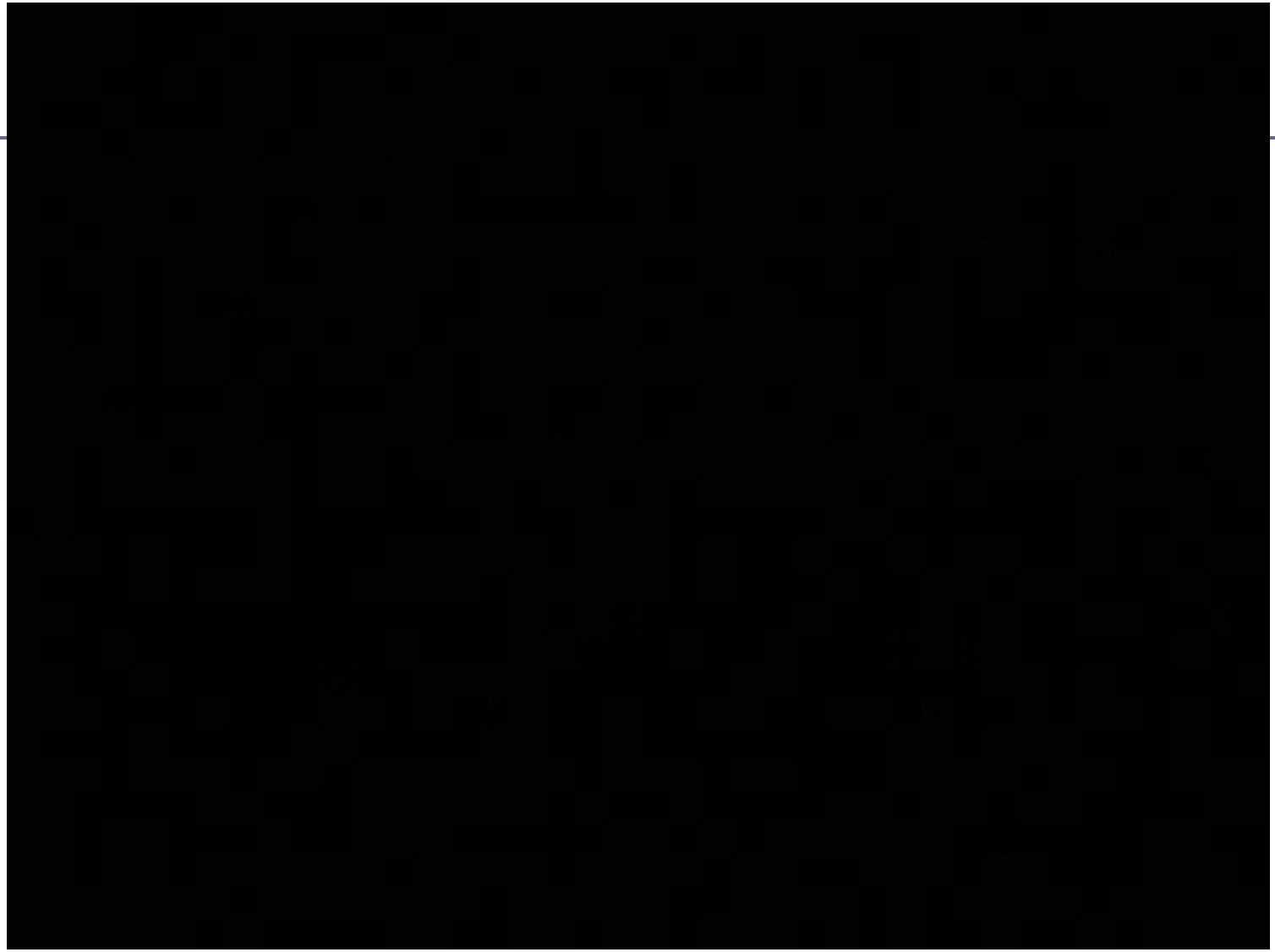
Brook R D et al. Circulation. 2010;121:2331-2378

Figure 3. Biological pathways linking PM exposure with CVDs. The 3 generalized intermediary pathways and the subsequent specific biological responses that could be capable of instigating cardiovascular events are shown.



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


Divisione simpatica
Divisione parasimpatica
Dilata la pupilla
Occhio
Restringe la pupilla
Nervo oculomotore (III)
Inibisce la salivazione e la masticazione
Stimola la salivazione e le lacrime
Nervo facciale (VII)
Nervo glossofaringeo (IX)
Craniale
Ghiandole lacrimali e salivari
Polmoni
Craniale
Cervicale
Rilassa le vie respiratorie
Costringe le vie respiratorie
Cervicale
Accelera i battiti cardiaci
Rallenta i battiti cardiaci
Cuore
Stimola la produzione e il rilascio del glucosio
Fegato
Toracico
Stomaco
Toracico
Inibisce la digestione
Nervo vago (X)
Stimola la digestione
Stimola la secrezione di adrenalina e noradrenalina della midollare surrenale
Pancreas
Stimola il rilascio pancreatico di insulina e di enzimi digestivi
Lombare
Lombare
Dilata i vasi sanguigni intestinali
Intestino tenue
Intestino crasso
Retto
Sacrale
Sacrale
Vescica
Fa rilassare la vescica urinaria
Induce la vescica urinaria a contrarsi
Catena del simpatico
Organi riproduttivi
Stimola l'orgasmo
Stimola l'eccitazione sessuale
Neuroni NA
Neuroni ACh
Neuroni preganglionari
Neuroni postgangliari
Neuroni preganglionari



Sympathetic Nervous System -1-

Major concepts

- "Fight or Flight" response

- SNS activation:

  increases heart rate, blood pressure, cardiac output and dilates large muscular arteries and the bronchioles.

- SNS prepare humans for physical confrontation or to respond to acute hemodynamic collapse or respiratory compromise.

- SNS improves a person's chance of survival and increases the likelihood that his or her genes will be passed on to the next generation.

