

Eurochamp – Andechs – 11.10.2005

An update on the human toxicity of particles



Benoit Nemery, MD, PhD

Research Unit of Lung Toxicology

K.U.Leuven

ben.nemery@med.kuleuven.be

Short-term effects of pollutant particles

Season and temperature modulate the
short-term association between mortality
and PM_{10}

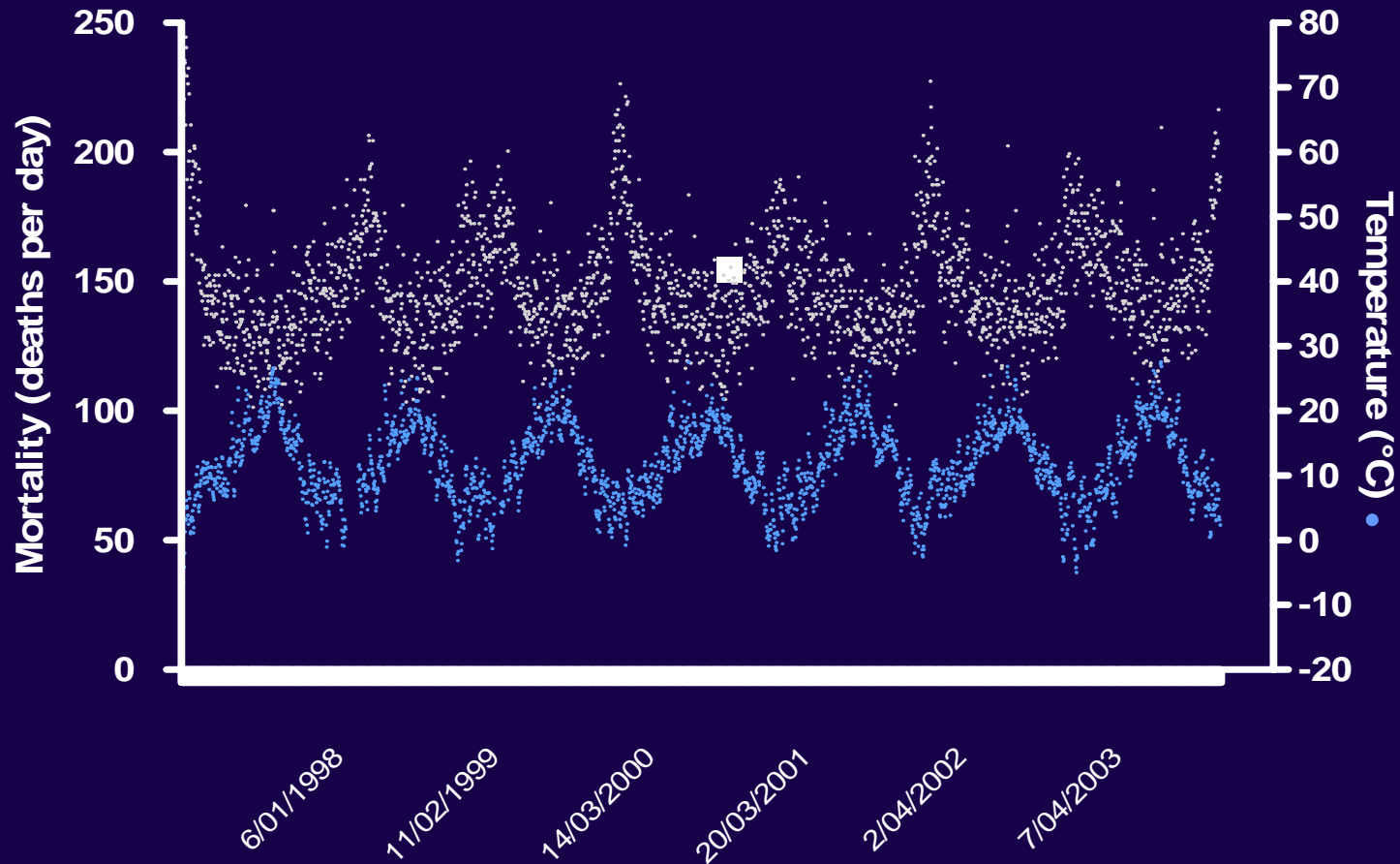
■
Analysis of data for Flanders, Belgium, 1997-
2003

