Inhalation Toxicities of Ambient Particles

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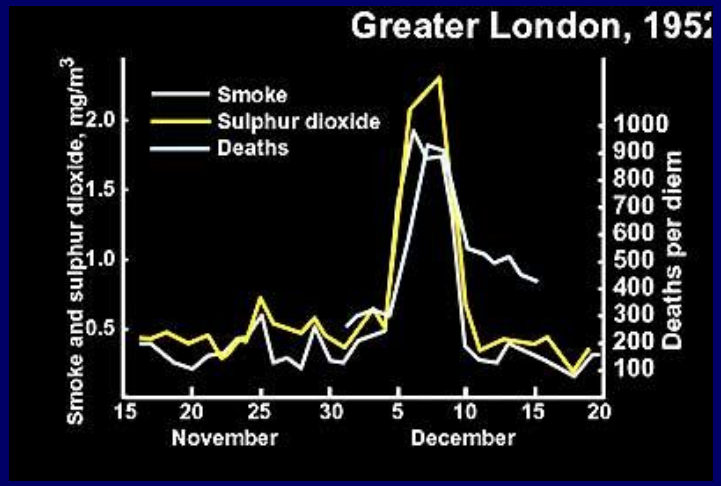
ISEM, 2015

Outlines

- Acute toxicity of ambient particles
  - Changes of heart rate , blood pressure and heart rate variability
- Sub-chronic toxicity of ambient particles
  - Glucose homeostasis and cardiovascualr damages in hyperglycemic and healthy rats

The London Fog of 1952



Ambient PM exposure and health effects

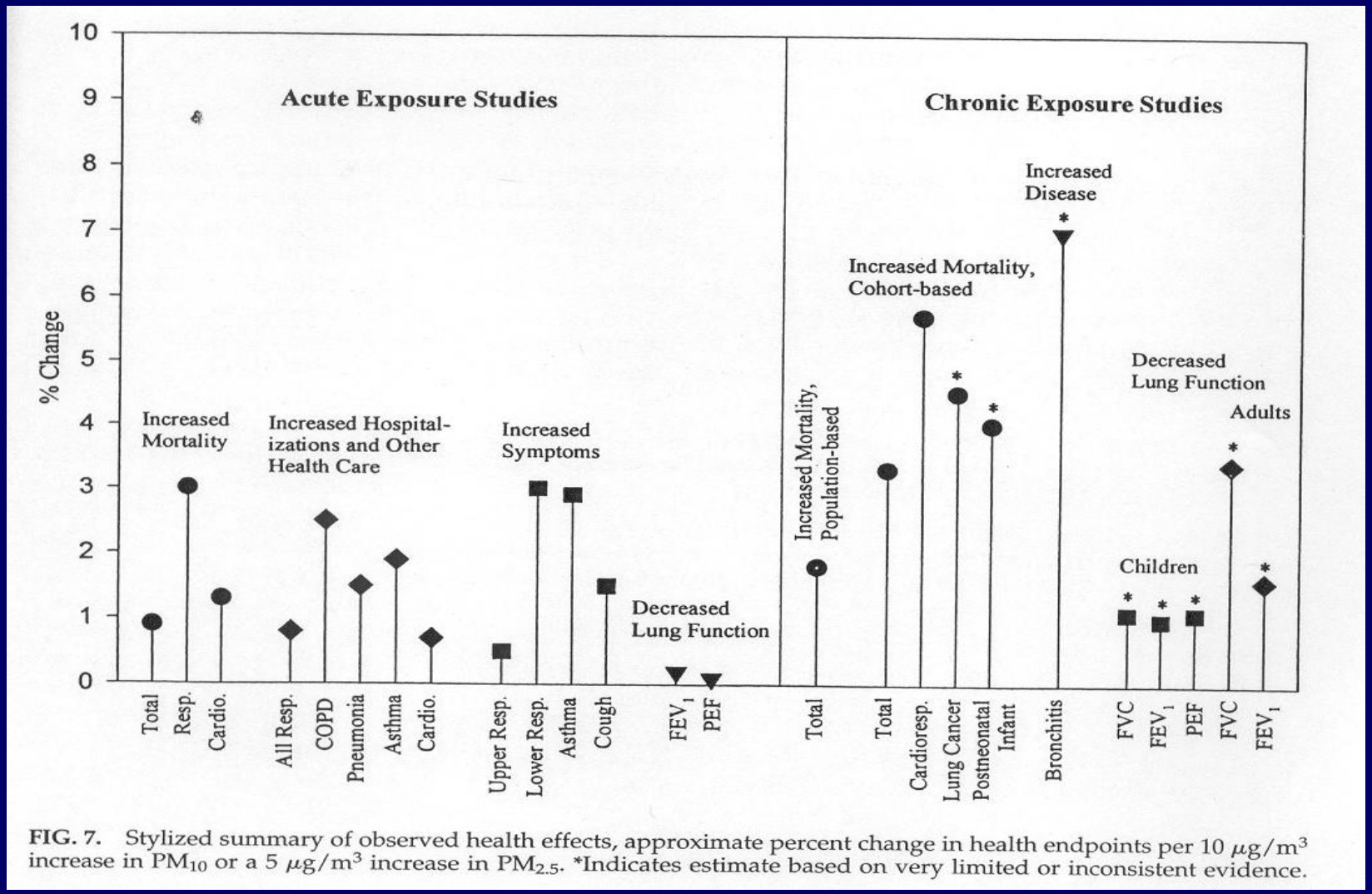
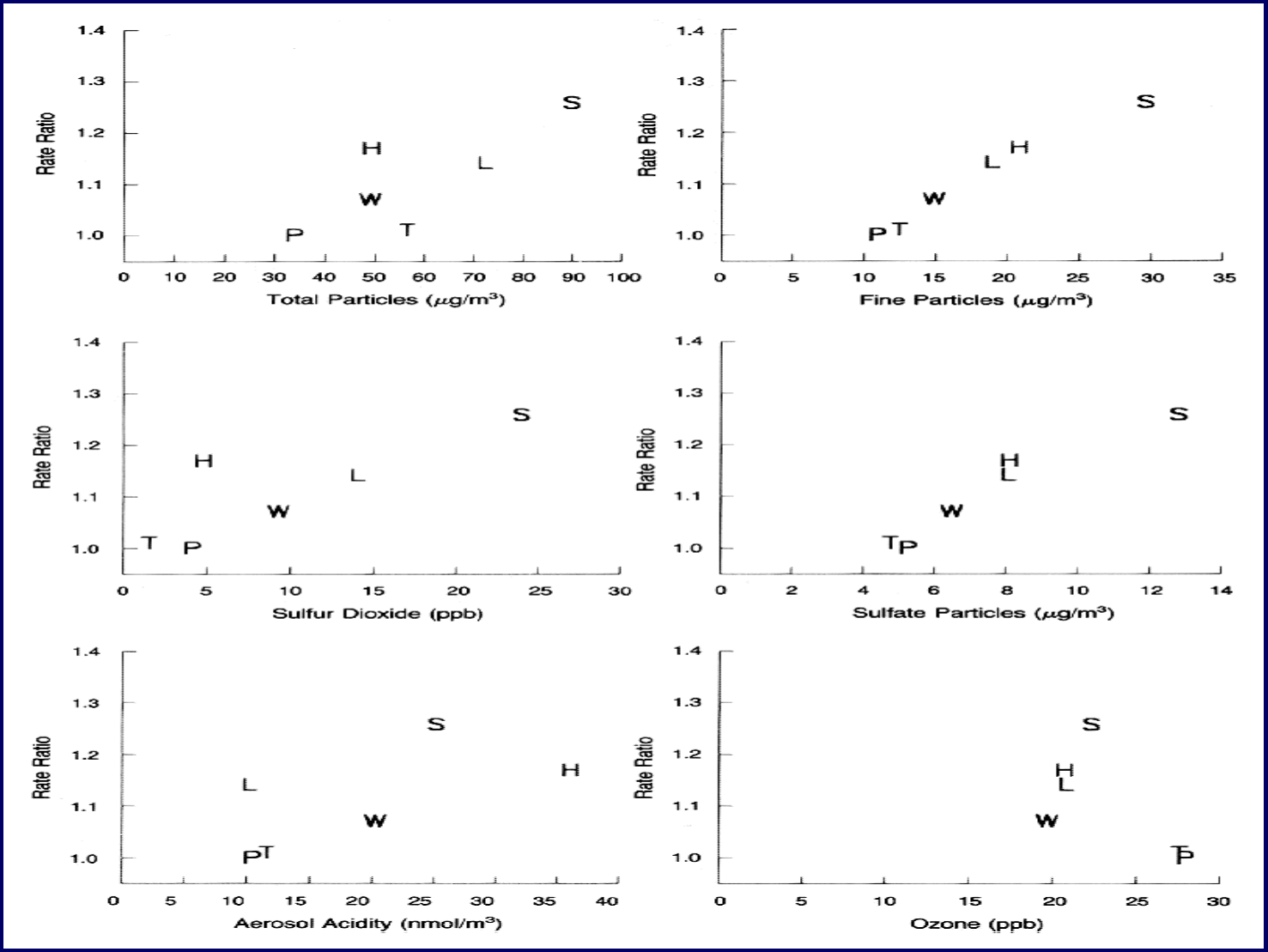


FIG. 7. Stylized summary of observed health effects, approximate percent change in health endpoints per 10 $\mu g/m^3$ increase in PM_{10} or a 5 $\mu g/m^3$ increase in $PM_{2.5}$. *Indicates estimate based on very limited or inconsistent evidence.

Pope et al. in Air Pollution and Health, 1999

Harvard Six Cities study



Dockery et al., NEJM, 1993

Particulate Matter: What is It?

A complex mixture of extremely small particles and liquid droplets

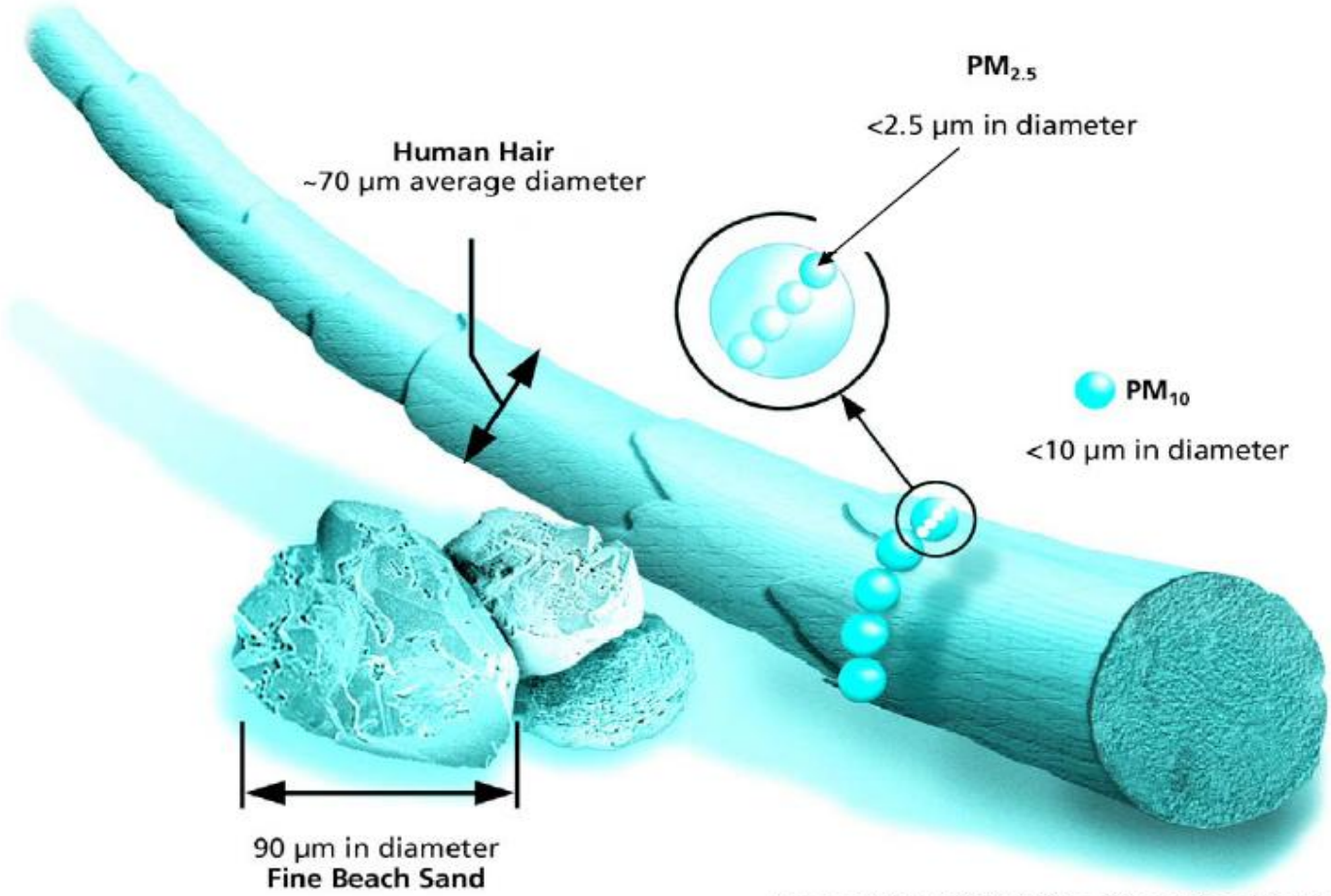


Image courtesy of EPA, Office of Research and Development

PM Components: fine and coarse

Fine Particles

Combustion, gases to particles

Sulfates/acids
Nitrate
Ammonium
Organics
Carbon
Metals
Water

Sources:

Coal, oil, gasoline, diesel, wood combustion
Transformation of SOx, NOx, organic gases including biogenics
High temperature industrial processes (smelters, steel mills)
Forest fires

Exposure/Lifetime:

Lifetime days to weeks, regional distribution over urban scale to 1000s of km

Inhalable Coarse Particles

Crushing, grinding, dust

Resuspended dusts (soil, street dust)
Coal/oil fly ash
Aluminum, silica, iron-oxides
Tire and brake wear
Inhalable Biological Materials (e.g., from soils, plant fragments)

Sources:

Resuspension of dust tracked onto roads
Suspension from disturbed soil (farms, mines, unpaved roads)
Construction/demolition
Industrial fugitives
Biological sources

Exposure/Lifetime:

Coarse fraction (2.5-10 µm) lifetime of hours to days, distribution up to 100s km

Biological plausibility and mechanisms

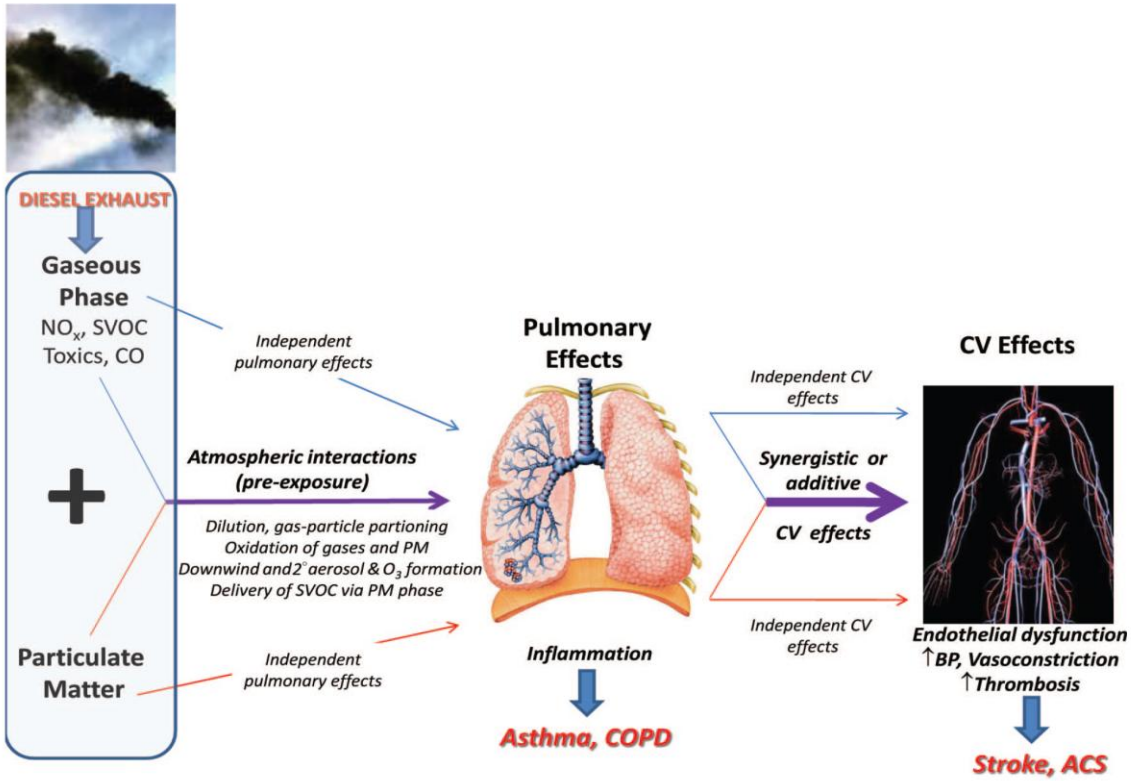


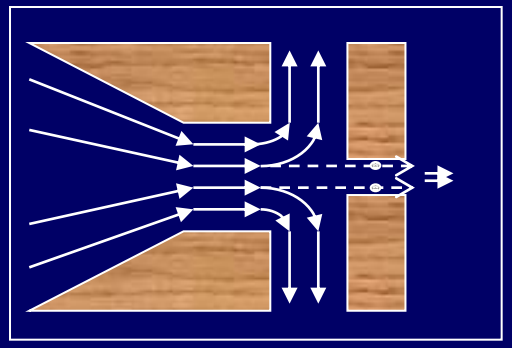
Figure. Overview of the complex interactions among air pollutants and effects of exposures on CV health in a multipollutant context. NO_x indicates nitrogen oxides; SVOC, semivolatile organic compounds; CO, carbon monoxide; O_3, ozone; PM, particulate matter; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; ↑ BP, increased blood pressure; 2°, secondary; and ACS, acute coronary syndrome.