Sympathetic Nervous System -2-

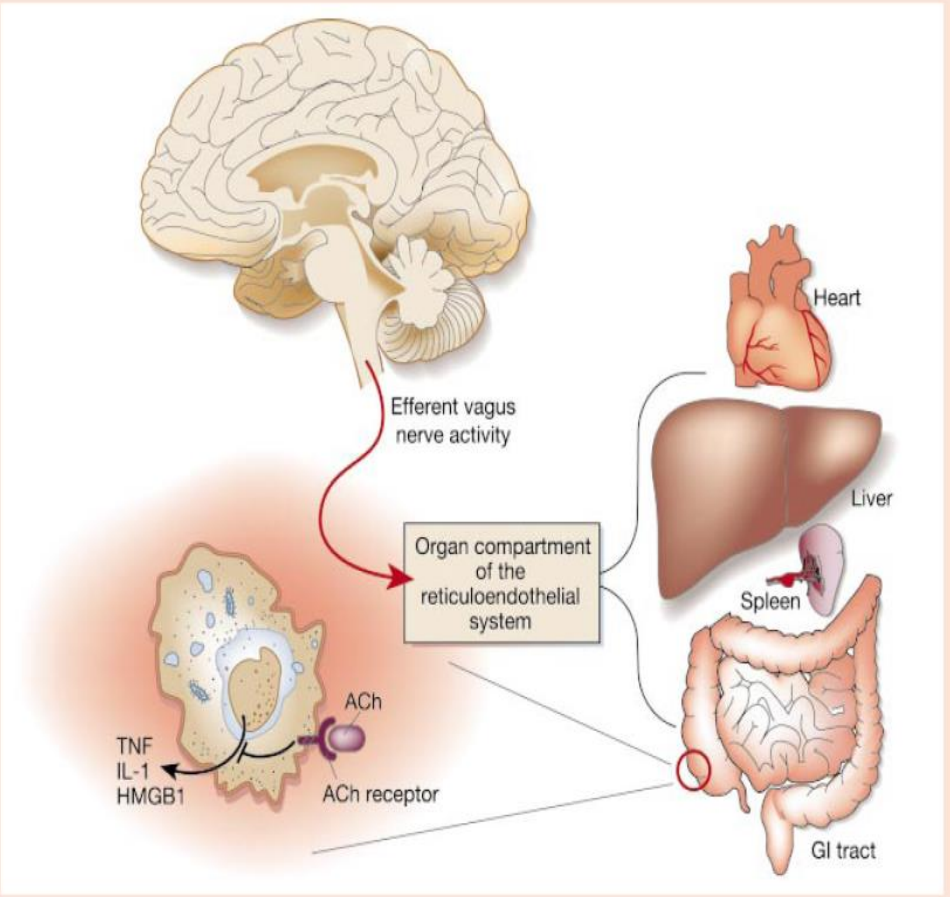
Major concepts

- The status of the ANS, although often ignored by clinicians, is a ***major determinant of cardiovascular health and prognosis***.

- Any therapy that chronically decreases the sympathetic activity and/or increases parasympathetic (vagal) tone will decrease the risk of cardiovascular events and viceversa.

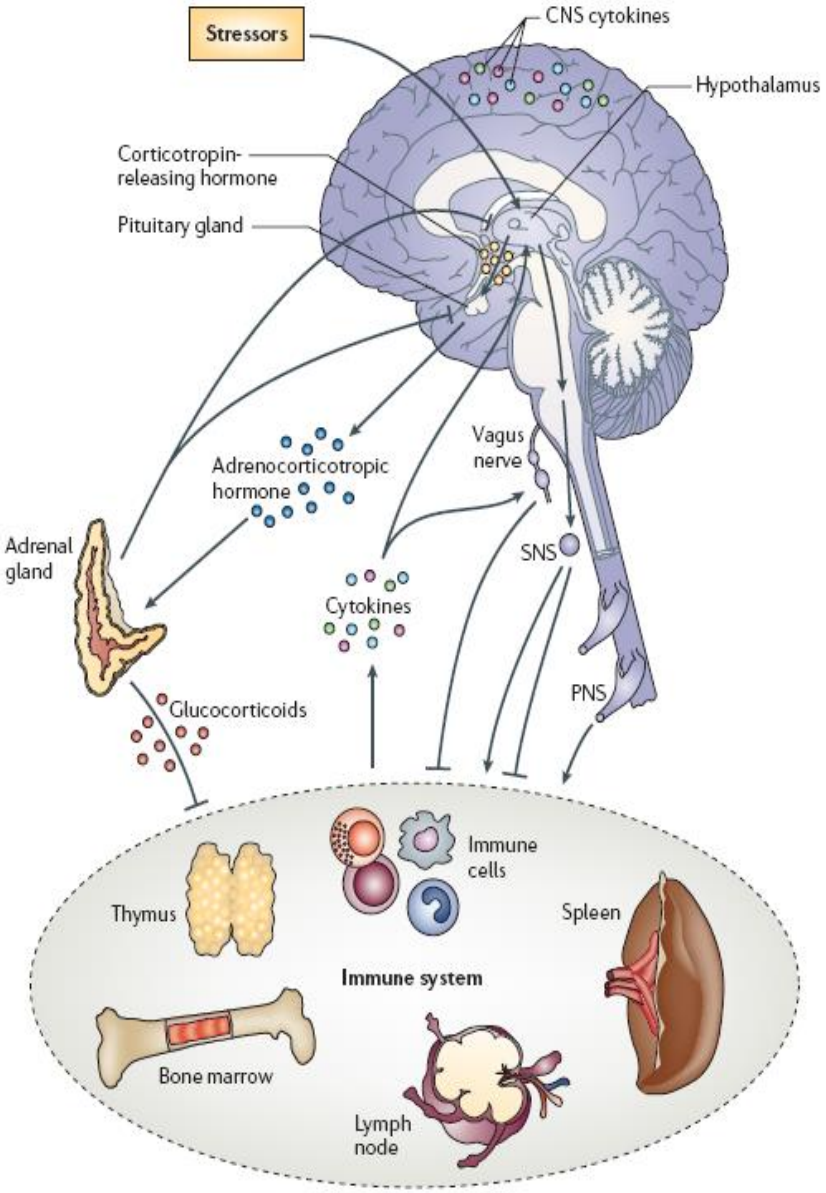
Inflammation and ANS

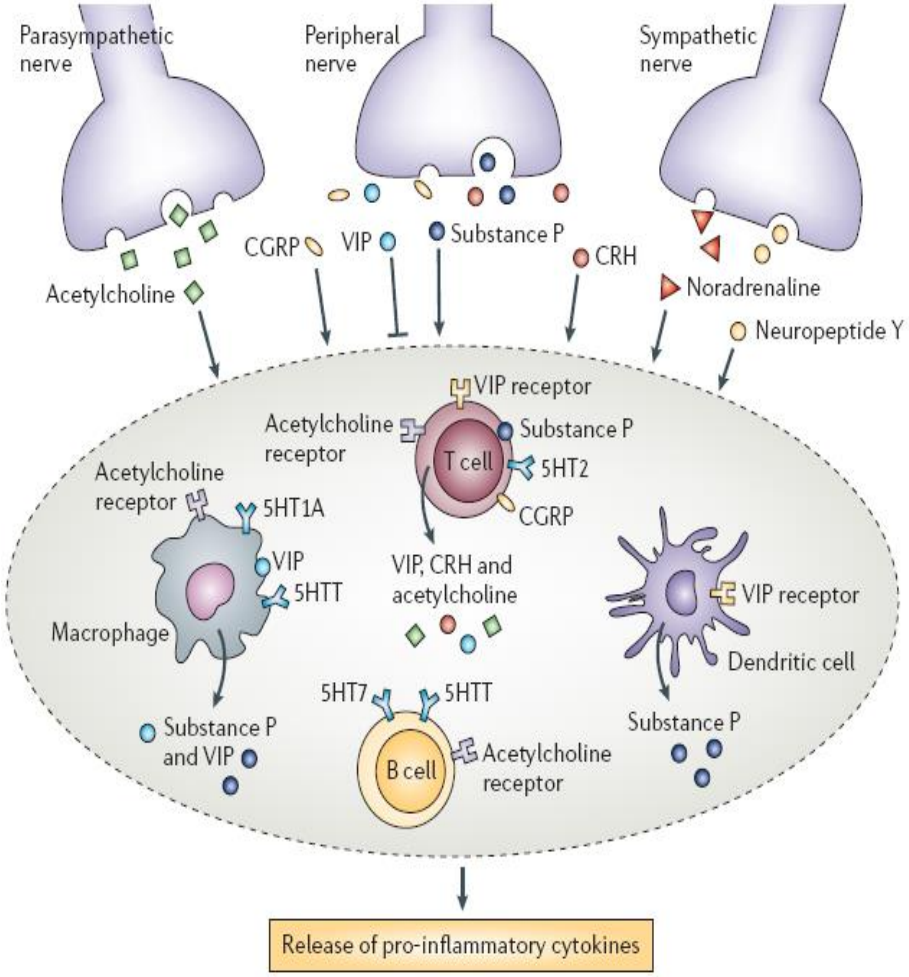
Figure 1 The cholinergic anti-inflammatory pathway. Efferent activity in the vagus nerve leads to acetylcholine (ACh) release in organs of the reticuloendothelial system, including the liver, heart, spleen and gastrointestinal tract. Acetylcholine interacts with α-bungarotoxin-sensitive nicotinic receptors (ACh receptor) on tissue macrophages, which inhibit the release of TNF, IL-1, HMGB1 and other cytokines.