T. Nawrot *et al.* submitted for publication

Background

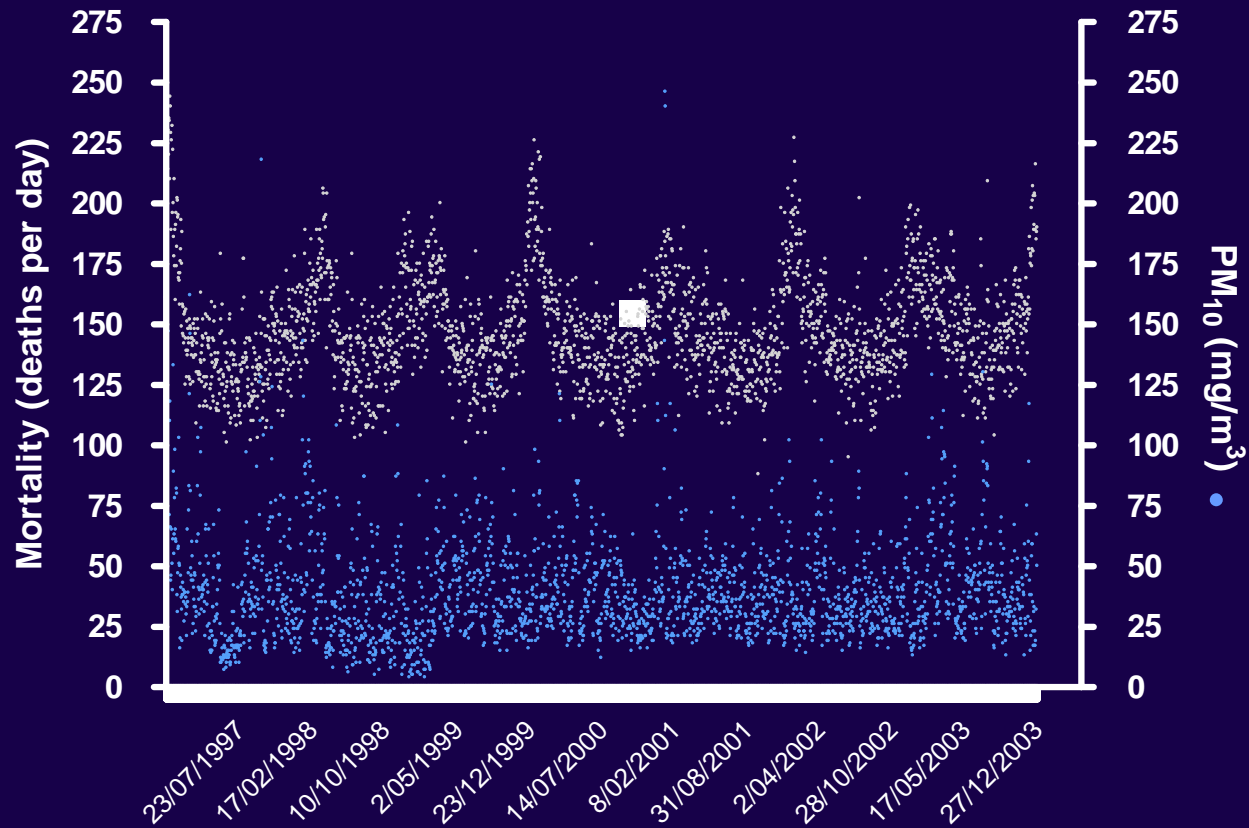
- **Most of the previous studies assumed that the association between daily mortality and PM_{10} is constant over the study period.**
 -
- **Because of the complex temperature and air pollution relation, simple adjustment for confounding may be inadequate.**

Variation in daily mortality and temperature, 1997-2003*



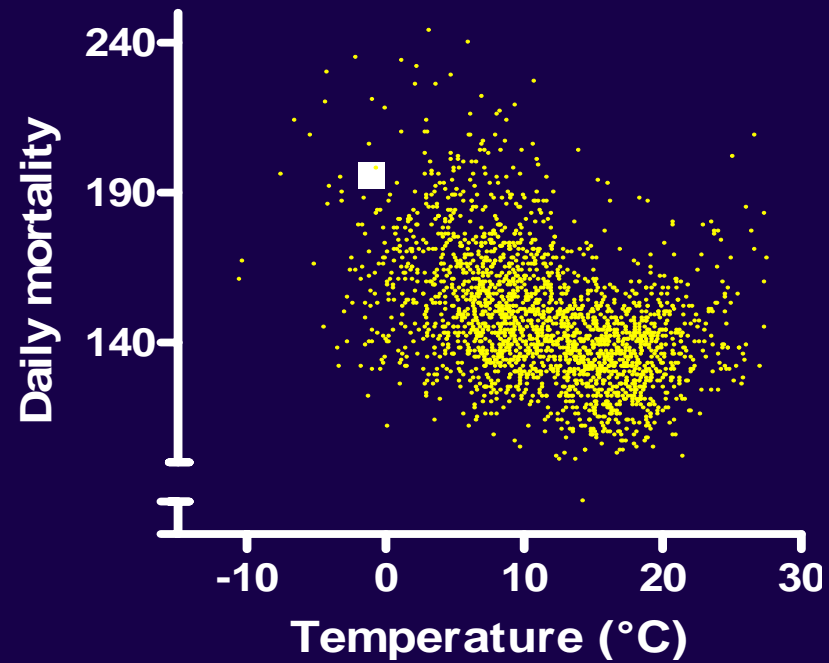
*non-traumatic death (n = 354 357)