Brook, Circulation, 2011

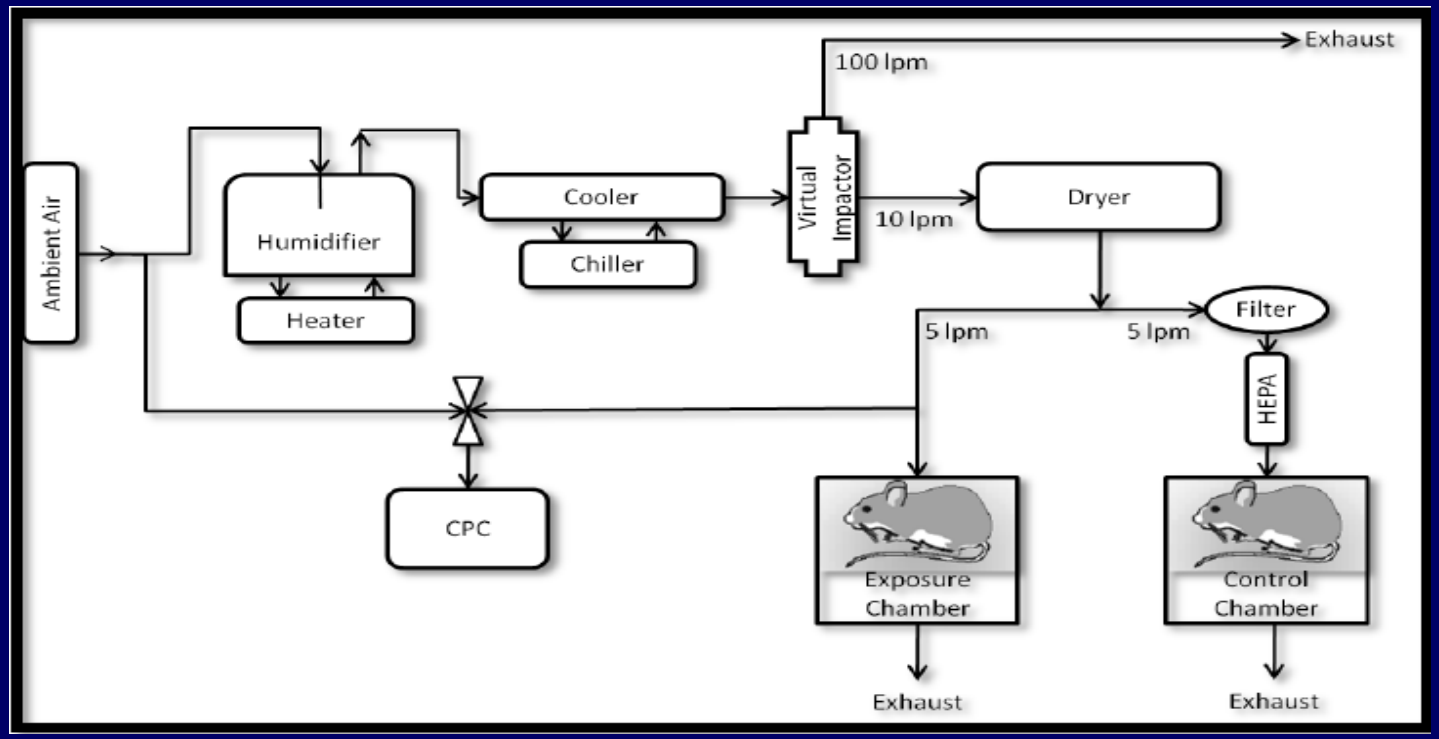
Acute toxicity of ambient particles

- Construction of an exposure system
- Telemetry system to monitor changes of heart rate , blood pressure and heart rate variability
- Self-controlled design and statistical analysis

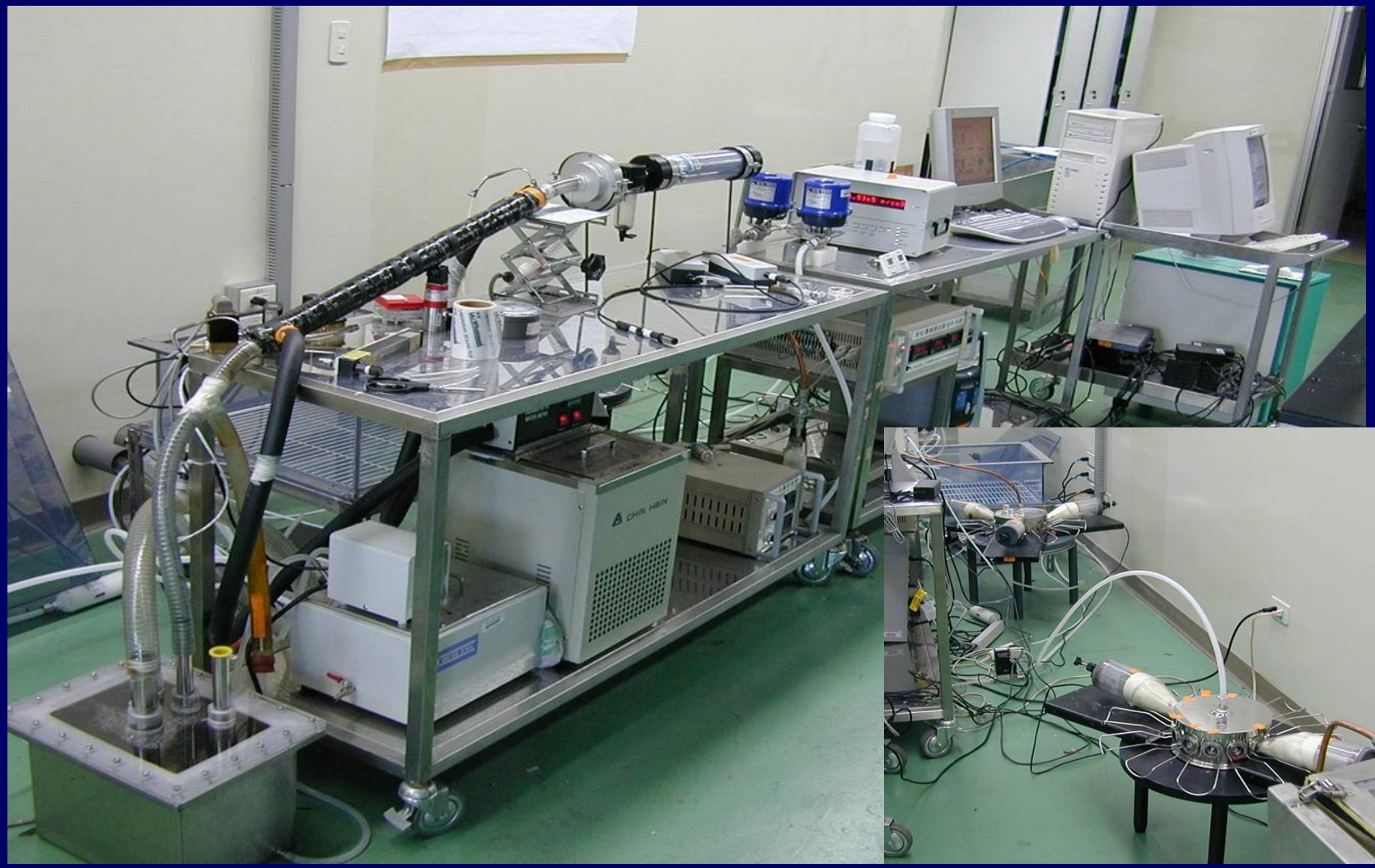
Ambient particle concentrator



- By Sioutas et al., USC
- 10 folds of concentration
- PM 0.01~2.5 μm.
- Saturator, cooler, virtual impactor, and dryer.

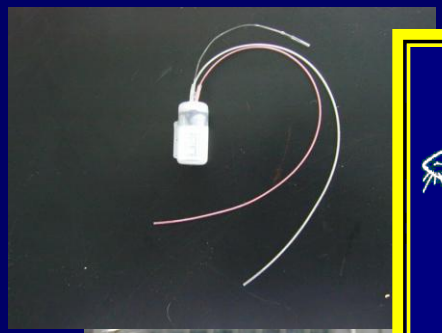


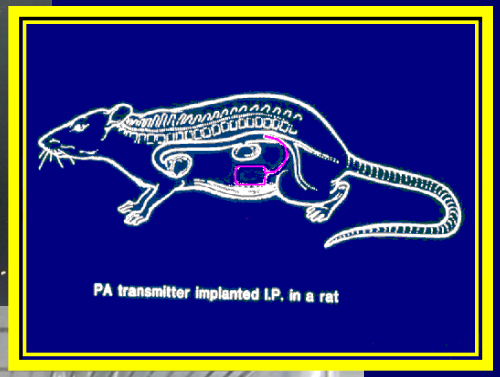
Ambient Particle Concentrator



Telemetry system

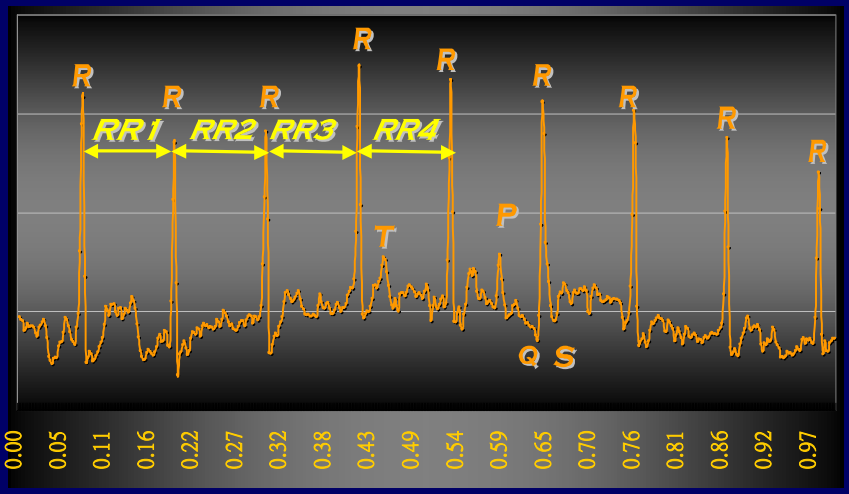
- Telemetry
  - Activity
  - ECG signals
  - Arterial Blood Pressure
  - Body Temp
- Data management and programming by Dr. CC Chang





Autonomic cardiac function parameters

- Heart rate
- Blood pressure
- Heart rate variability (HRV)
  - SDNN
    - The 5-minute standard deviation of the NN intervals
  - RMSSD
    - The 5-minute root mean square of successive differences of adjacent NN intervals

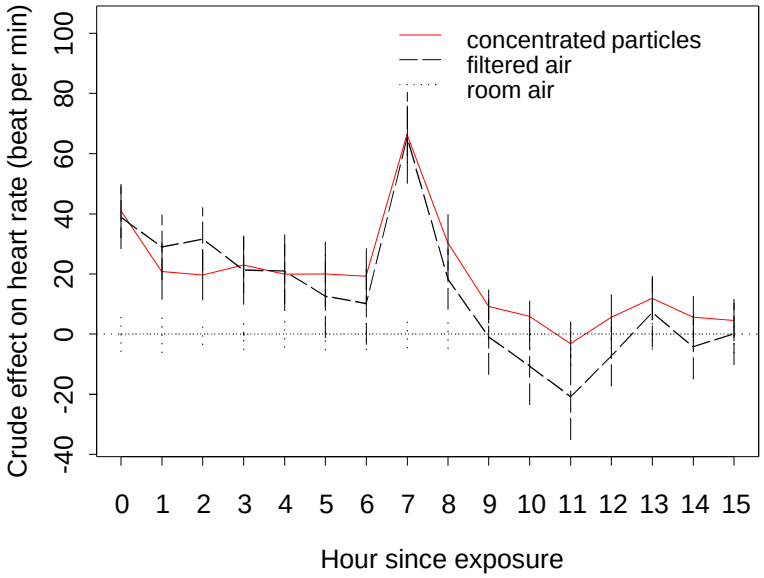


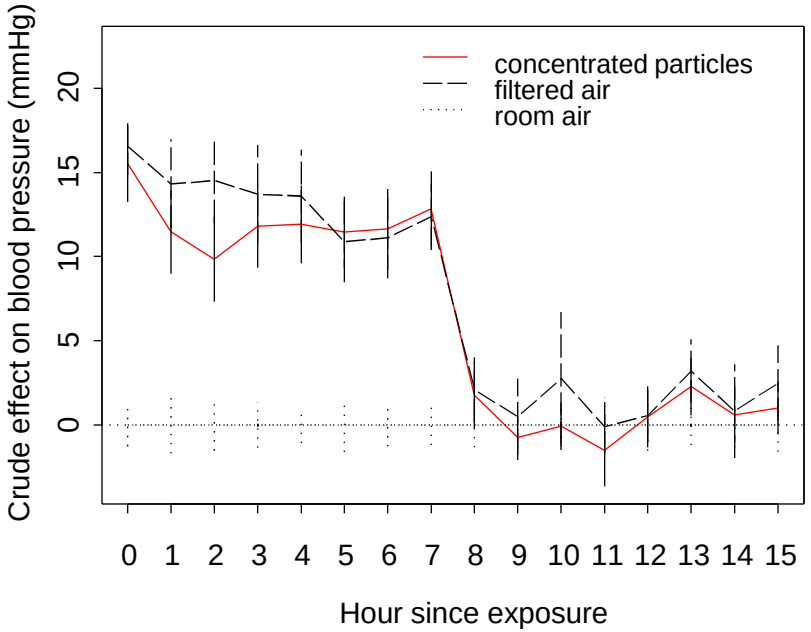
$$\mathrm{rMSSD} = \sqrt{\frac{\sum \left(rr_{i+1} - rr_i\right)^2}{\mathrm{nc}}}$$