(Tracey K, Nature 420:852-56, 2002)

ANS-Immune system interactions





(Sternberg EM, *Nat Rev Immun 2006, 6:318-328*)

ANS assessment techniques

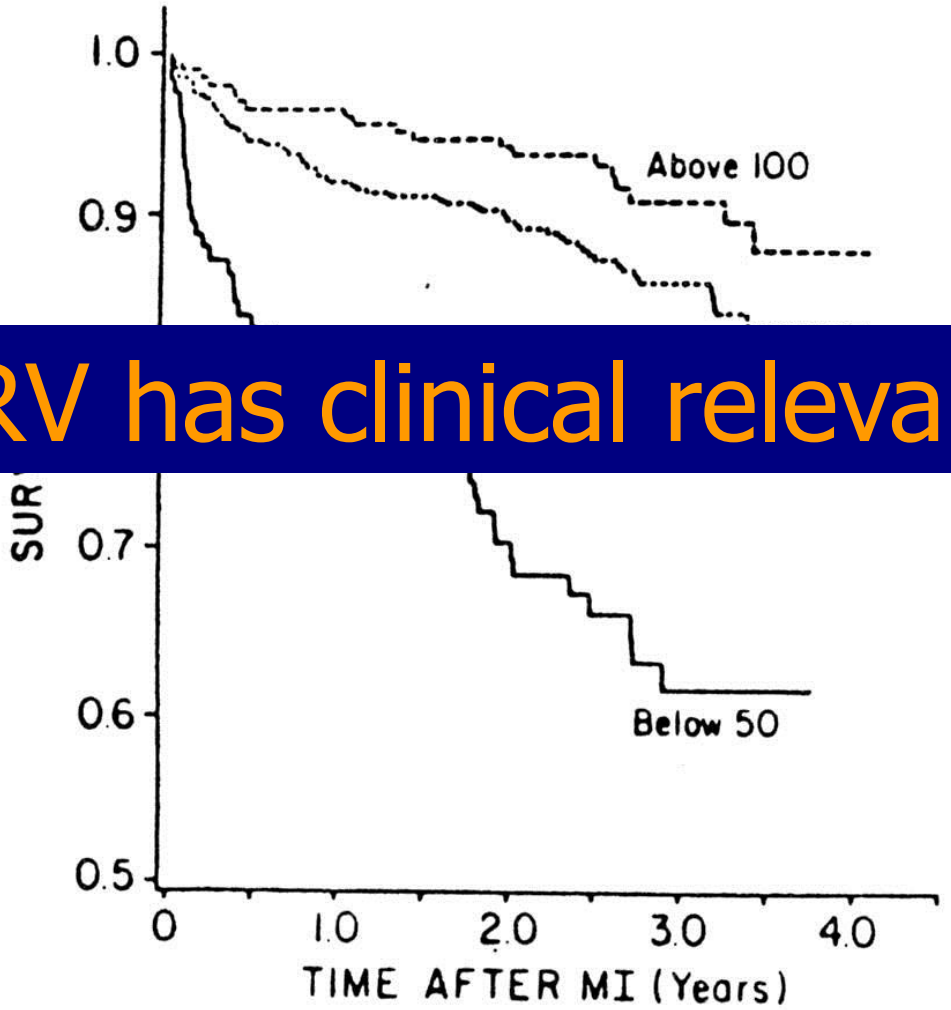
- Plasma catecholamines
- Catecholamine spillover (cardiac catheterism)
- Muscle Sympathetic Nerve Recordings (MSNA) by microneurographic technique
- **Heart Rate Variability (HRV)**

HRV Metodology

- Time domain
- Linear methods (frequency domain)
  - autoregressive algorithms
  - FFT
  - time-varying algorithms
- Non-linear methods

HRV AND SURVIVAL AFTER MI

(Kleiger R et al, *Am J Cardiol* 1987, 107: 565-570)



HRV has clinical relevance!

HRV- Ageing

(Paolisso et al, *Clinical Science* 1999)

	Aged subjects (⩾ 75 years) (n = 25)	Healthy centenarians (⩾ 100 years) (n = 30)	p
R–R interval (ms)	825±15	951±10	0.001
Total power (ms^2)	2050±935	1257±621	0.001
LF (ms^2)	634±118	510±96	0.020
LF (n.u.)	51±15	29±20	0.001
HF (ms^2)	698±130	742±108	0.050
HF (n.u.)	49±20	71±18	0.030
LF/HF	0.95±0.03	0.41±0.08	0.010
CHF (Hz)	0.21±0.03	0.25±0.02	0.050

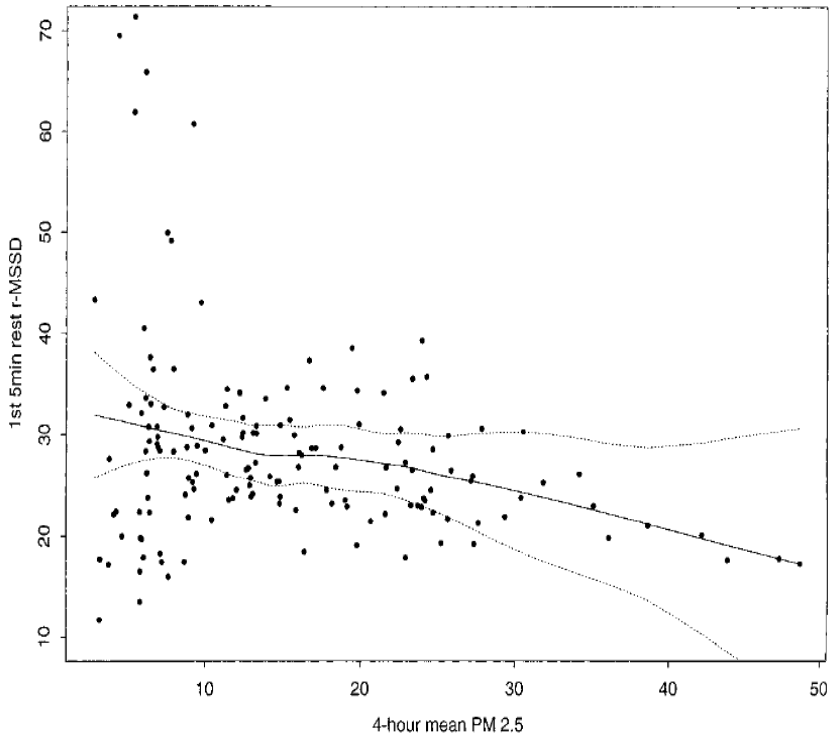
Effects of air pollution levels on HRV

- Several studies reported that air pollution is associated with a decreased HRV (mostly time domain measures):
  - Pope et al, Am Heart J, 1999
  - Gold et al, Circulation 2000
  - Devlin et al, Eur Resp J, 2003,
  - Pope et al, Environ Health Perspect 2004
  - ……..