Variation in daily mortality and PM₁₀, 1997-2003*

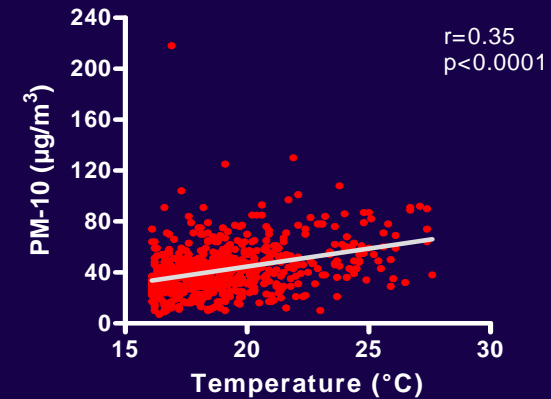
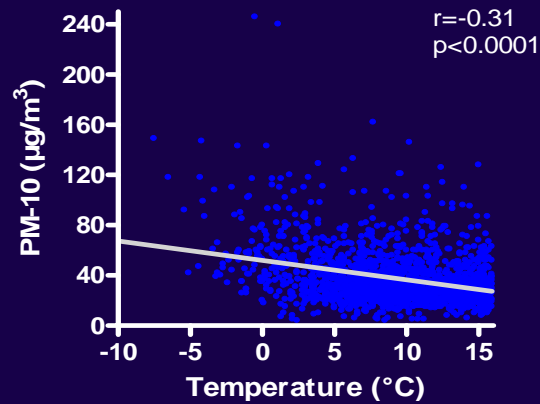
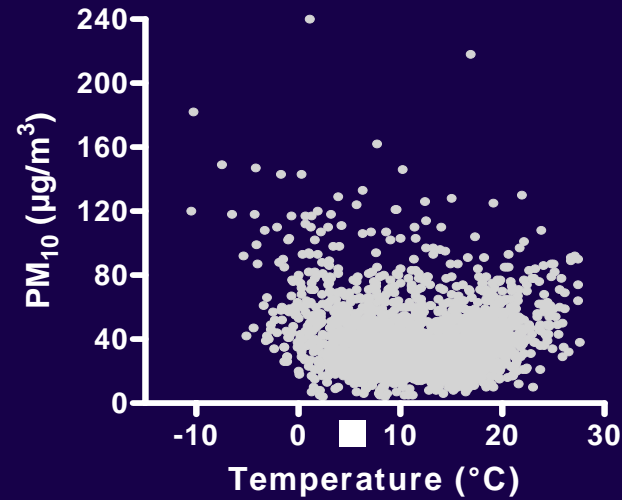


*non-traumatic death (n = 354 357)

Mortality and outdoor temperature



PM₁₀ and outdoor temperature



Conclusions

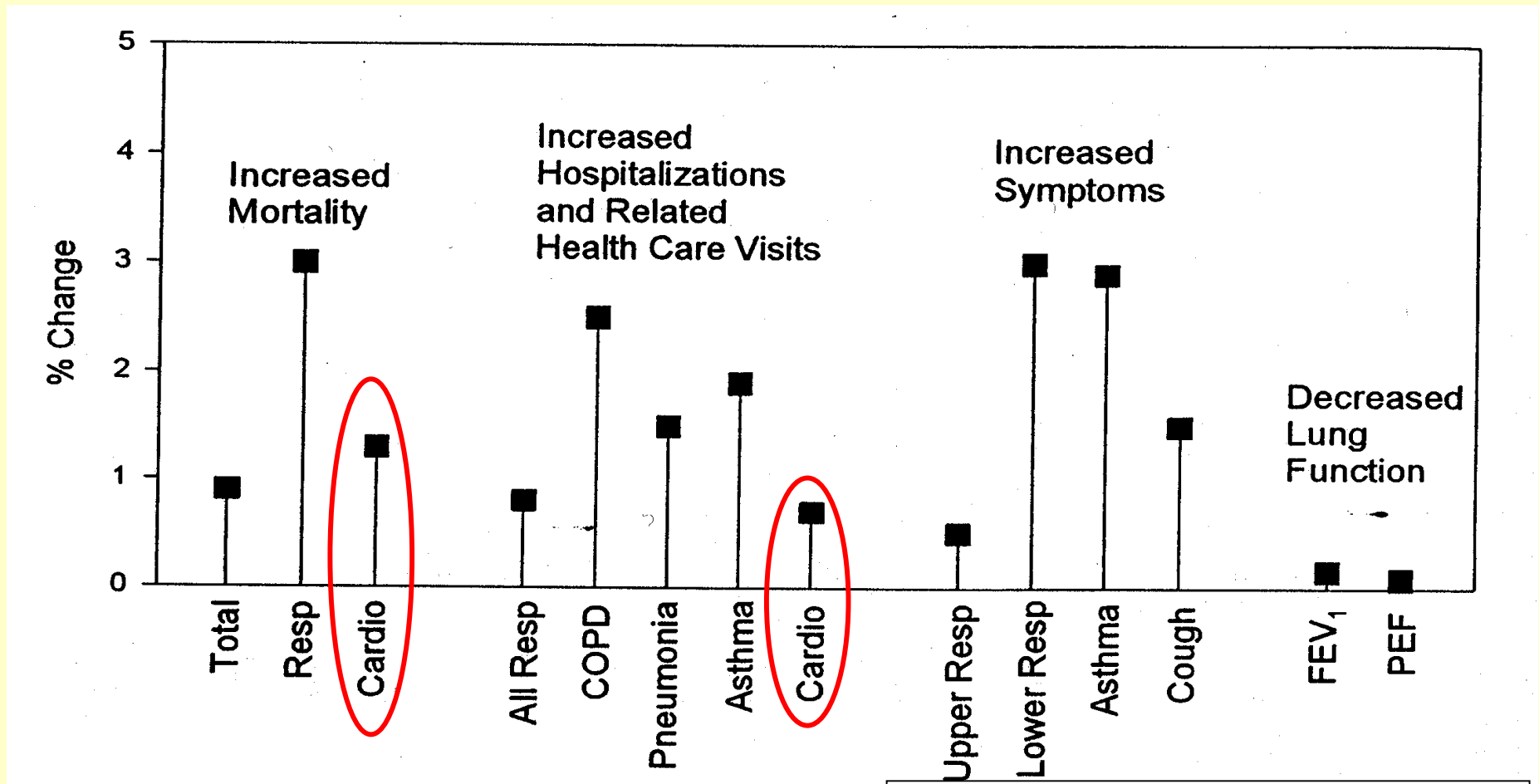
- The association between mortality and PM_{10} concentration is complex and depends largely on outdoor temperature. ■
- We observed a threshold during the winter period and on days with a mean outdoor temperature of less than $10^{\circ}C$.