Study design

- Crossover self-controlled design with repeated exposure to CAP, filtered air and room air.
  - Inter-individual difference and environmental changes
- Same time of the day
  - Circadian
- Mixed-effects model
- Small number of animals

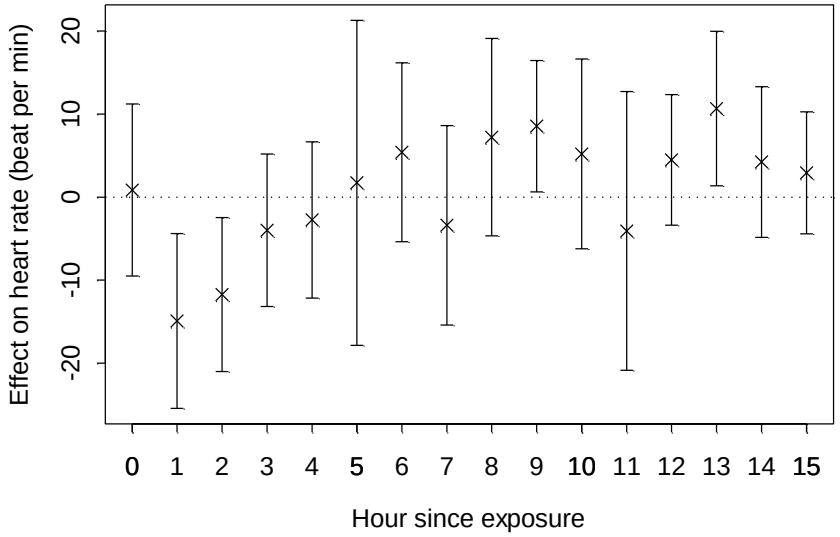
Heart rate and blood pressure in pulmonary hypertensive rats

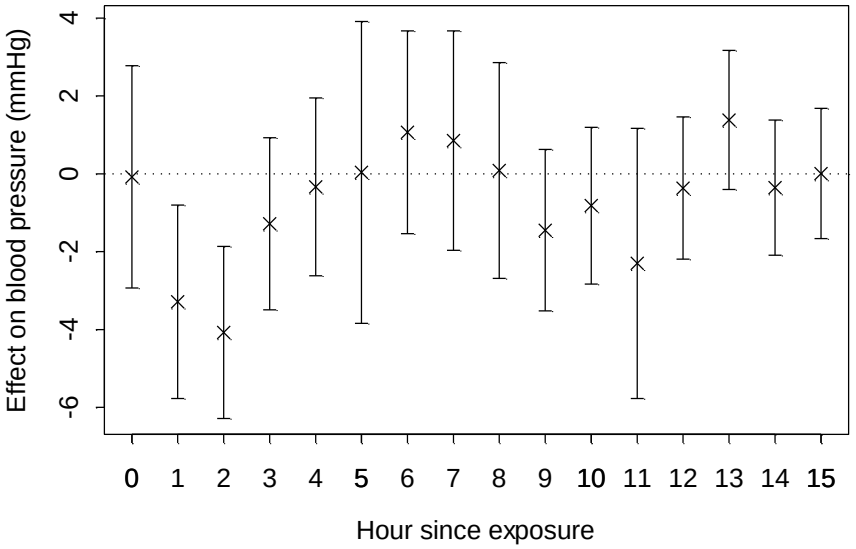




Cheng et al.,EHP, 2003

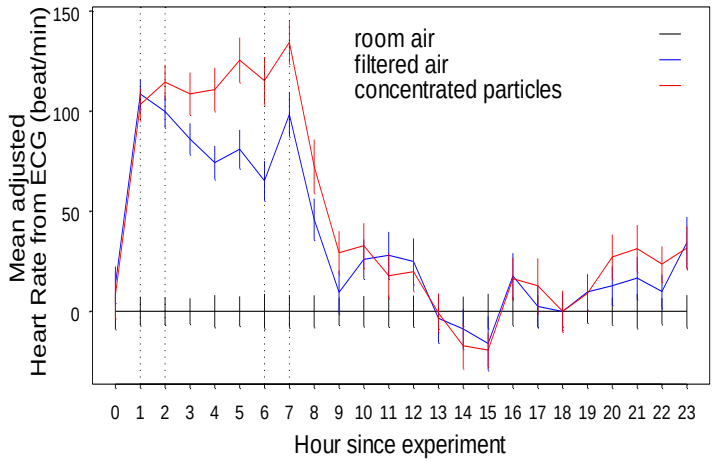
PM effects on heart rate and blood pressure

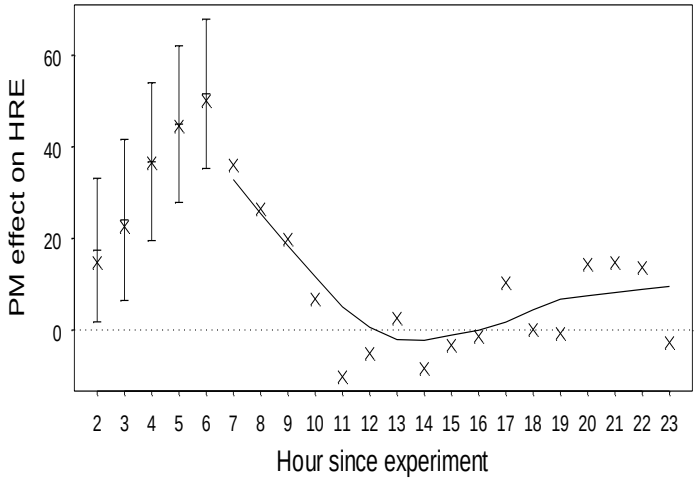


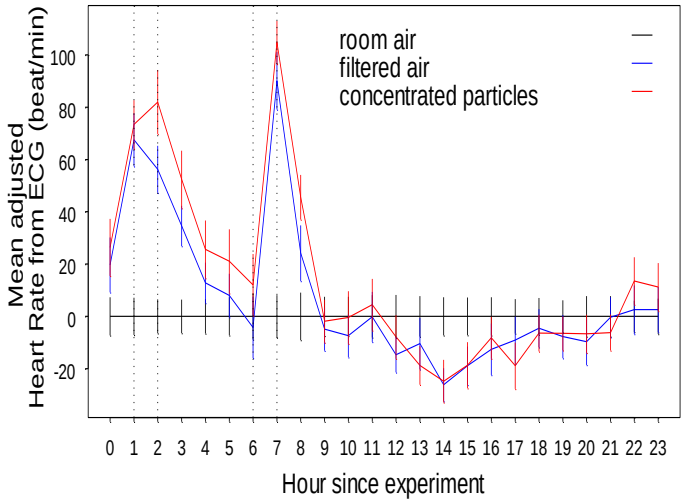


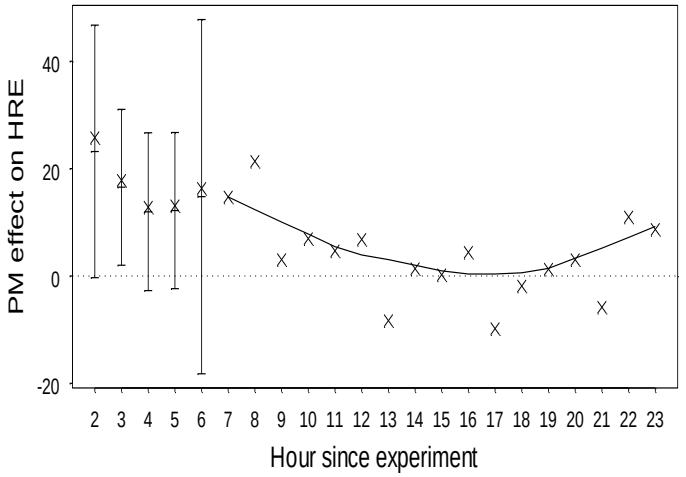
Cheng et al.,EHP, 2003

Heart rate changes during and after CAP exposures in spontaneously hypertensive rats (SHR)