Ambient pollution and HRV

(Gold et al, Circulation 2000)

21 Boston residents
12 observations per subject
June-September 1997



Fgure 2. Covariate adjusted smoothed plot and 95% confidence limits of r-MSSD vs $PM_{2.5}$ averaged over the 4 hours before and including the hour during Holter monitoring. r-MSSD was adjusted for indicator variables for each of the participants and variables for whether the participant took a β-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, or sympathomimetic medication on the testing day. ● represent individual covariate adjusted observations for each individual for each day.

Effects of air pollution in young adults.

(Chuang et al, AJRCCM 2007)

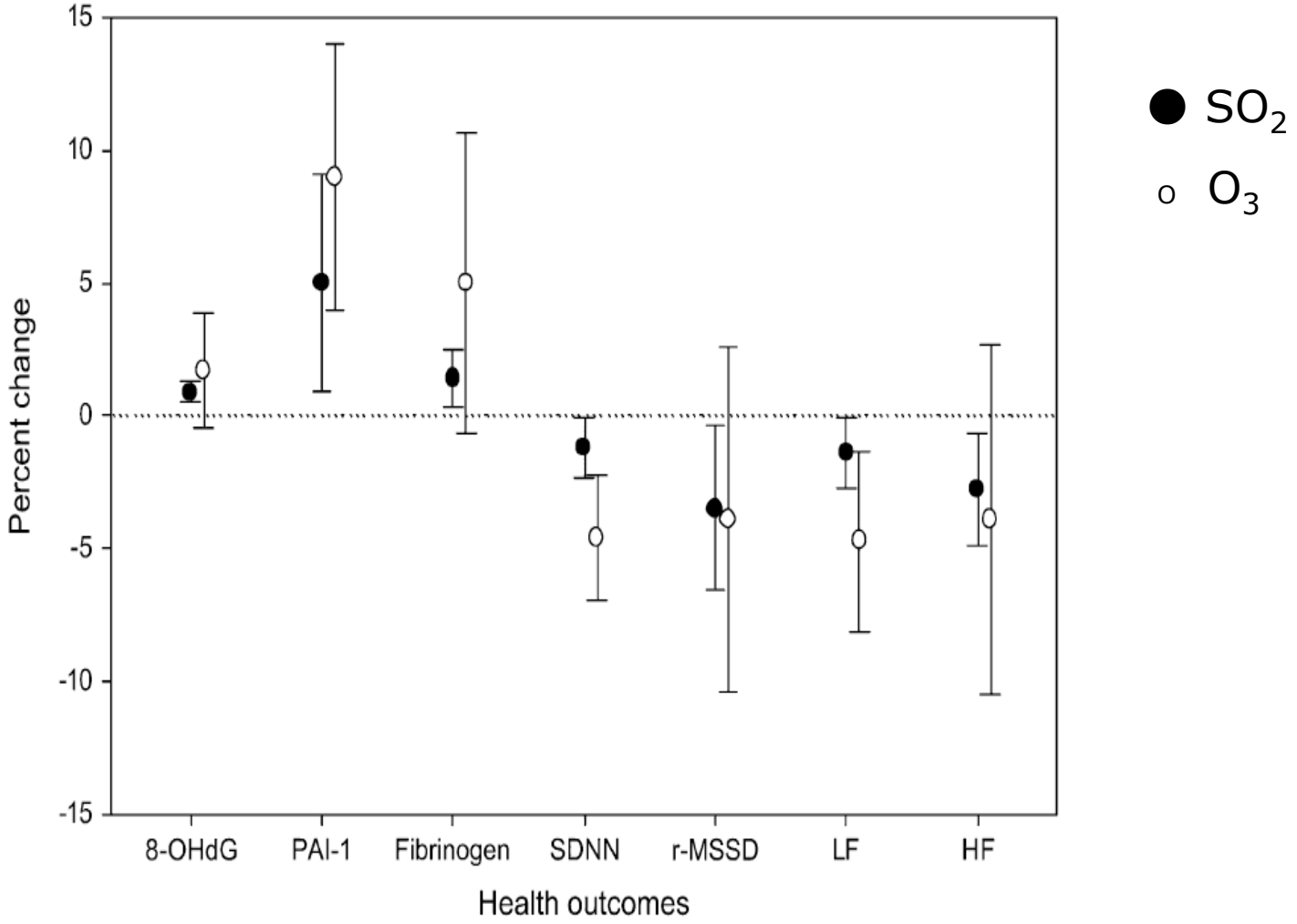
76 young, healthy university students in Taipei.

Three measurements were made of high-sensitivity C-reactive protein, 8-hydroxy-2-deoxyguanosine,plasminogen activator fibrinogen inhibitor-1 (PAI-1), tissue-type plasminogen activator (tPA) in plasma, and heart rate variability (HRV).

Gaseous air pollutants were measured at one air-monitoring station inside their campus, and particulate air pollutants were measured at one particulate matter supersite monitoring station 1 km from their campus.

Effects of air pollution in young adults.

(Chuang et al, AJRCCM 2007)



HRV – Limitations of the study on pollution effects

- Imprecision in the measurement of pollution exposure
- Effect of potential confounding environmental and social factors
- No mechanistic data (causal relationship)
- No clear data on the effects of single components of air pollution (sinergistic effect?)

Reducing the confounding factors…

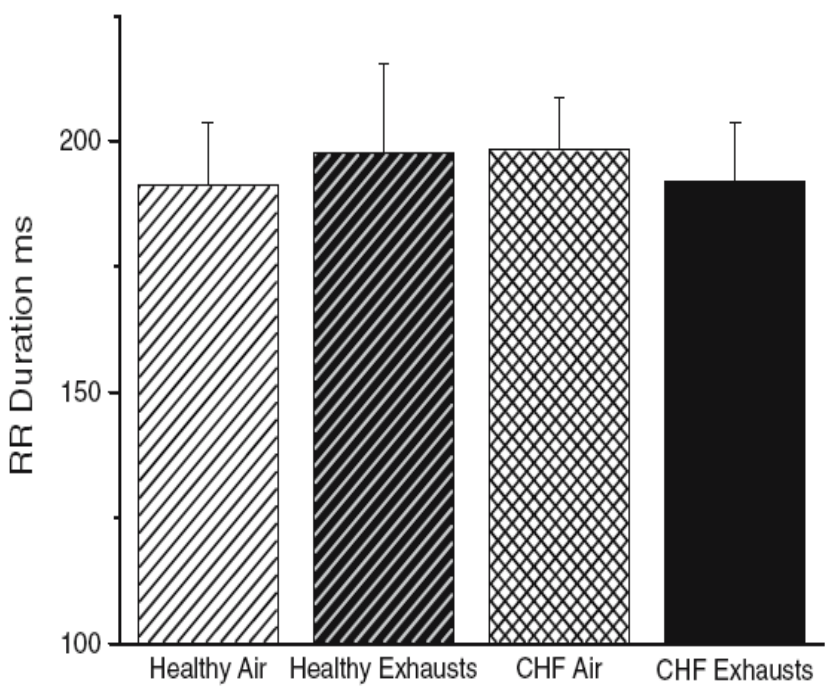
(Arch Toxicol, 2007)