How can we explain the seasonal influence on the mortality - air pollution association?

- The PM_{10} toxicity may vary by season.
- Higher relative effects in summer as a result of more time spent outdoors.
- The PM_{10} effect on mortality in winter could be swamped by the more powerful effect of cold spells on mortality.

PM₁₀ & mortality/morbidity (short term)

Stylized summary: % change per 10 µg/m³ change in PM₁₀



Cardiovascular morbidity

Peters *et al.* “Exposure to traffic and the onset of myocardial infarction” *N Engl J Med*, 2004, 351, 1721-30

Case-crossover study, 691 nonfatal MI (Augsburg; 1999-2001)
activity before onset of MI (standardized interview-based diary)?
activity 1h before MI vs control (24-71 h before MI)

- any means of transportation → O.R.=2.92
 - car → O.R.=2.60
 - bicycle → O.R.=3.94
 - public transport → O.R.=3.04
- severe exertion → O.R.=6.38

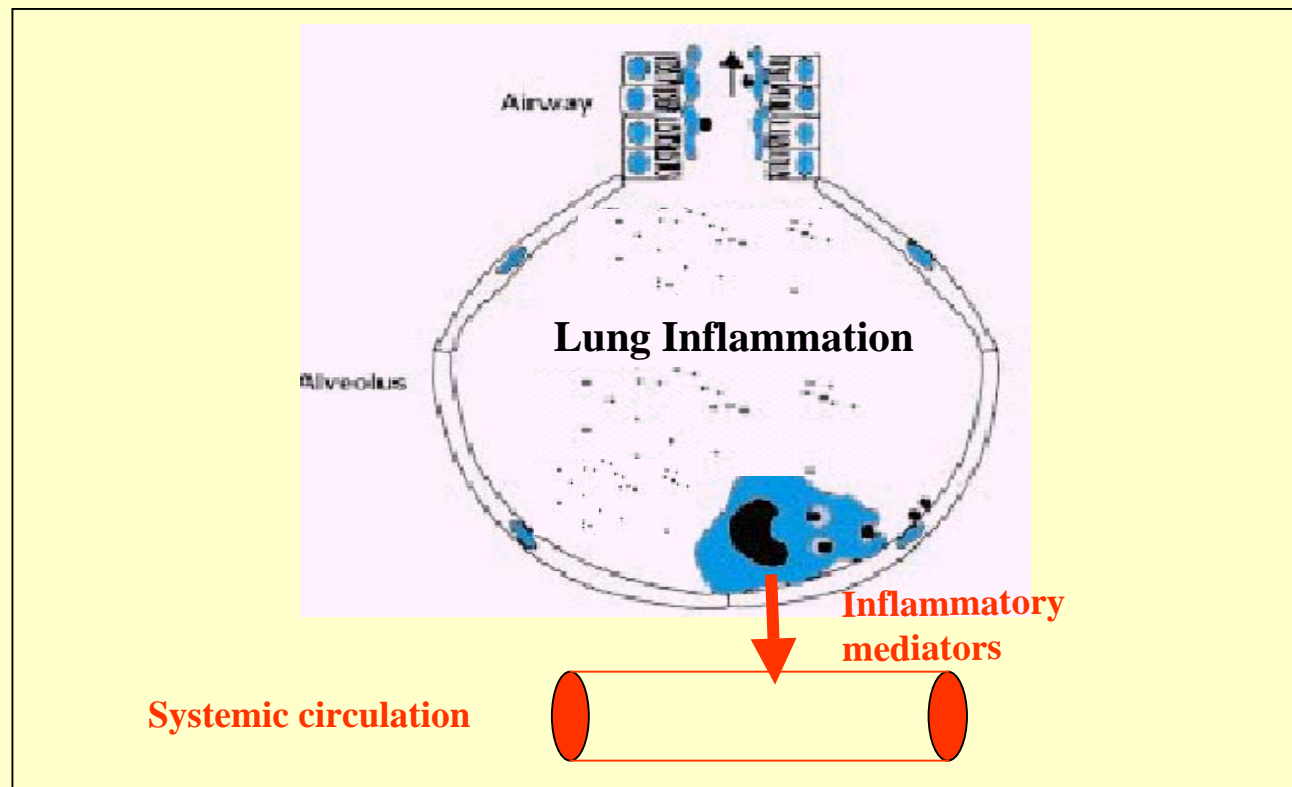
Cardiovascular morbidity

Short-term increases in particulate pollution & cardiovascular morbidity

- experimental toxicology:
 - which constituents of the particles?
 - by what mechanisms?
- “biological plausibility”?