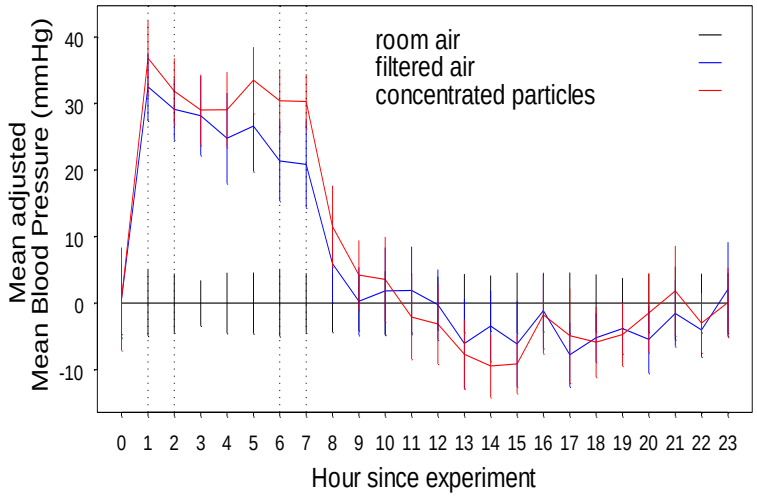


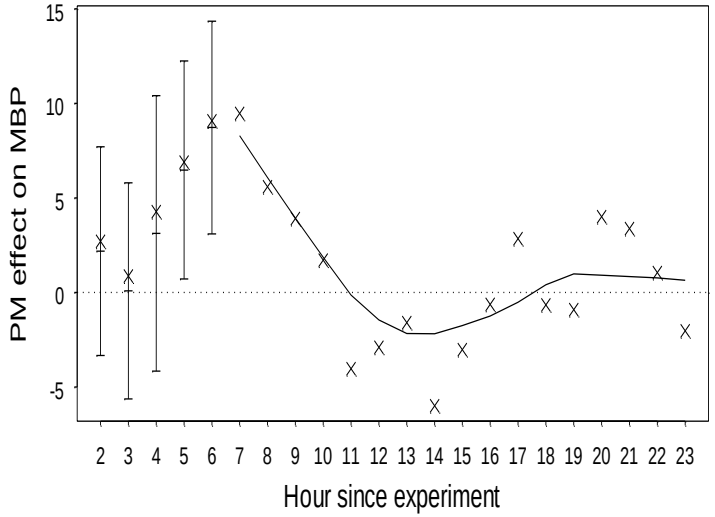


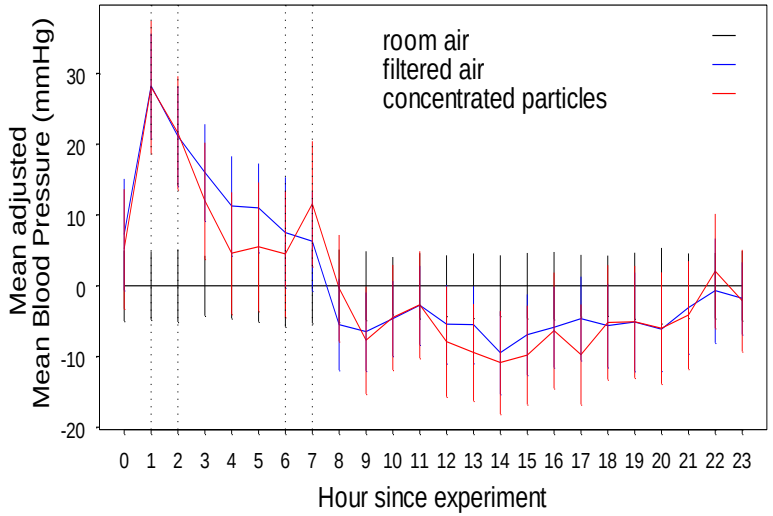


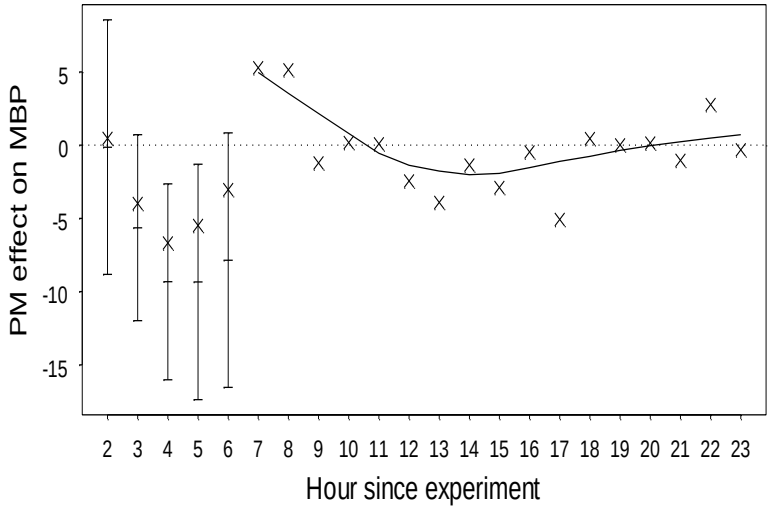
Chang, *Inhal Toxicol* 2004

Blood pressure changes during and after CAP exposures

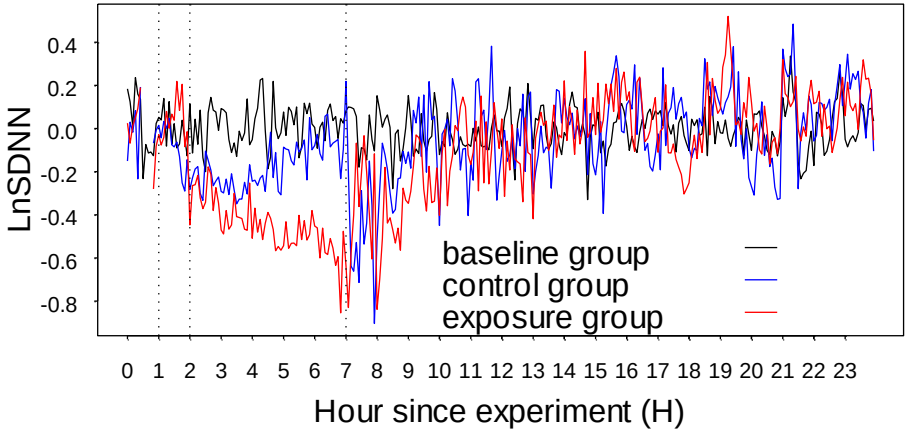


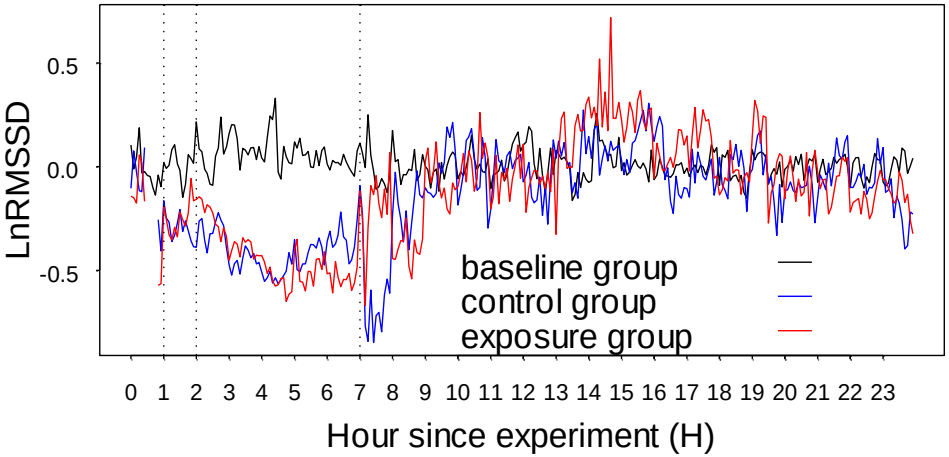


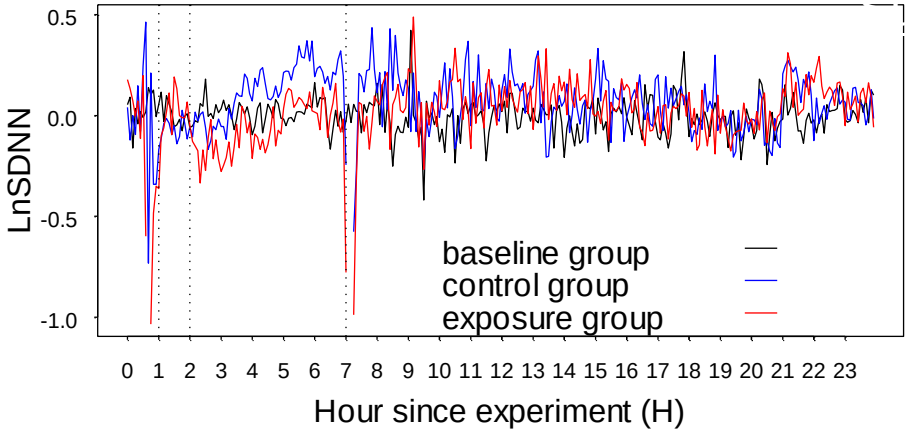


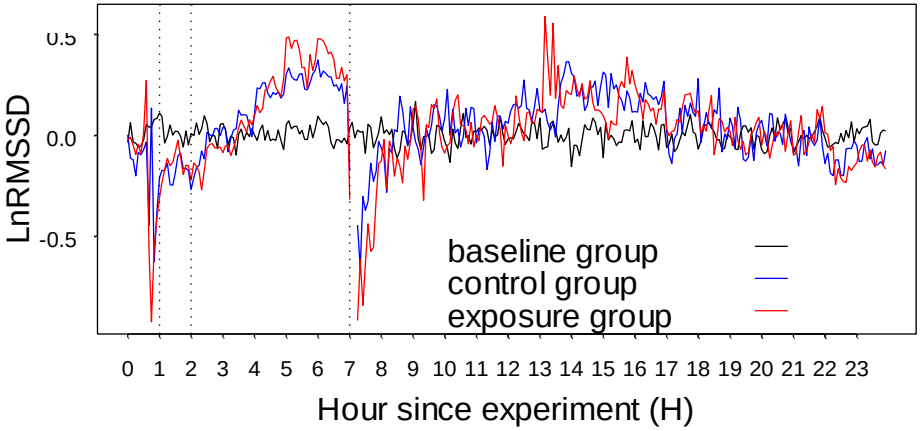


Log-transformed SDNN and RMSSD during and after CAP exposures

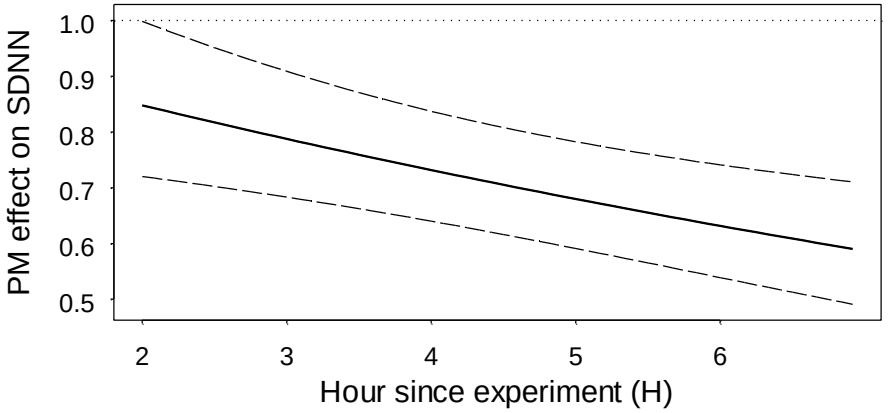


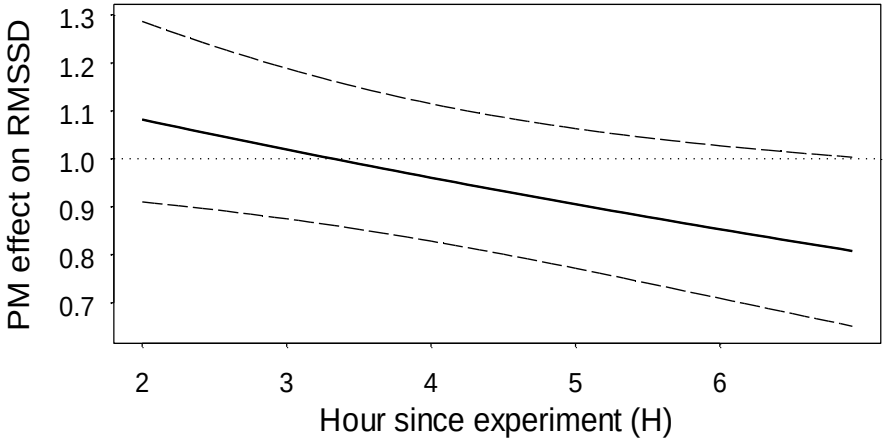


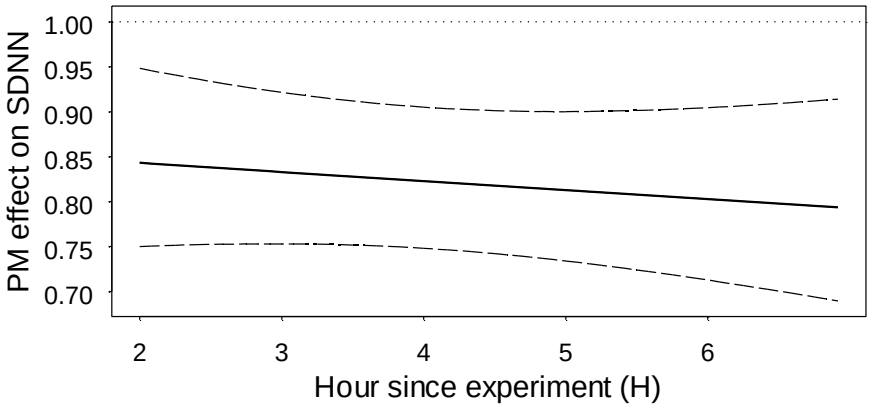




The estimated mean PM effects with 95% CI on SDNN and RMSSD

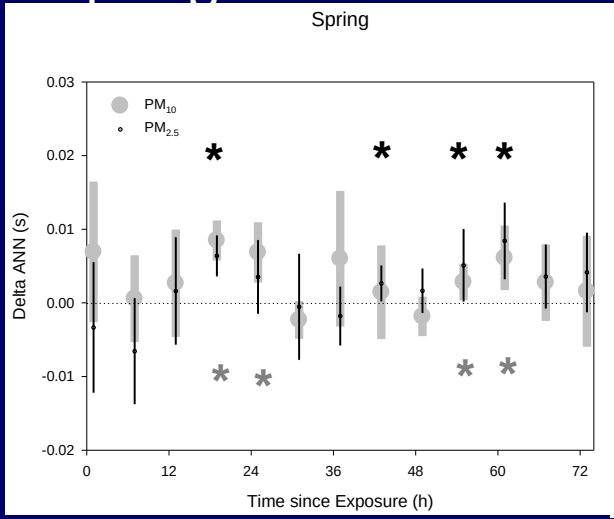


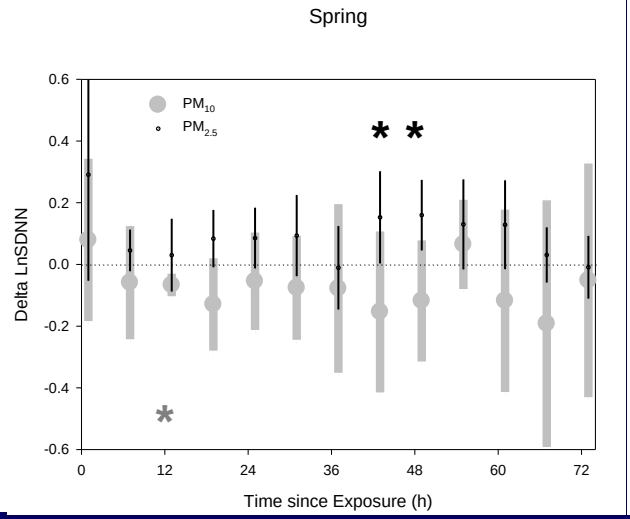


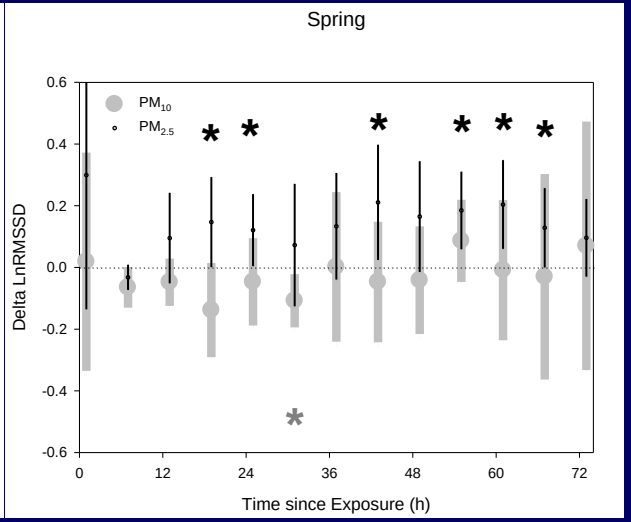


HRV induced by PM_{10} and $PM_{2.5}$ in SHR: IT

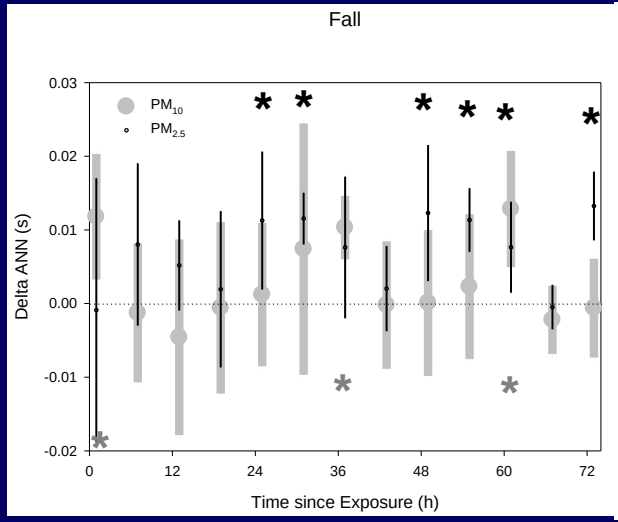
Spring

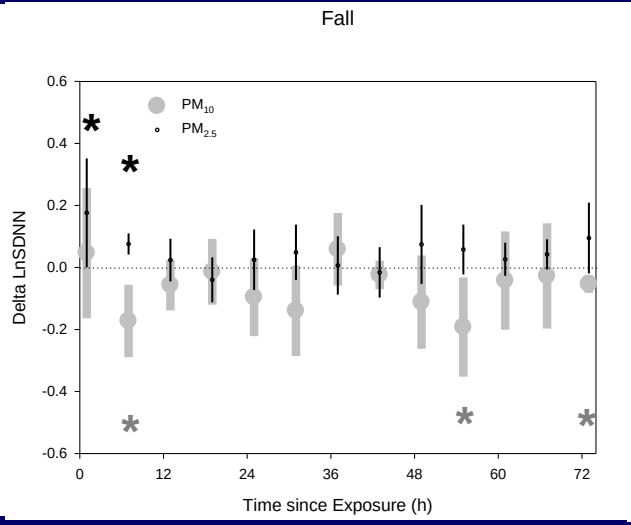


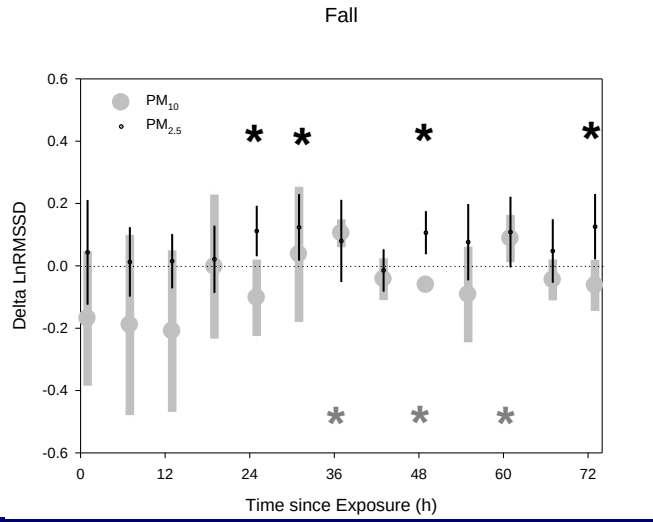




Fall



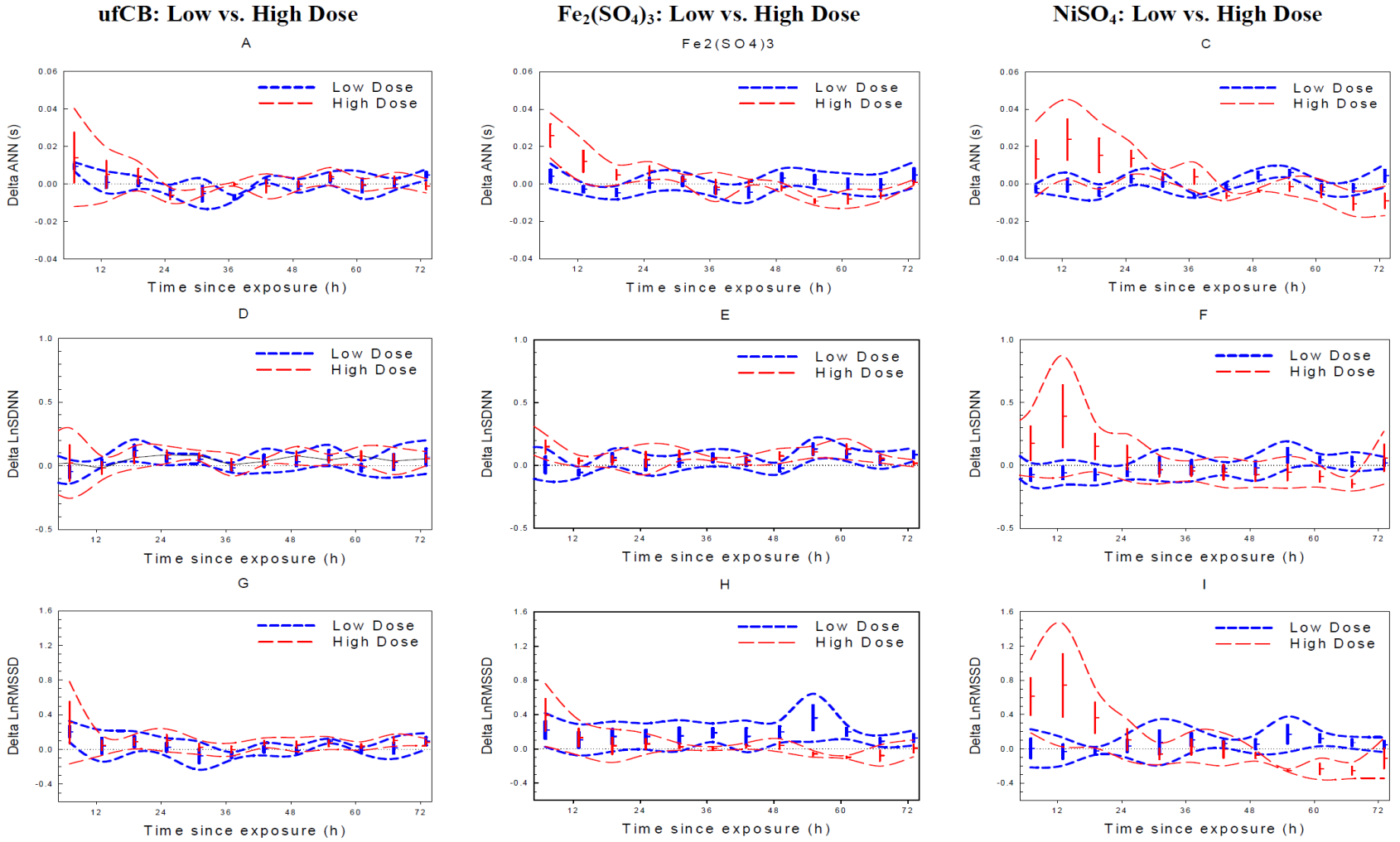




ANN SDNN RMSSD