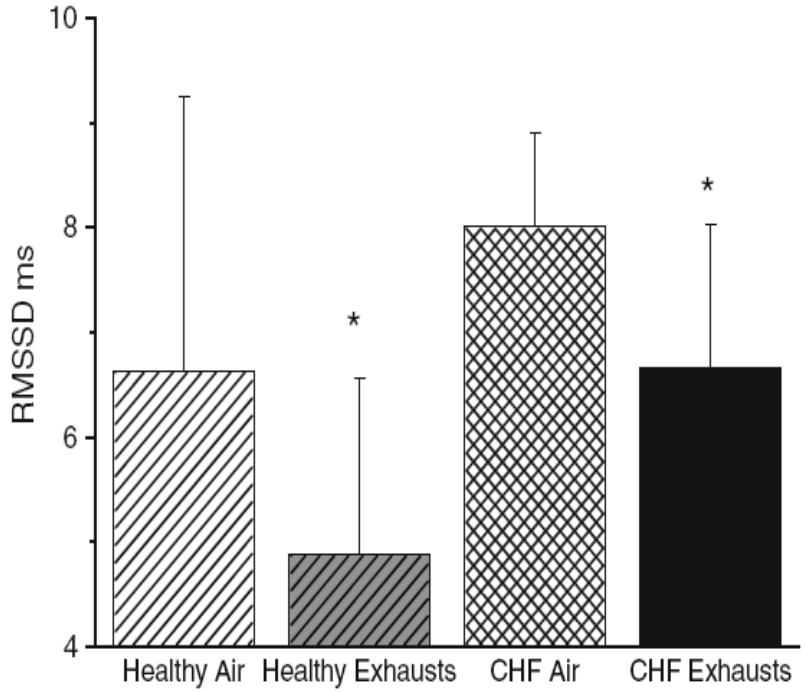
Inhalation of diluted diesel engine emission impacts heart rate variability and arrhythmia occurrence in a rat model of chronic ischemic heart failure

Frédéric Anselme · Stéphane Loriot · Jean-Paul Henry · Frédéric Dionnet · Jean-Gérard Napoleoni · Christian Thuillez · Jean-Paul Morin

Reducing the confounding factors..

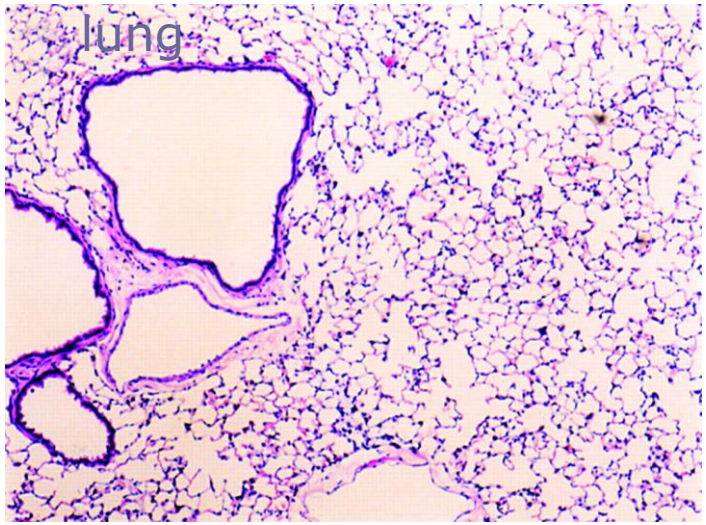
(Anselme et al, Arch Toxicol, 2007)



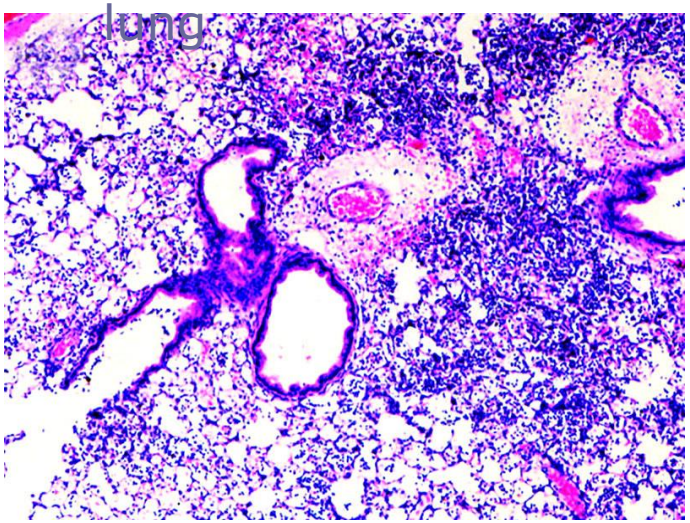


Mouse lung exposed to Diesel Exhaust

Normal mouse lung



Exposed mouse lung



Diesel Exhaust Particles (DEP) augment inflammation by increasing receptors for bacterial lipopolysaccharide. The effect is to make the lungs highly sensitive to the presence of normal levels of bacteria. This results in greatly heightened production of pro-inflammatory mediators from the cells.

…and in humans?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 13, 2007 VOL. 357 NO. 11

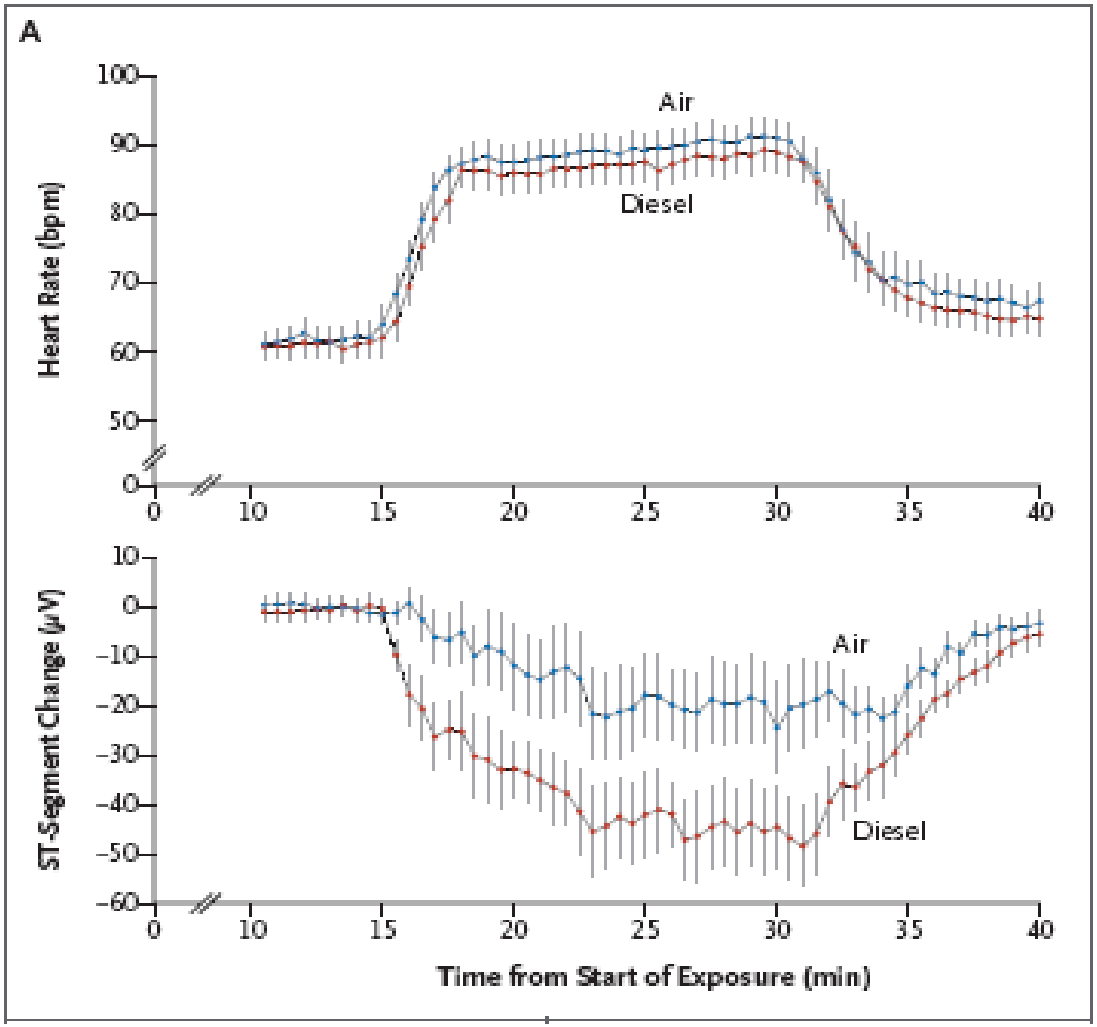
Ischemic and Thrombotic Effects of Dilute Diesel-Exhaust Inhalation in Men with Coronary Heart Disease