Mechanisms

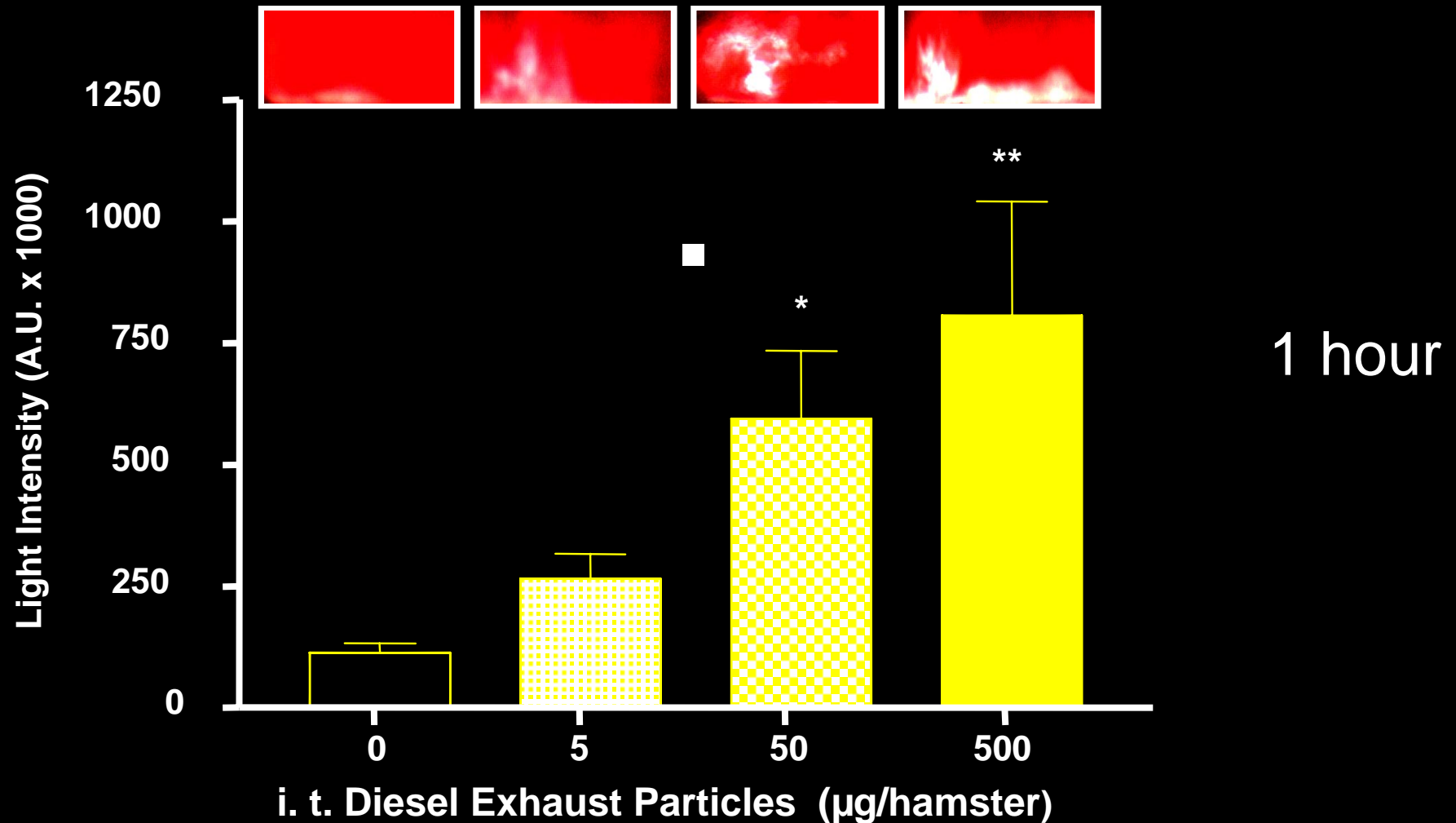
inhaled particles cause pulmonary inflammation with systemic release of cytokines



Nemmar *et al.* Circulation, 2003,107,1202-8

- Within 1 hour after their deposition in the lungs of hamsters, Diesel Exhaust Particles
 - cause pulmonary inflammation
 - **aggravate** vascular thrombosis *in vivo*, via platelet aggregation, as substantiated *ex vivo* and *in vitro*.