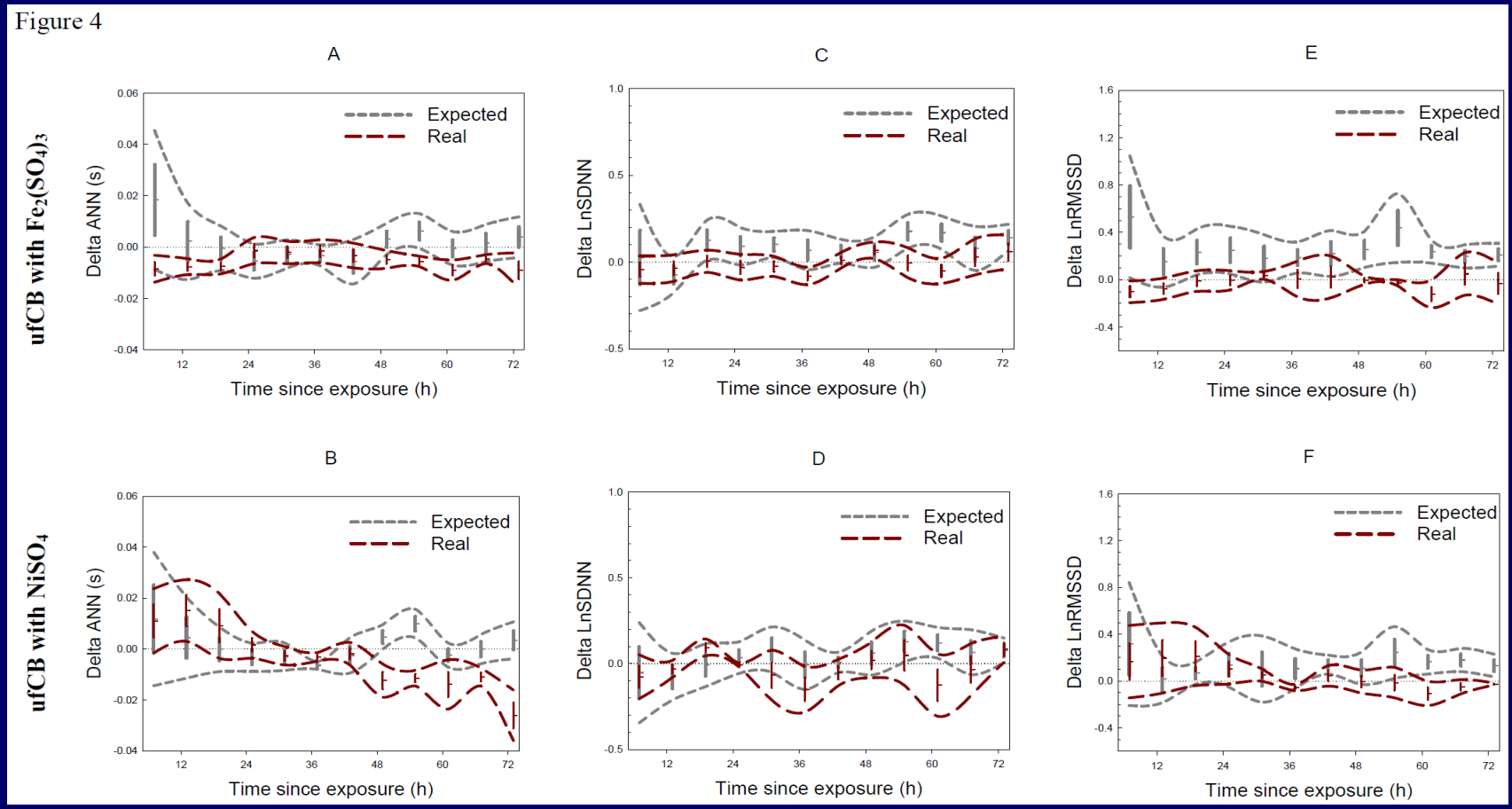
Heart rate variability by different components of PM: IT

Figure 3.

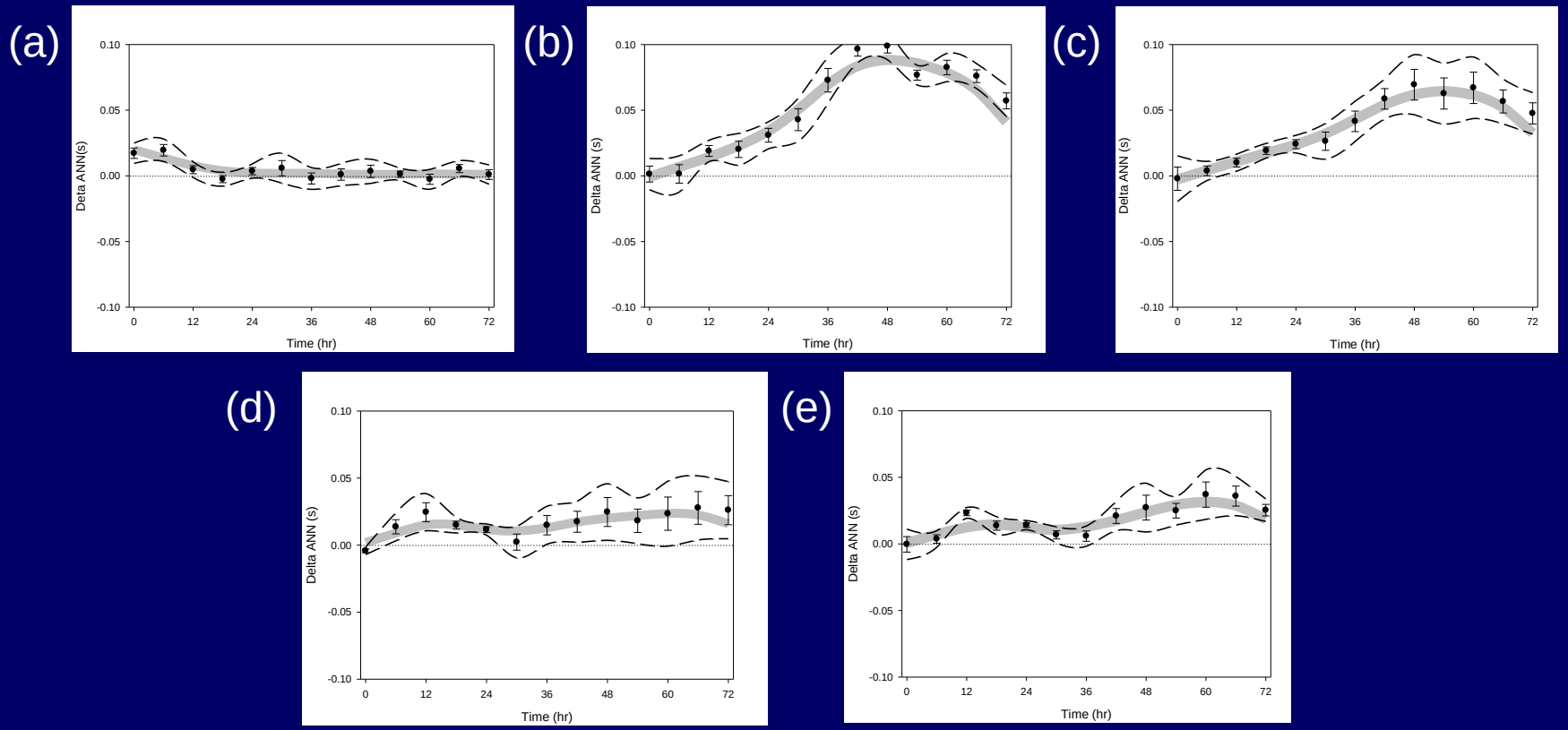


Chang, EHP, 2007

Heart rate variability by combined effects of PM components: IT



Nickel regulated heart rate: IT



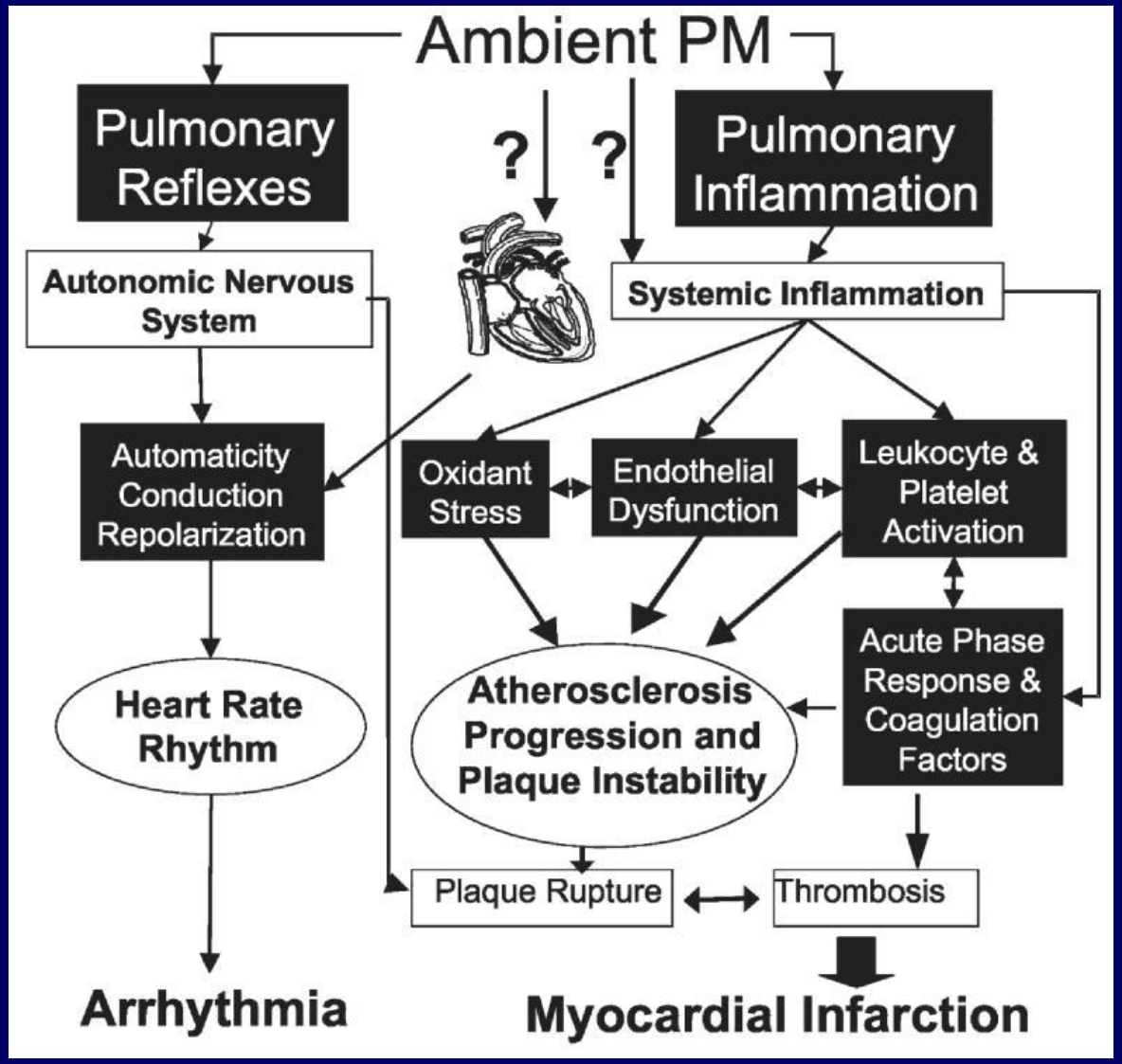
(a) WKY; (b) SHR; (c) SHR treated with NAC*1; (d) SHR treated with NAC*4; (e) SHR treated with Celecoxib*4。 NAC, N-acetylcystein, antioxidant; Celecoxib, anti-inflammatory agent

Chuang, Toxicol Appl Pharmacol, 2013

Summary

- PM induces the alterations of cardiac autonomic function.
- PM components account for the difference of effects.
- PM-induced autonomic dysfunction is mediated through oxidative stress and inflammation.
- Our results support the epidemiological findings.

Proposed biological mechanisms linking PM with cardiovascular disease



Brook et al., *Circulation*. 2004; 109: 2655-2671

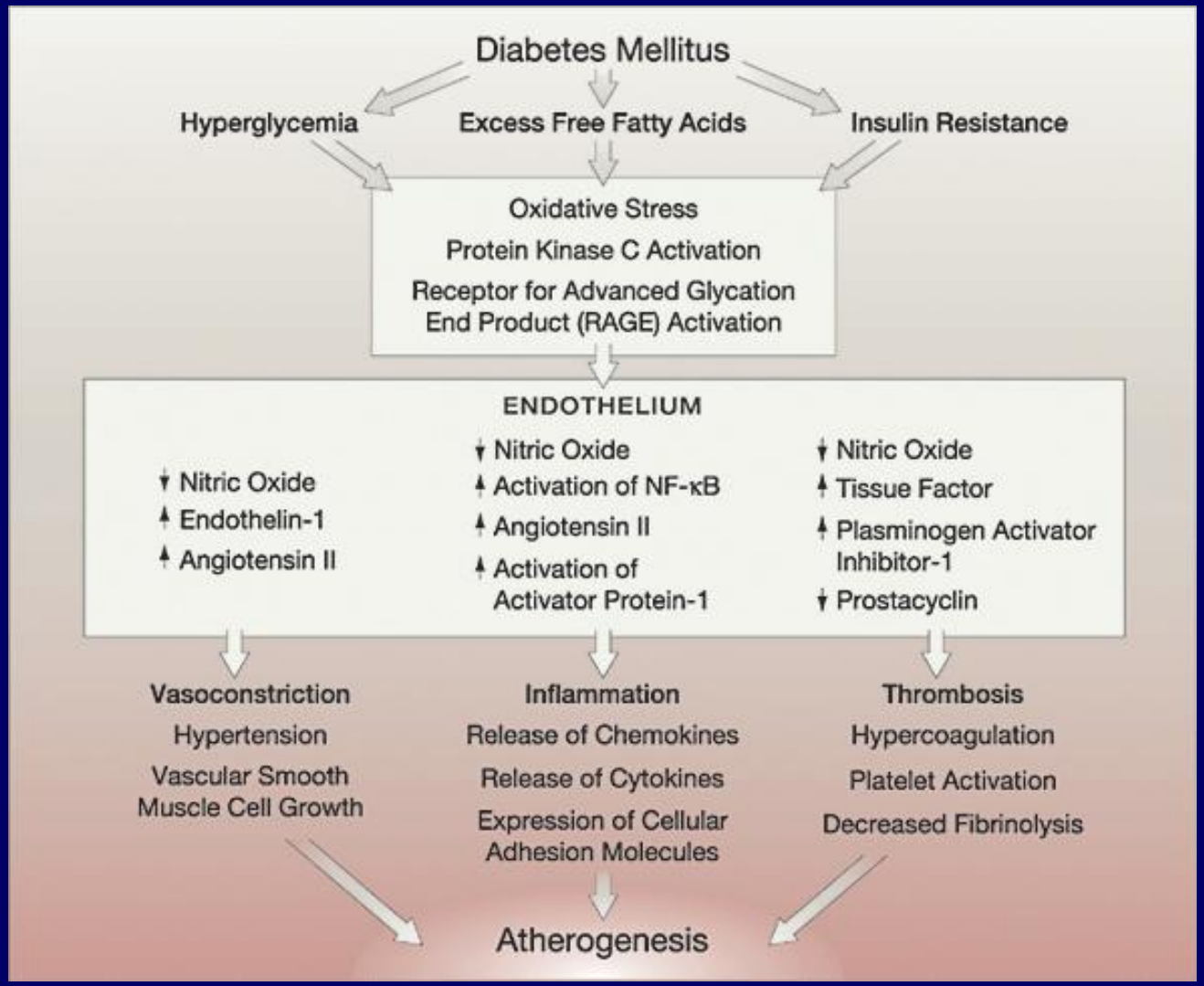
Diabetics have **double the risk** of a PM10 -associated cardiovascular admission compared with nondiabetics.