Nicholas L. Mills, M.D., Håkan Törnqvist, M.D., Manuel C. Gonzalez, M.D., Elen Vink, B.Sc., Simon D. Robinson, M.D., Stefan Söderberg, M.D., Ph.D., Nicholas A. Boon, M.D., Ken Donaldson, Ph.D., Thomas Sandström, M.D., Ph.D., Anders Blomberg, M.D., Ph.D., and David E. Newby, M.D., Ph.D.

Exposure chamber

Effects of diesel exhaust and filtered air

(Mills et al, *NEJM* 2007)



Effects of diesel exhaust and filtered air

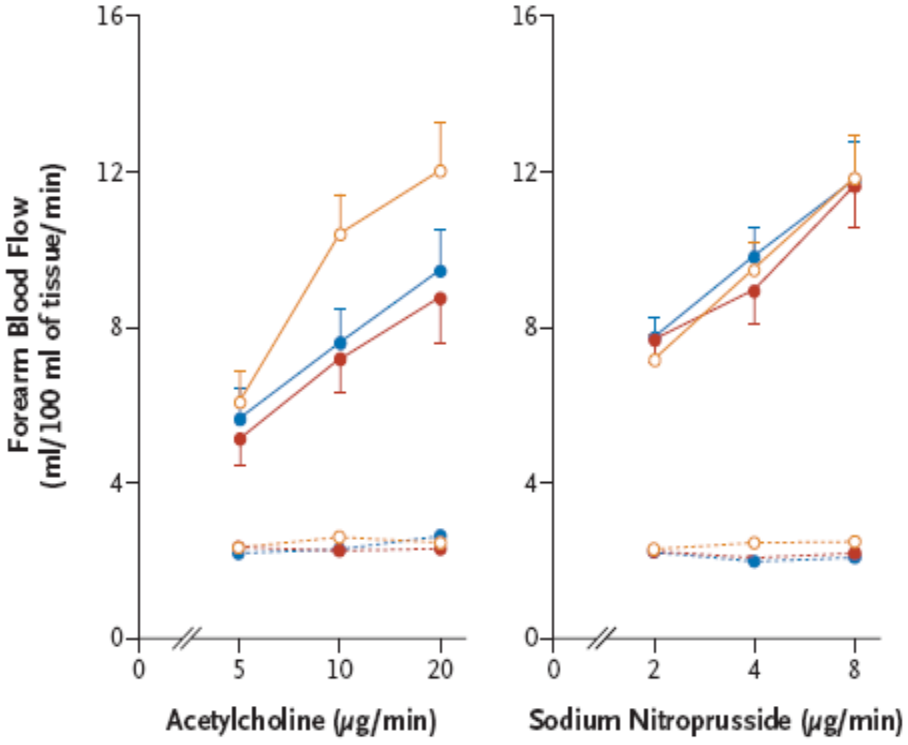
(Mills et al, *NEJM* 2007)

Characteristic	Filtered Air	Diesel Exhaust	P Value†
Exercise phase 1			
Heart rate — bpm			
Baseline	63±2	61±2	0.24
Maximum	87±3	86±3	0.67
Maximum ST-segment change (μV)			
Lead II	−28±13	−56±10	0.03
Lead V_2	−28±10	−41±12	0.18
Lead V_5	−14±8	−33±9	0.04
Change in ischemic burden (mVsec)			
Lead II	−11±5	−23±4	0.004
Lead V_2	−13±5	−21±6	0.04
Lead V_5	−4±3	−12±4	0.01
Exercise phase 2			
Heart rate (bpm)			
Baseline	67±2	65±2	0.35
Maximum	91±3	87±3	0.12
Maximum ST-segment change (μV)			
Lead II	−17±15	−49±12	0.006
Lead V_2	−18±12	−41±13	0.04
Lead V_5	−7±9	−28±10	0.02
Change in ischemic burden (mVsec)			
Lead II	−8±6	−22±4	0.0007
Lead V_2	−11±5	−20±6	0.02
Lead V_5	−2±3	−12±5	0.006

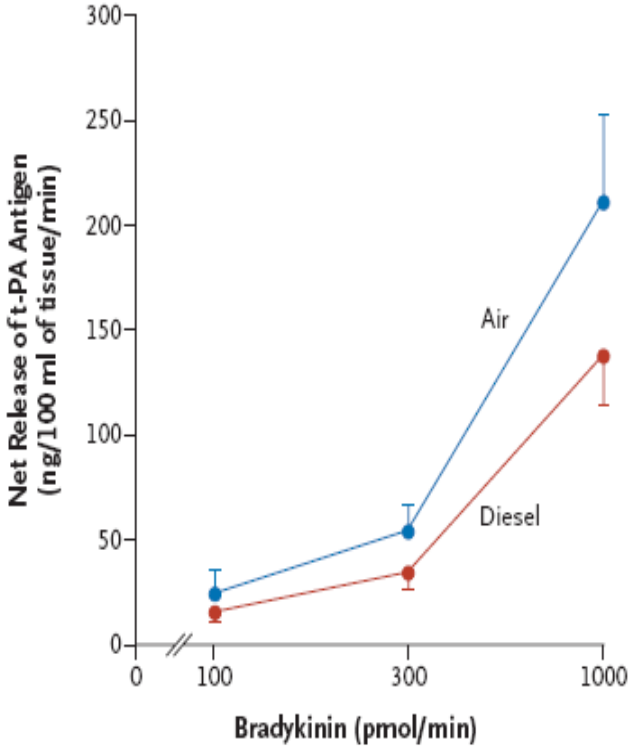
…after 6-8 hours from exposure..