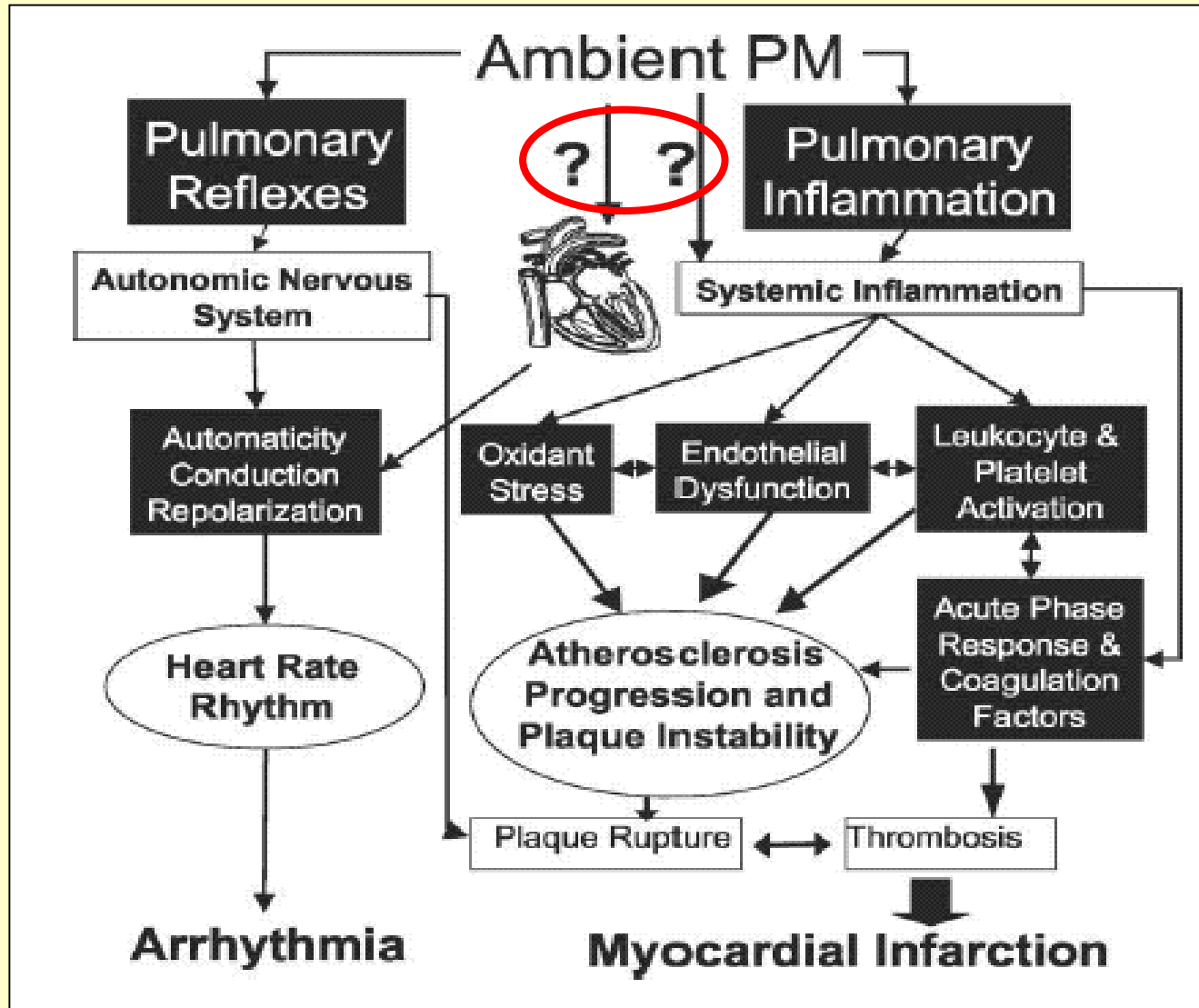
Peripheral venous thrombosis (chemically induced)



Summary of our further studies

- Intratracheally instilled DEP (and some ultrafine model particles) **aggravate** peripheral vascular thrombosis, probably via platelet activation
- Early effect (1 h) of i.t. DEP (and ultrafine model particles) on peripheral vascular thrombosis is compatible with direct penetration of particles (or constituents) into the circulation
- Late effect (24 h) of i.t. DEP on peripheral vascular thrombosis is probably due to pulmonary inflammation and can be blocked by pretreatment with **H1-inhibitor, dexamethasone, cromoglycate**

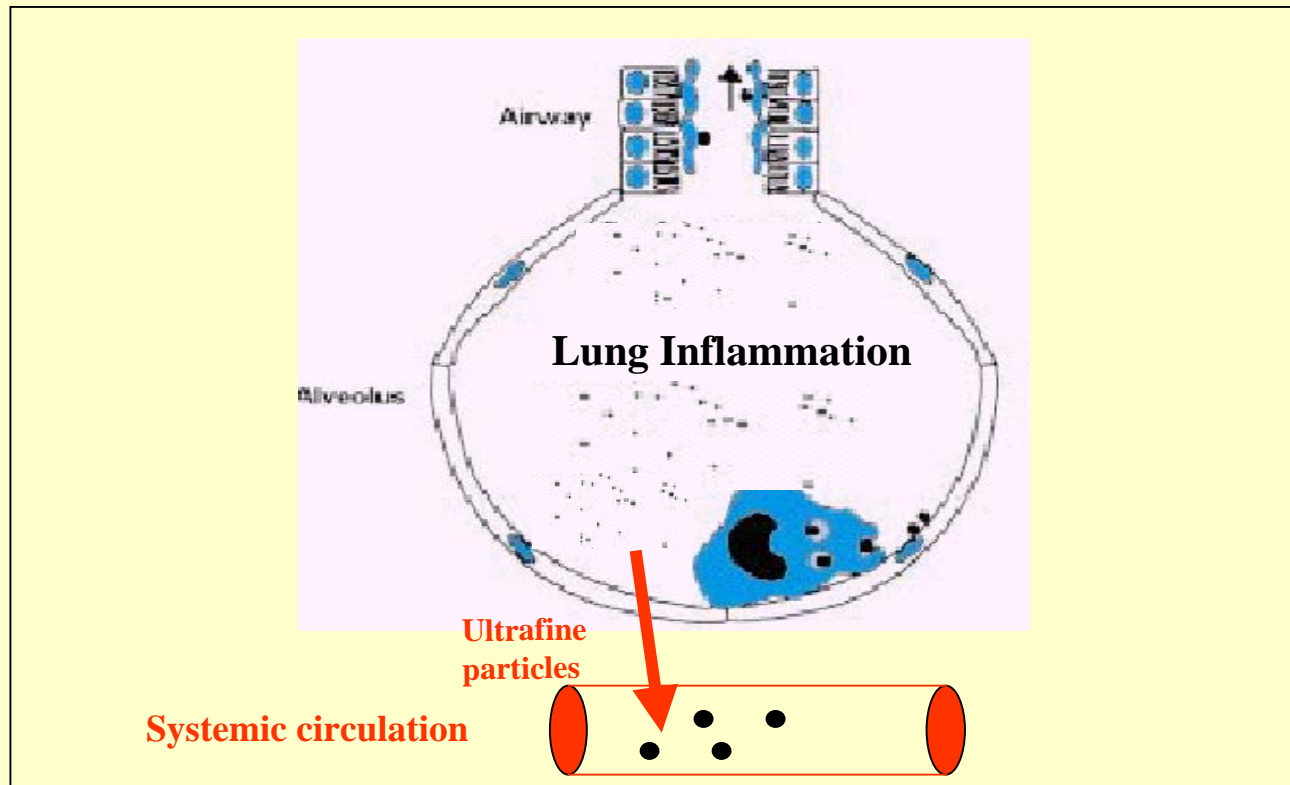
Brook RD *et al.* Air pollution and cardiovascular disease. A statement for health-care professionals from the expert panel on population and prevention science of the American Heart Association. *Circulation* 2004 (June 1); 109: 2655-71