TABLE 2. City-Specific Percentage Increase, for a 10 $\mu g/m^3$ Increase in PM_{10}, in Hospital Admissions for Cardiovascular Disease by Concurrent Diagnosis for Diabetes and by Age Group

	With Diabetes		Without Diabetes	
	%	95% CI	%	95% CI
Chicago	2.0	1.4–2.6	0.9	0.6–1.3
≤75 years	1.9	1.1–2.7	0.7	0.2–1.2
75+ years	2.0	1.1–3.0	1.2	0.8–1.7
Detroit	1.6	1.0–2.3	1.2	0.9–1.5
≤75 years	1.3	0.5–2.2	1.2	0.7–1.7
75+ years	2.1	1.0–3.1	1.2	0.7–1.6
Pittsburgh	1.5	0.8–2.2	1.2	0.9–1.6
≤75 years	1.8	0.9–2.7	0.6	0.1–1.2
75+ years	0.9	−0.2–2.0	1.6	1.2–2.1
Seattle	2.2	0.9–3.5	0.9	0.4–1.5
≤75 years	1.9	0.1–3.7	0.8	0.0–1.6
75+ years	2.7	0.7–4.8	0.9	0.2–1.6

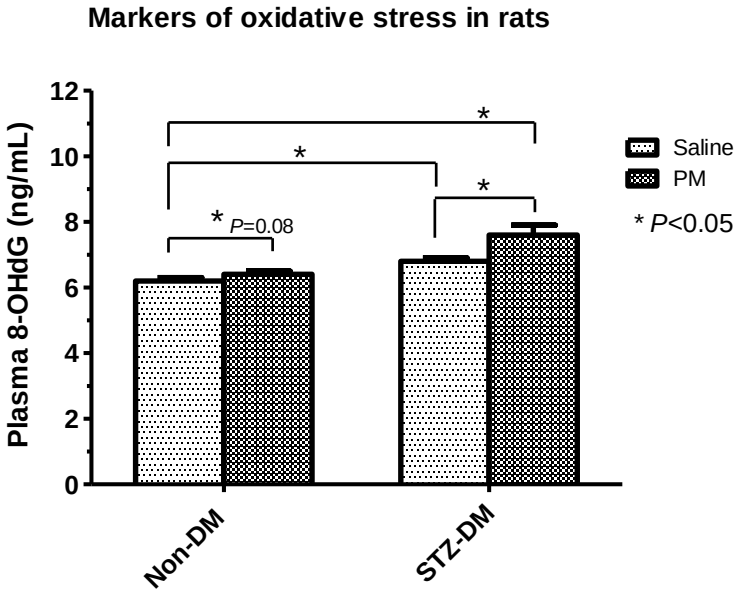
Zanobetti & Schwartz, Epidemiology. 2002 13:588-592.

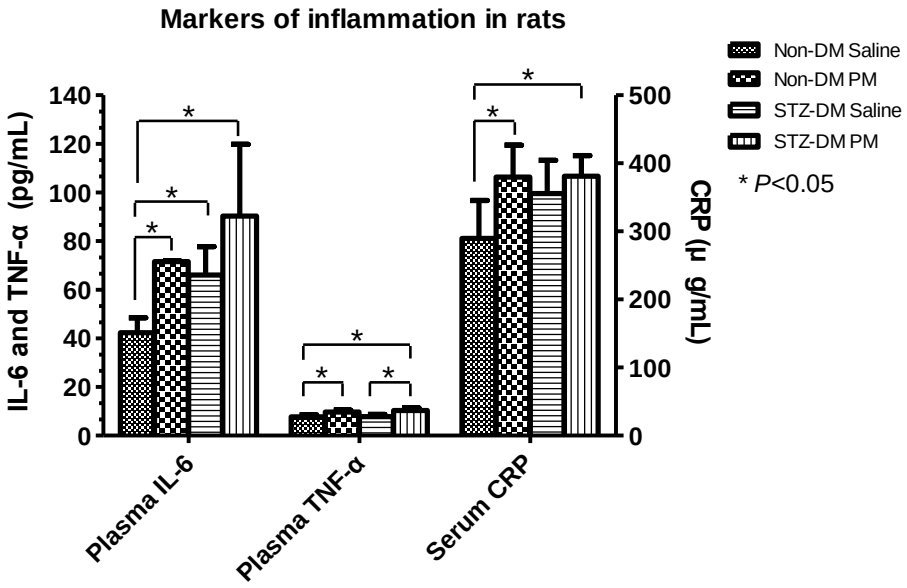
Pathophysiology of diabetes

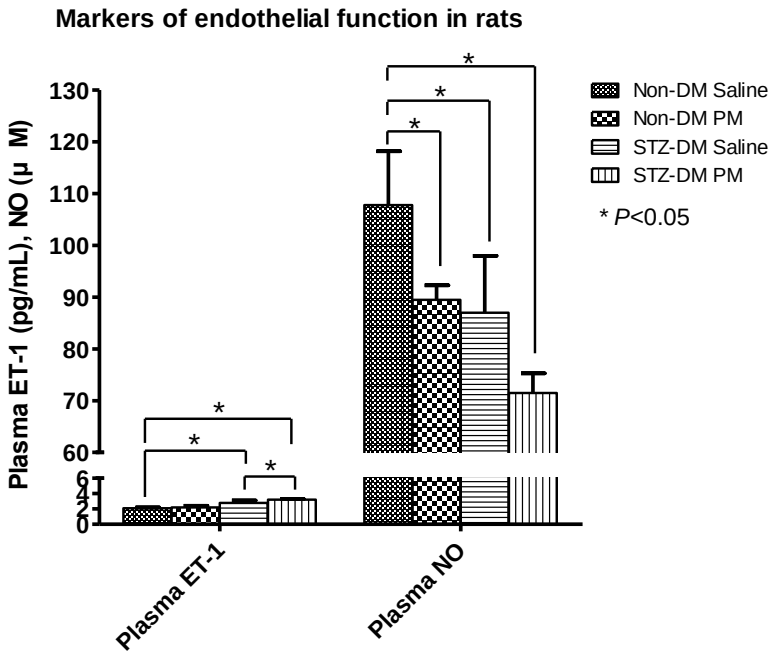


Beckman et al., JAMA, 2002, 287: 2570-2581

Markers induced by PM: IT







Lei, Environ Res 2005

Traffic-Related Air Pollution and Incident Type 2 Diabetes: Results from the SALIA Cohort Study

Ursula Krämer,[1] Christian Herder,[2]* Dorothea Sugiri,[1] Klaus Strassburger,[3] Tamara Schikowski,[1] Ulrich Ranft,[1] and Wolfgang Rathmann[3]*

[1]Institut für Umweltmedizinische Forschung (IUF), Leibniz Center at Heinrich Heine University Düsseldorf, Düsseldorf, Germany; [2]Institute for Clinical Diabetology, and [3]Institute of Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany

EHP, 2010

Association of long term PM exposure and risk factors of atherosclerosis

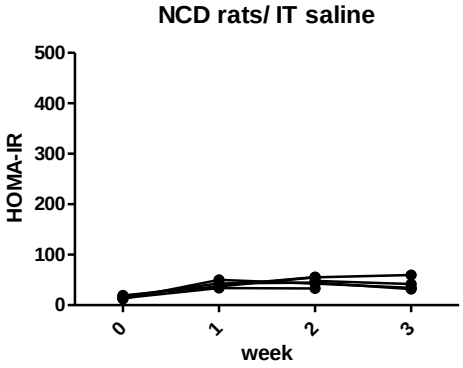
Table 4 Changes (95% CI) in blood pressure and blood markers for interquartile range increases in annual air pollution estimated by generalised additive models

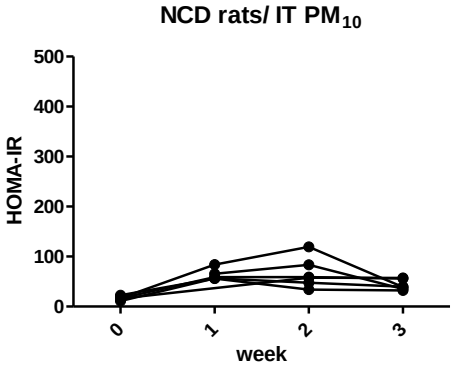
	PM_{10} ($\mu g/m^3$)	$PM_{2.5}$ ($\mu g/m^3$)	O_3 (ppb)	NO_2 (ppb)	SO_2 (ppb)
Systolic blood pressure (mm Hg)	16.34 (12.27 to 20.42)	32.08 (21.57 to 42.58)	21.51 (16.90 to 26.13)	14.40 (10.98 to 17.82)	0.97 (−5.22 to 7.15)
Diastolic blood pressure (mm Hg)	14.87 (12.73 to 17.02)	31.29 (25.43 to 37.14)	20.56 (18.14 to 22.97)	12.43 (10.63 to 14.23)	0.55 (−2.72 to 3.83)
Total cholesterol (mg/dl)	42.86 (34.59 to 51.13)	75.39 (54.30 to 96.48)	56.47 (47.26 to 65.69)	39.31 (32.38 to 46.24)	1.53 (−10.95 to 14.00)
Triglycerides (mg/dl)	3.39 (−14.13 to 20.91)	30.65 (−18.27 to 79.57)	2.13 (−18.10 to 22.36)	−0.94 (−15.61 to 13.73)	−22.16 (−48.56 to 4.25)
HDL-cholesterol (mg/dl)	−1.19 (−4.17 to 1.79)	0.19 (−2.29 to 2.67)	−0.48 (−3.69 to 2.73)	−0.15 (−1.93 to 1.63)	0.76 (−1.22 to 2.74)
Fasting glucose (mg/dl)	22.88 (14.93 to 30.82)	36.55 (19.20 to 53.90)	21.10 (12.03 to 30.17)	17.03 (10.37 to 23.69)	4.95 (−7.05 to 16.95)
Haemoglobin A1c (%)	1.40 (1.11 to 1.69)	2.24 (1.47 to 3.00)	1.30 (0.97 to 1.63)	1.08 (0.84 to 1.33)	0.20 (−0.23 to 0.64)
Interleukin 6 (pg/ml)	0.38 (0.08 to 0.68)	0.24 (−0.58 to 1.06)	0.14 (−0.18 to 0.46)	0.32 (0.06 to 0.59)	0.05 (−0.38 to 0.49)
Neutrophils (%)	11.80 (9.81 to 13.78)	16.77 (11.33 to 22.21)	13.74 (11.50 to 15.99)	9.54 (7.88 to 11.21)	−1.46 (−4.45 to 1.53)

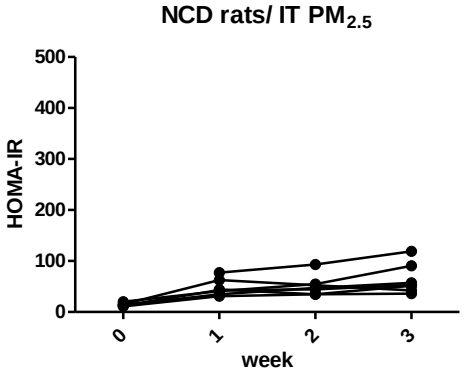
All models are adjusted for age, sex, body mass index, current smoking, drinking, and smooth functions of visit date and yearly temperature.
HDL, high-density lipoprotein; PM_{10}, particulate matter <10 μm in aerodynamic diameter; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter; NO_2, nitrogen dioxide; O_3, ozone; SO_2, sulfur dioxide.

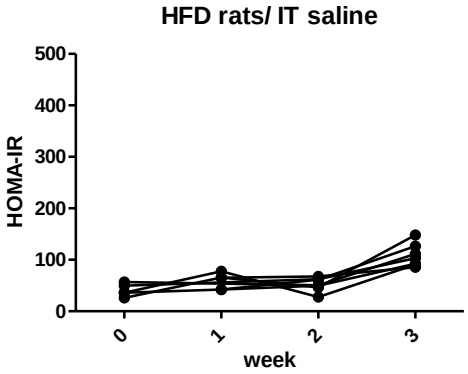
Chuang, OEM, 2011

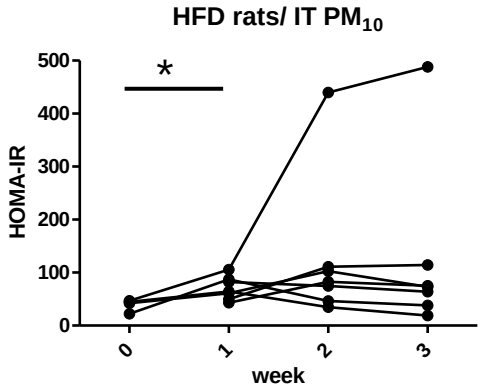
PM and insulin resistance (IT)

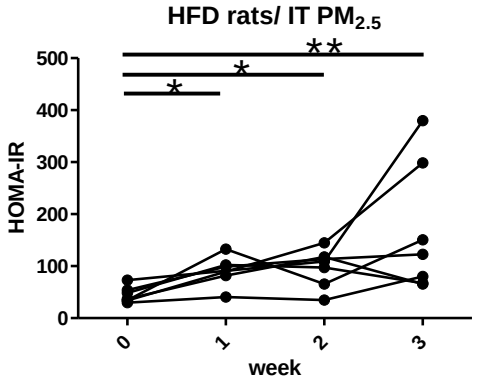












HOMA	HOMA-IR index= insulin（μU/mL）× glucose（mmol/L）/22.5 （換算glucose 1 mg/dL= 0.0555 mmol/L）