(Mills et al, *NEJM* 2007)

No change in endothelial dysfunction



Decrease in t-PA release



Still unsolved questions

- Acute vs chronic effect
- Fine particulate matter vs gaseous pollutants
- Controlled expositions
- Simultaneous assessment of composite variables

Acute particulate matter exposure, cardiovascular autonomic modulation and epigenetics

Randomized, placebo-controlled, cross-over trial in healthy volunteers (filtered air vs. filtered air+particulate matters)

AIMS:

1) to assess the impact of PM on sympathetic and parasympathetic control of heart function, independently, and using controlled conditions, in absence of other potential confounding factors

2) to assess changes in epigenetic (DNA metylation) and possible correlation with autonomic changes

Acute particulate matter exposure, cardiovascular autonomic modulation and epigenetics

METHODS:

- **Subjects:** 12 healthy volunteer subjects,
- **Protocol:** two random sessions

  1) inhalation of filtered air mixture or

  2) inhalation of filtered air containing particulate mixture with the following titer: PM 10, PM 2.5, PM 1.0 and PM 0.5 μm (under an oxygen tent)

- **Variables:** ECG and respiration via a telemetric system, blood drawing for DNA methylation and Mitochondrial DNA copy number

Experimental Protocol

AIR MIXTURES

- Provided by SIAD, an international Italy-based group, leader in industrial and medical gases production.
  - 1) Mixture of pure air,
  - 2) Mixture of pure air with the addition of particulate. Fine particulate was characterized by its dimensions in these classes in μm: PM 0,3-0,5; 0,5-1; 1-3; 3-5; 5-10; >10
- The total concentrations of particulate were similar to those measured at the peak level in Milan air during a polluted winter day, as indicated by ARPA (Regional Agency for Environment Protection) analyses.

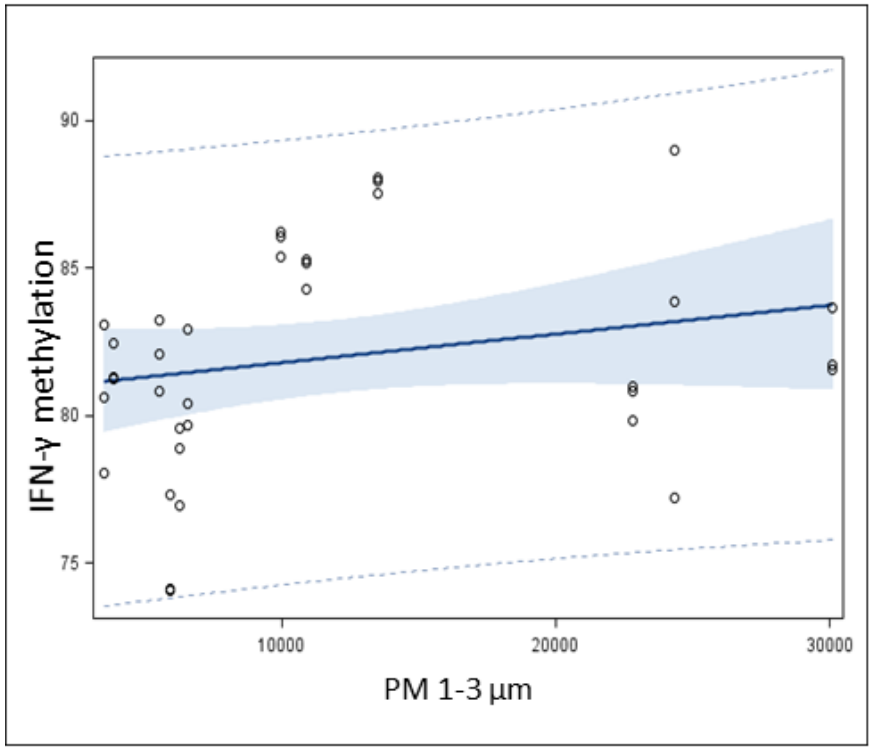
DATA ANALYSIS

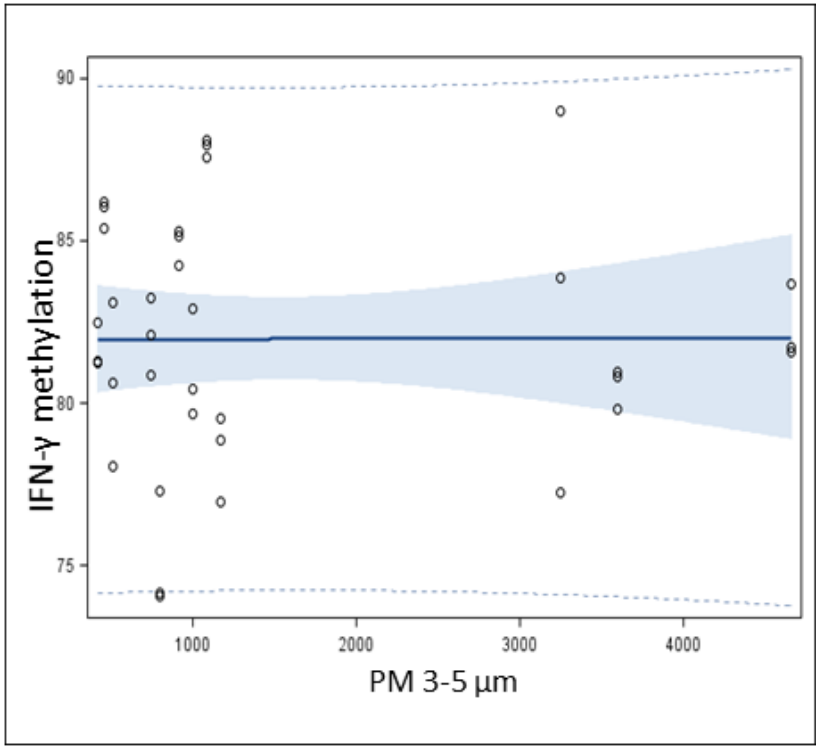
- Spectral and symbolic analysis of HRV has been applied for the assessment of cardiac autonomic control.

- DNA methylation analysis was carried out using bisulfite-PCR-pyrosequencing. Sites within the promoter regions of the following genes were investigated: LINE-1, ALU, SATalpha, IL6, ICAM, TLR2, TLR4, ET1, IFNγ, iNOS, eNOS. Every sample was tested in triplicate to confirm reproducibility and to increase the accuracy of the findings.