Mechanisms ?

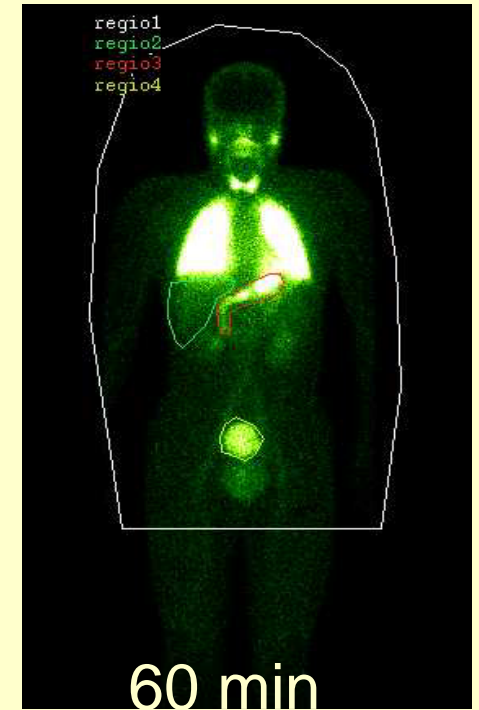
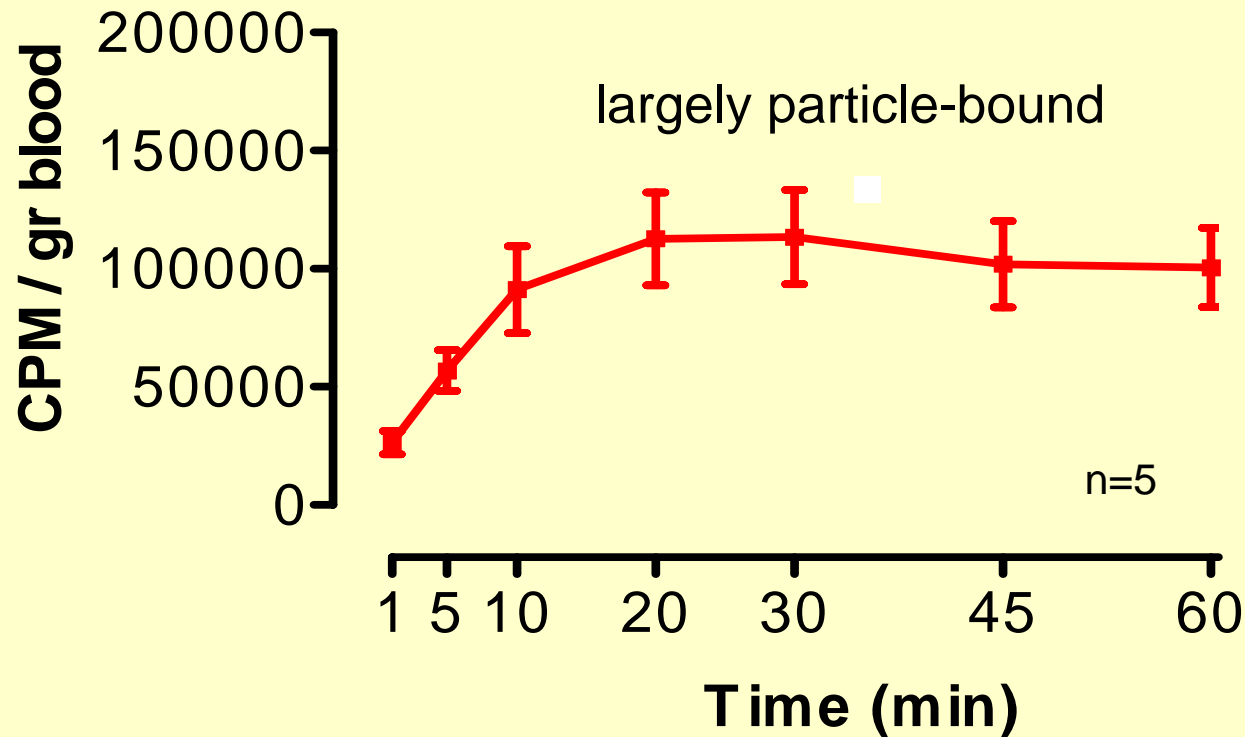
inhaled ultrafine particles ($\text{\O} < 0.1 \mu\text{m}$)