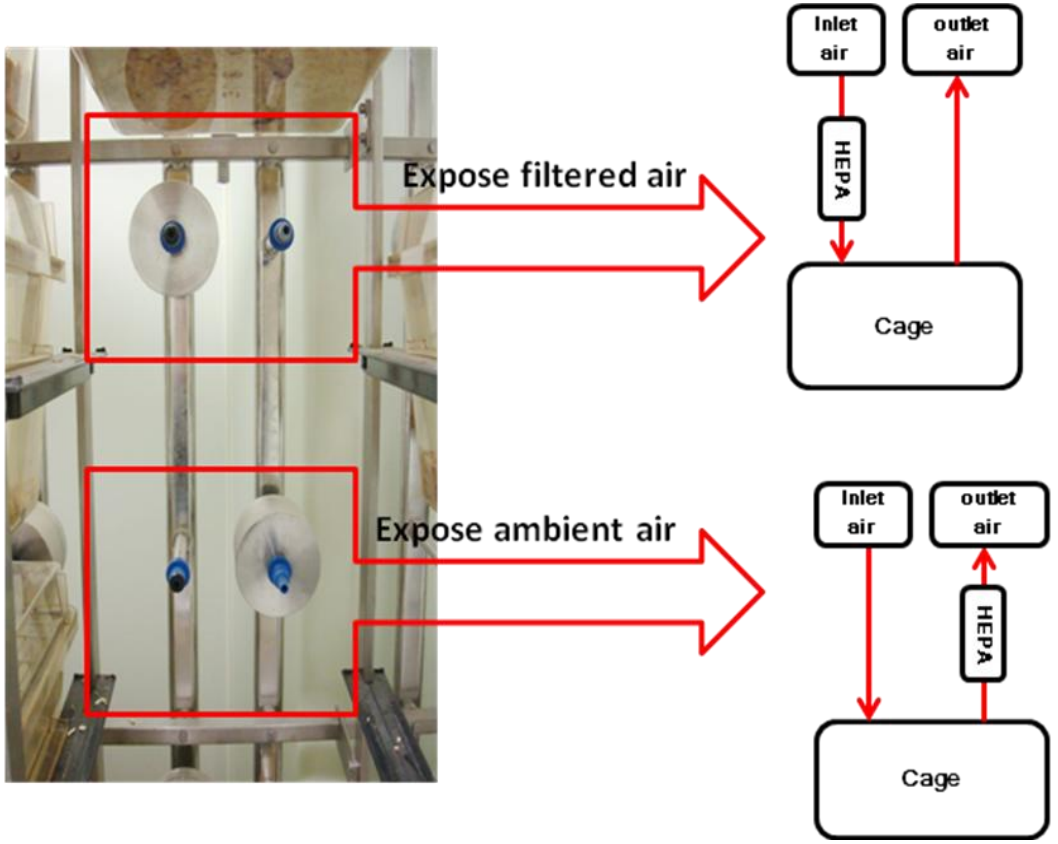
Yan, Inhalation Toxicology, 2011

Sub-chronic toxicity of ambient particles

- Construction of chronic exposure system
- Insulin resistance and cardiovascular damages in hyperglycemic and healthy rats

Individual ventilation exposure system (IVC)

Taipei Air Pollution Exposure System for Health Effects (TAPES)



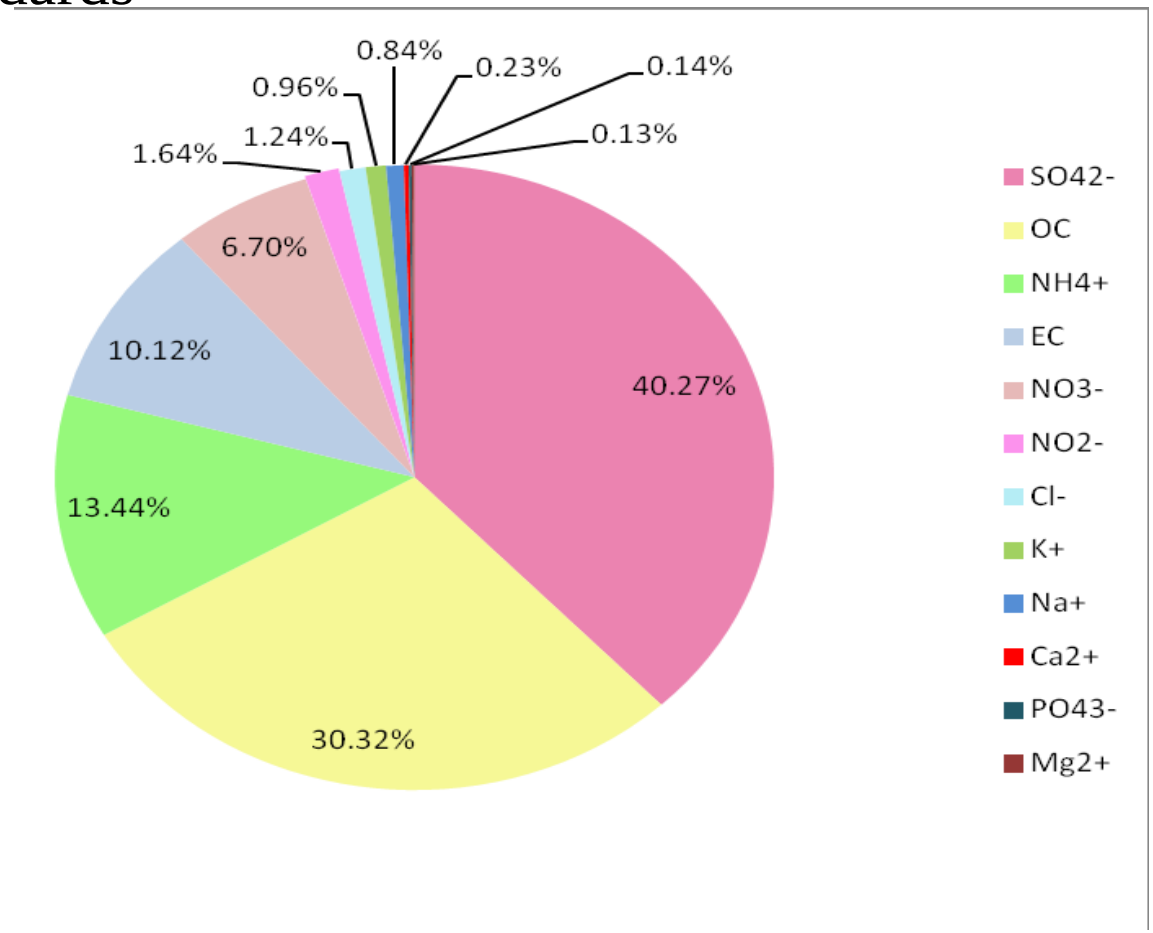
Located at the 9th floor, College of Public Health Building

TAPES

- $PM_{10-2.5}$: 0.4%; $PM_{2.5}$: 99.6%
- $PM_{2.5}$ loss: 20%
- Components reflect urban $PM_{2.5}$ air pollution during winter time in Taipei: no selection
- Difference of PM levels in chambers within 20%
- No difference for gas pollutants between exposure and control chambers

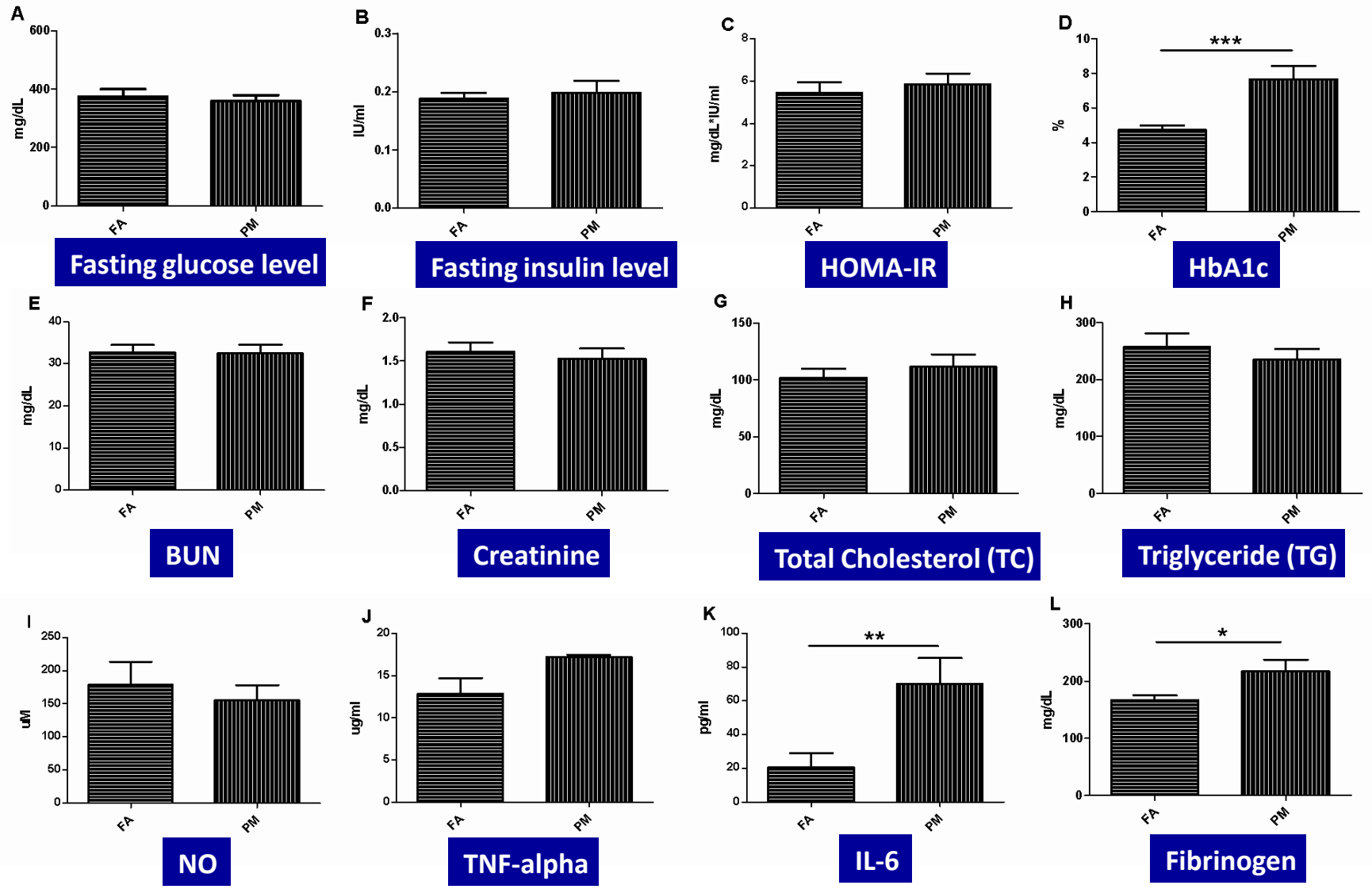
Concentration and components of PM2.5

- 13.3 (μg/m3) during experiment
- Guidelines or standards
  - WHO: 10
  - USA: 12
  - Taiwan: 15



Yan, Toxicol Appl Pharmacol, 2014

Effects of PM in hyperglycemic rats



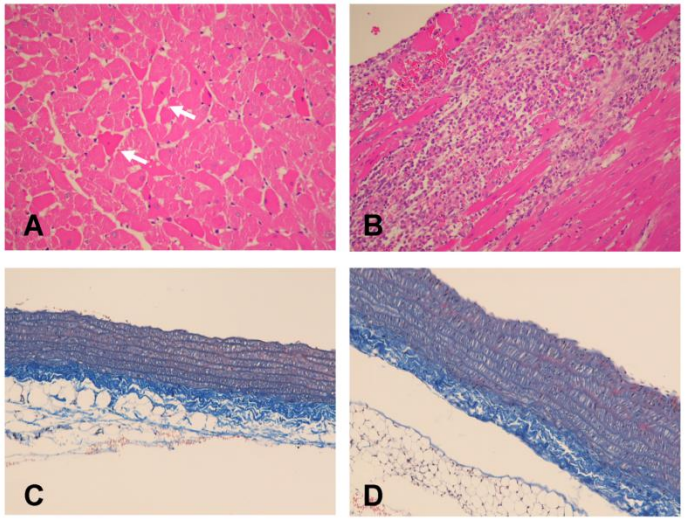


Figure 2. Representative photomicrographs of Hematoxylin-Eosin staining of myocardium (A and B), Masson's trichrome staining of abdominal aortic sections (C and D). Original magnification X200.

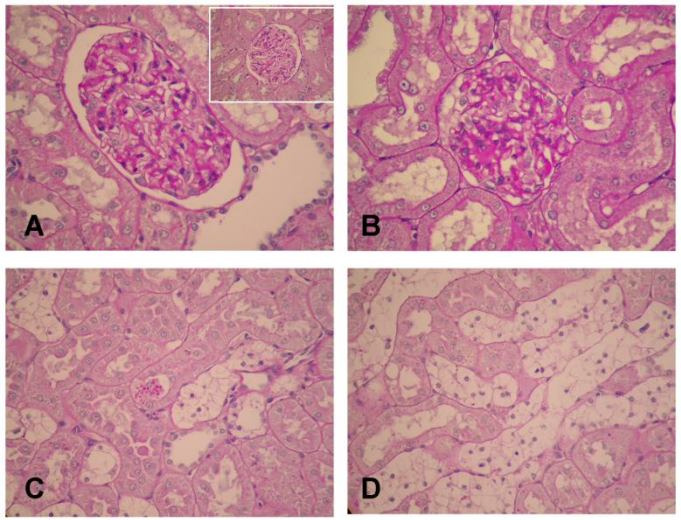


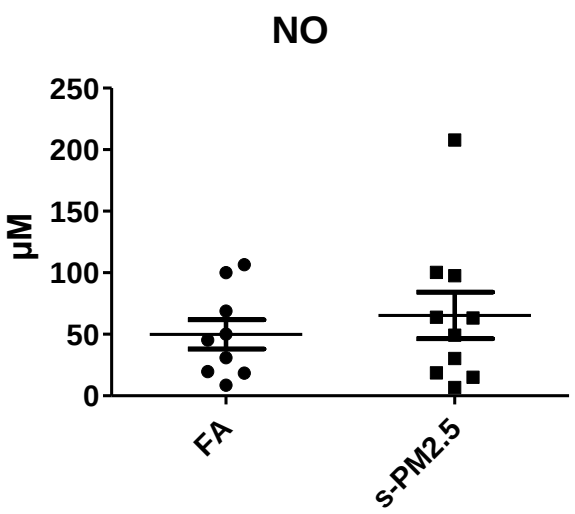
Figure 3. Representative photomicrographs of Periodic Acid-Schiff staining of glomerulus (A and B) and tubules of the kidney (C and D). Original magnification X200.

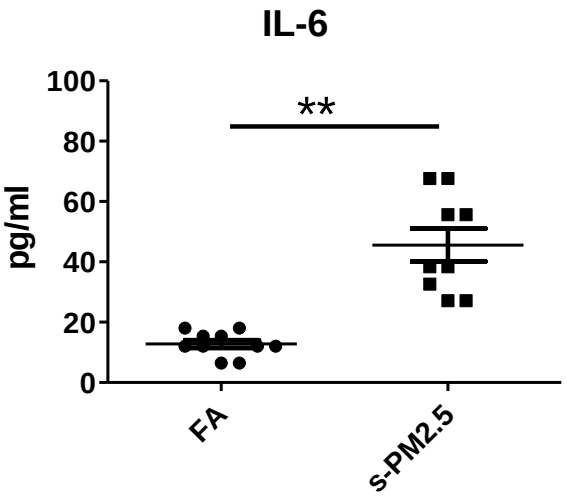
Table 1. Semi-quantitative measurements of histopathology in STZ-induced type 1 DM rats exposed to FA and PM. *p<0.05

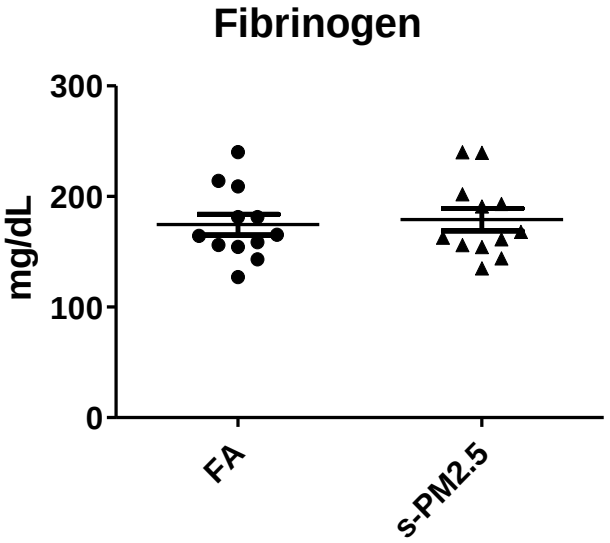
Organ	Score	FA	PM
Heart	Severity of inflammation (score 1-4)	0.08 (0.22)	1.10 (0.93)*
Aorta	Medial thickness (mm)	0.11 (0.02)	0.16 (0.02)*
Kidney	Glomerular score (grade 0-4)	0.86 (0.43)	0.91 (0.36)
	Glomeruli with advanced glomerulosclerosis (%)	30.6	47.2 *
	Tubular damage index (grade 0-3)	1.15 (0.36)	1.76 (0.77)*

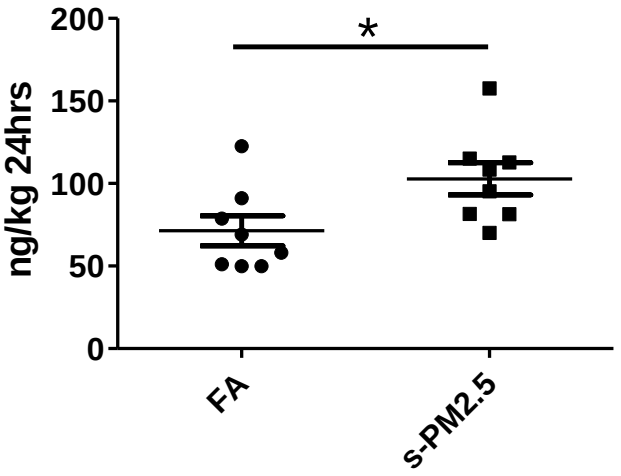
Data are presented as mean (SD).