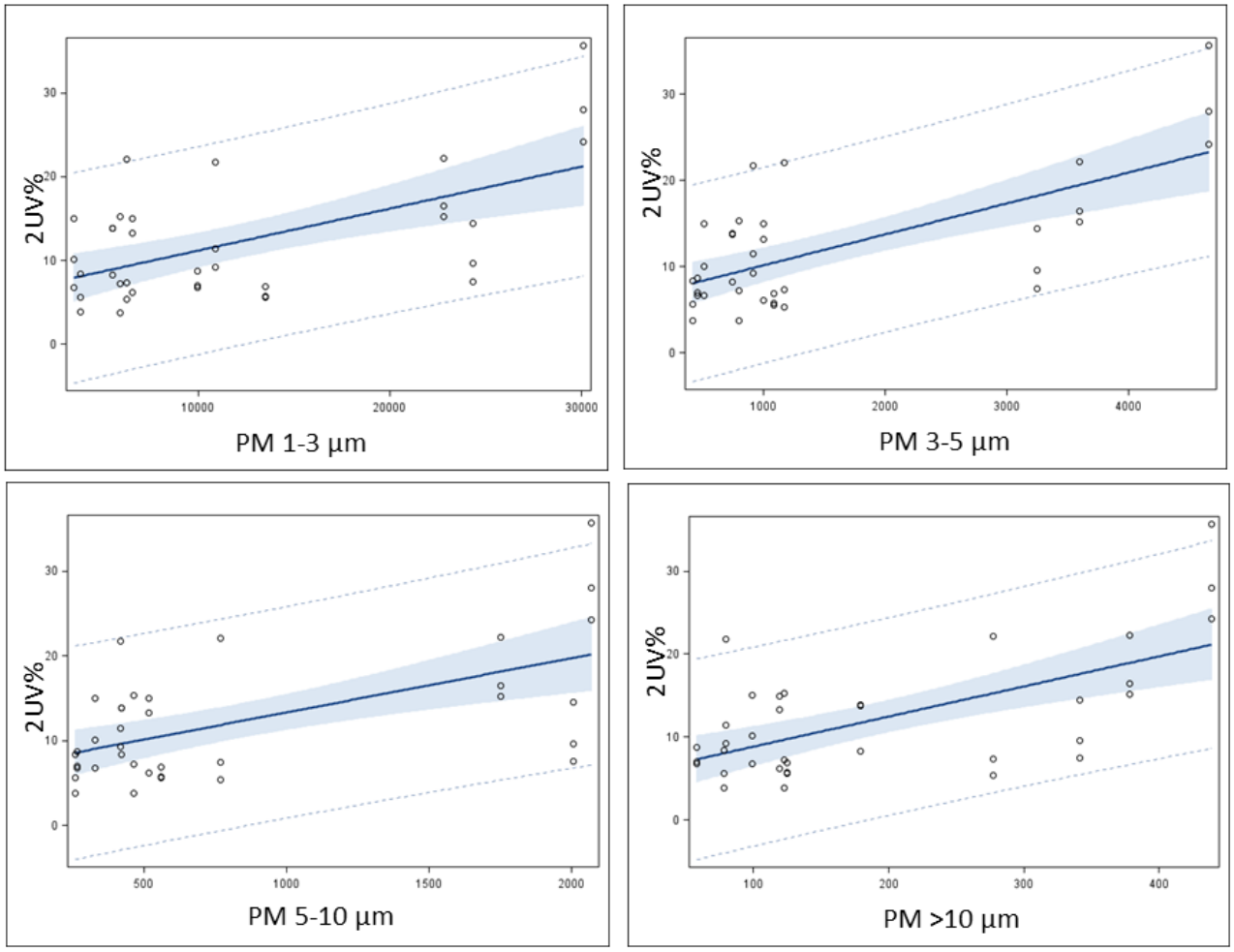
- Relative mtDNAcn was measured by quantitative real-time polymerase chain reaction (PCR).

RESULTS


IFN-γ methylation
90
85
80
75
10000
20000
30000
PM 1-3 µm


IFN-γ methylation
90
85
80
75
1000
2000
3000
4000
PM 3-5 µm

RESULTS

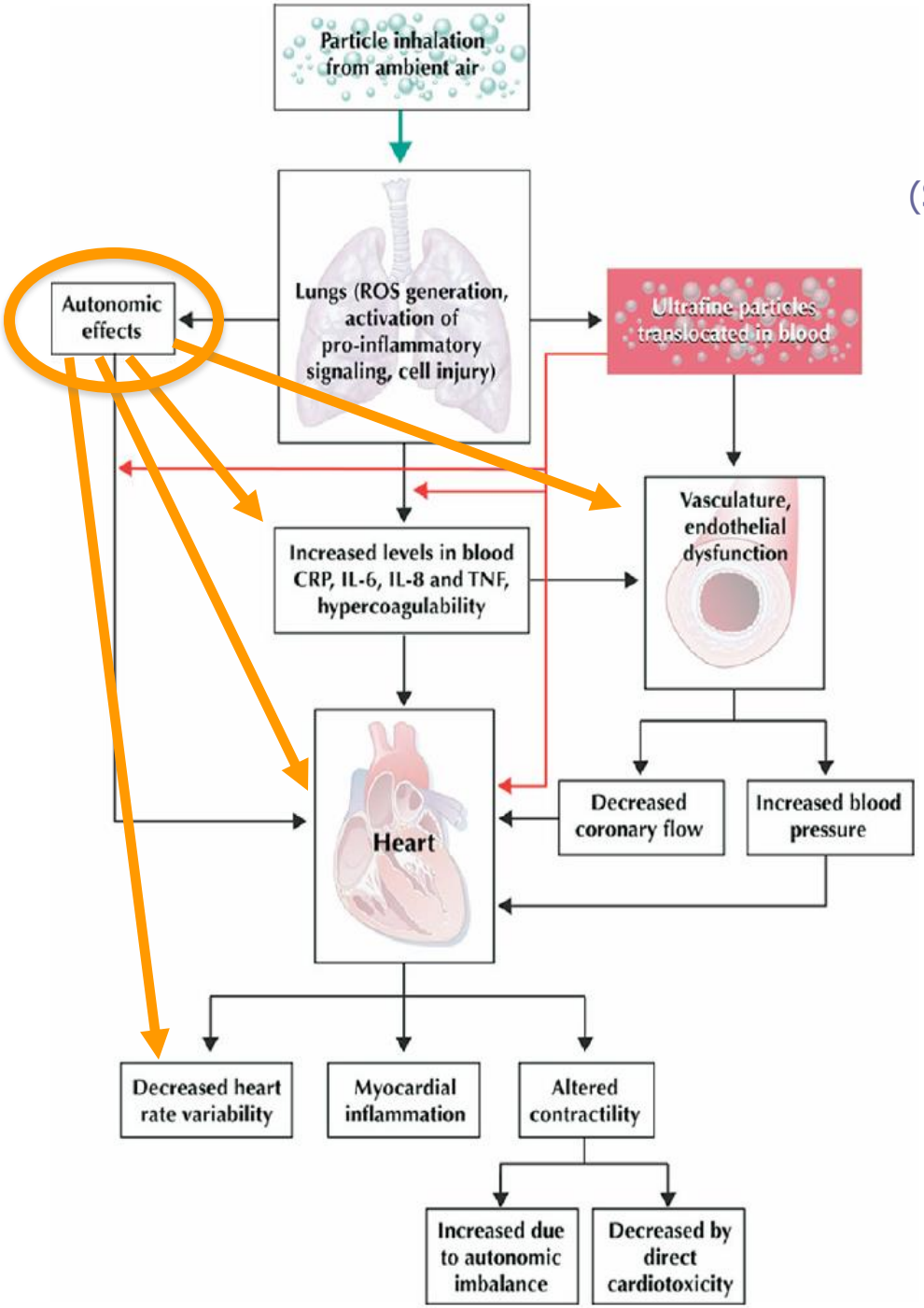

2UV%
30
20
10
0
10000
20000
30000
PM 1-3 µm
2UV%
30
20
10
0
1000
2000
3000
4000
PM 3-5 µm
2UV%
30
20
10
0
500
1000
1500
2000
PM 5-10 µm
2UV%
30
20
10
0
100
200
300
400
PM >10 µm

CONCLUSIONS

- Although with a limitation of a small sample size, our study, performed in healthy individuals, provides the following new evidence:

- **1) PM impairs parasympathetic control of myocardial function**

- **2) PM exposure induces an increased methylation of IFN- γ.**



(Simkhovic et al, JACC 2008)

Get some fresh air!