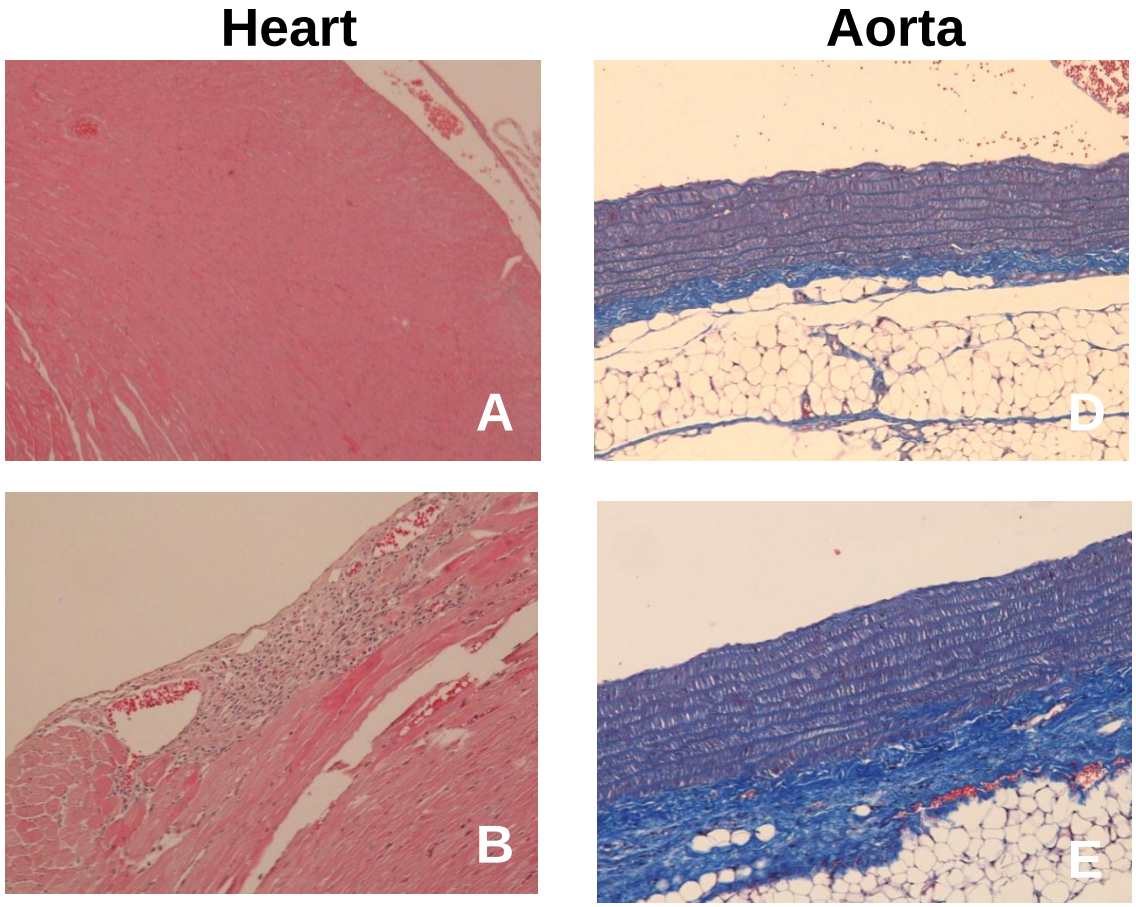
Effects of PM in healthy rats







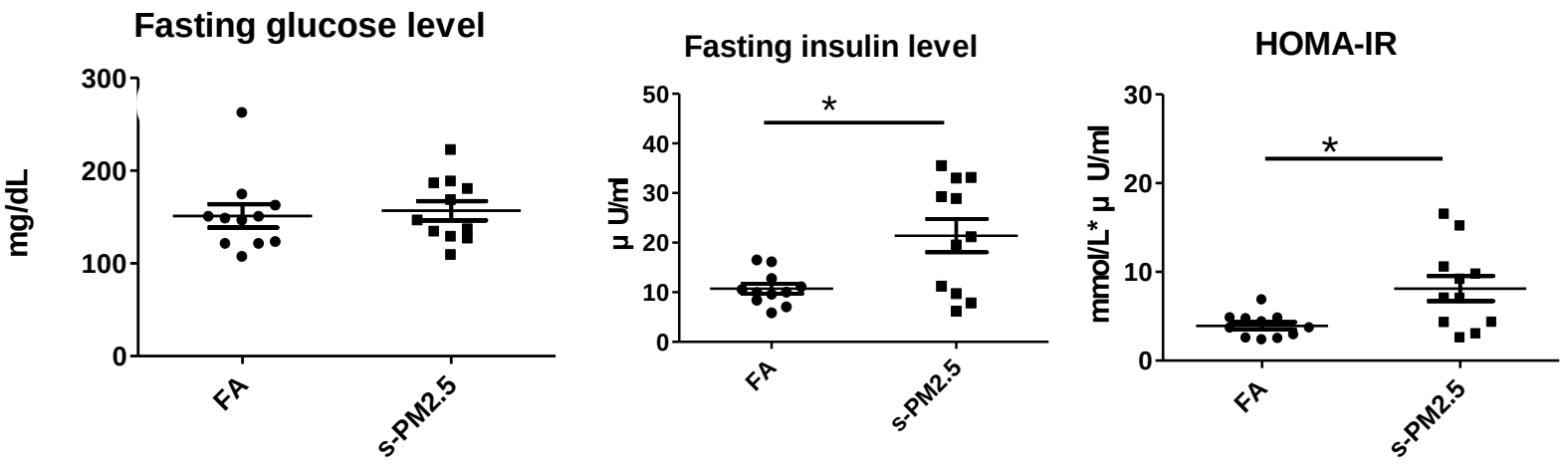




Semiquantitative measurements

Figure 4. Representative photomicrographs of Hematoxylin-Eosin staining of the myocardium (A and B) and Masson's trichrome staining of abdominal aortic sections (D and E). Semiquantitative measurements are illustrated in (C) and (F). FA indicates filtered air. S-PM2.5 indicates straight ambient particles of <2.5 µm. *p<.05.

Effects of PM in healthy rats



Summary

- PM-induced macro- and micro-vascular changes are more susceptible in hyperglycemic subjects.
- PM may induce diabetes through insulin resistance.
- The role of oxidative stress and inflammation on the development of insulin resistance needs further study.

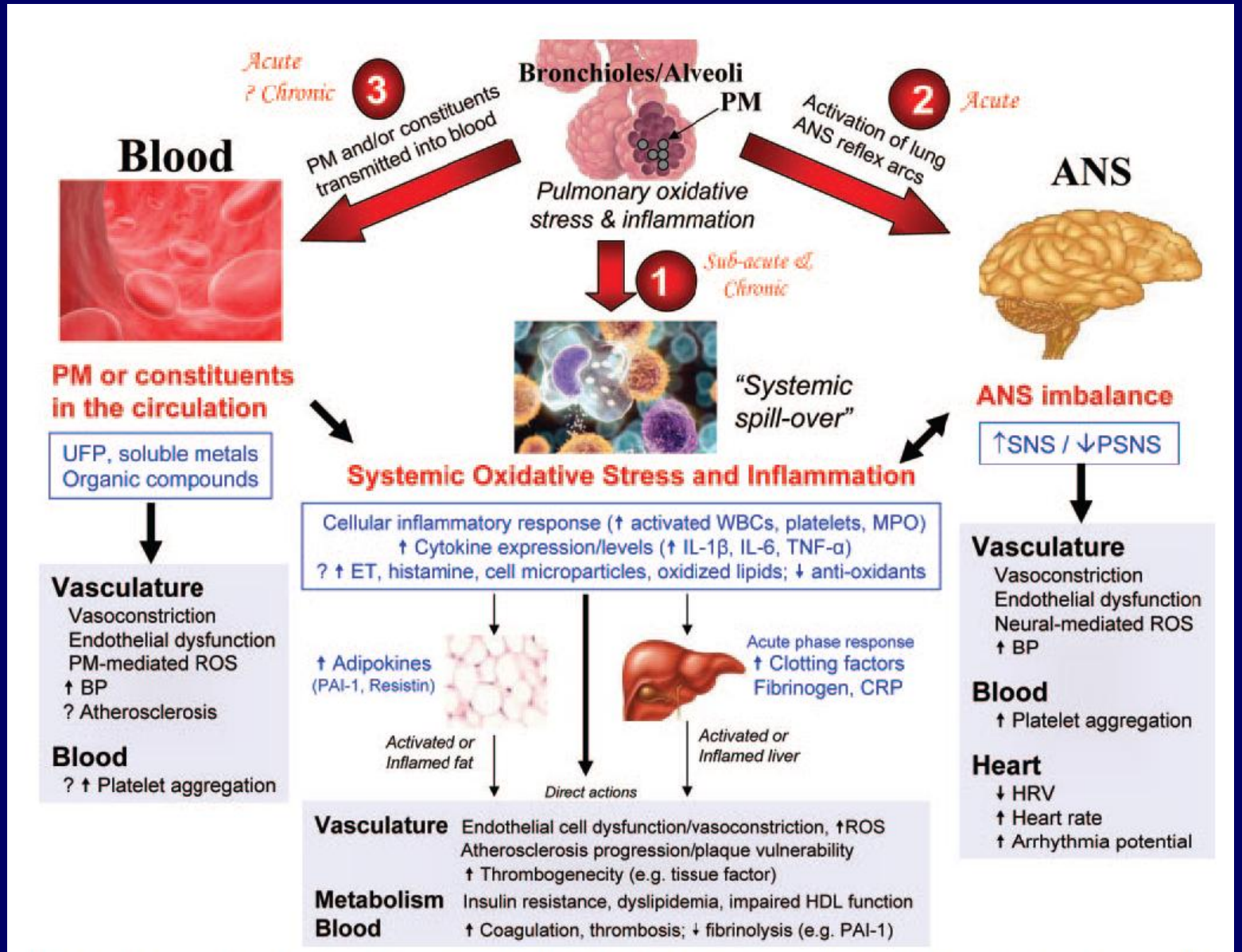
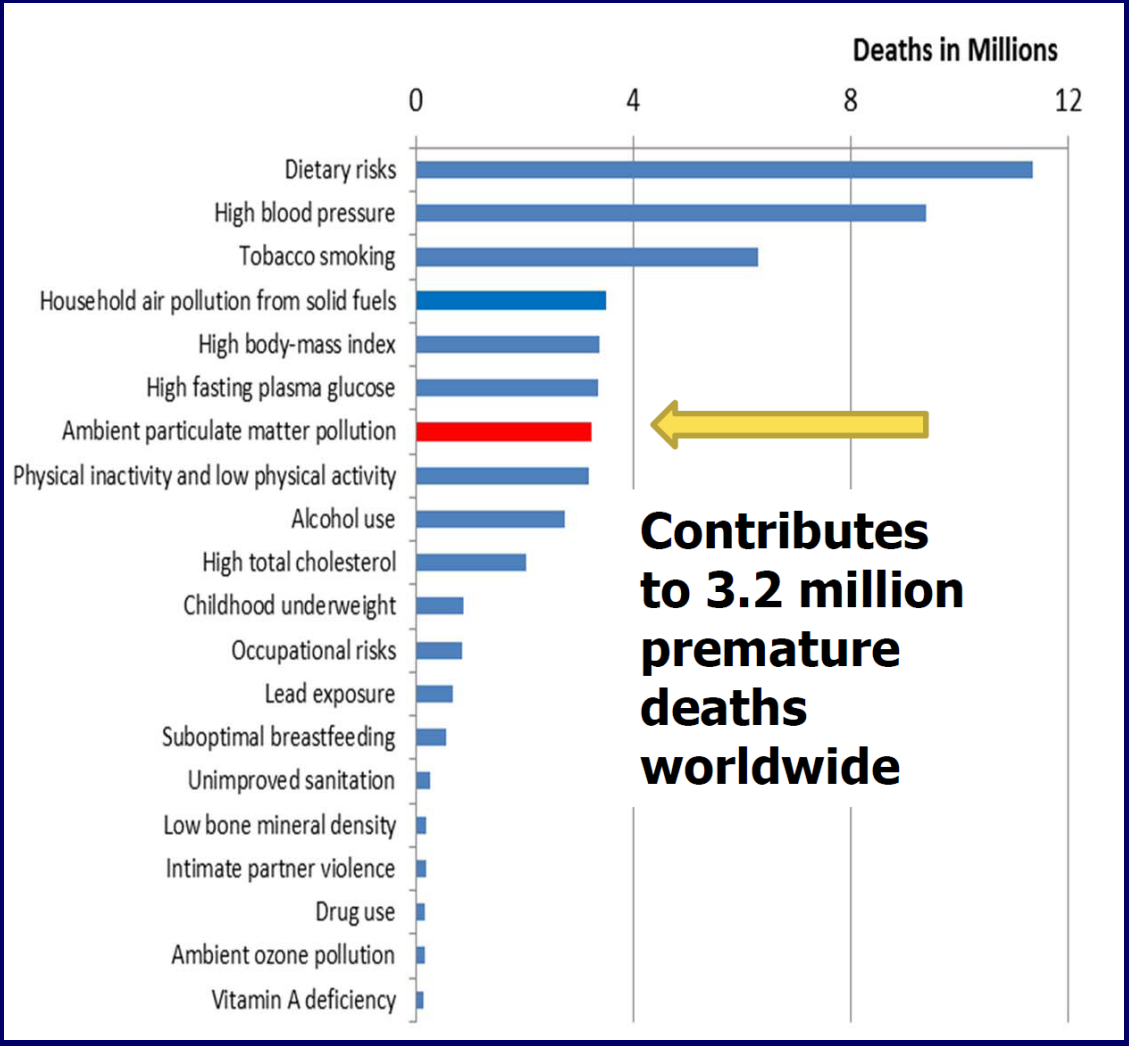


Figure 3. Biological pathways linking PM exposure with CVDs. The 3 generalized intermediary pathways and the subsequent specific biological responses that could be capable of instigating cardiovascular events are shown. MPO indicates myeloperoxidase; PAI, plasminogen activator inhibitor; PSNS, parasympathetic nervous system; SNS, sympathetic nervous system; and WBCs, white blood cells. A question mark (?) indicates a pathway/mechanism with weak or mixed evidence or a mechanism of likely yet primarily theoretical existence based on the literature.

Brook et al., Circulation, 2010

Leading global risk factors for mortality



Lim et al 2012,
modified by O'Keefe

Future studies

- Toxicity of other organs and systems, e.g., central nervous system toxicity and behavior changes
- Components and sources of ambient particles responsible for the toxicity

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- Kai Luo（羅凱）

Thank you!