- pass into the circulation
- exert “direct” effects on cardiovascular endpoints



Humans

Inhalation of ^{99m}Tc -carbon particles (“Technegas”)



Polystyrene particles (60 nm)

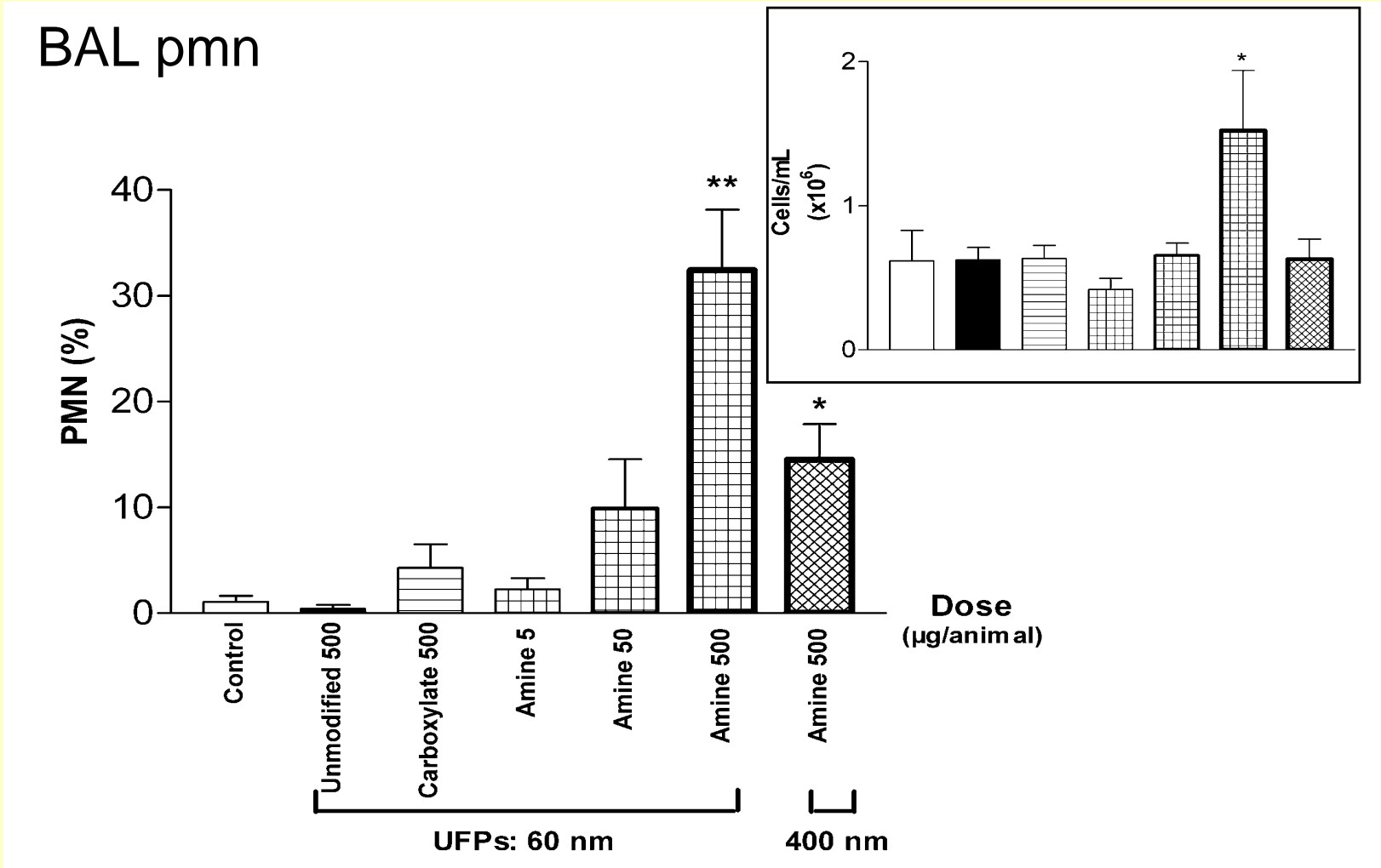
- Intravenous and intratracheal administration of ultrafine particles have an impact on thrombus formation depending on their **size** and their **surface charge**.



- ✓ Nemmar *et al.* Am. J. Respir. Crit. Care Med. 2002;166:998-1004.
- ✓ Nemmar *et al.* Toxicol. Appl. Pharmacol. 2003;186:38-45.

Polystyrene particles i.t.

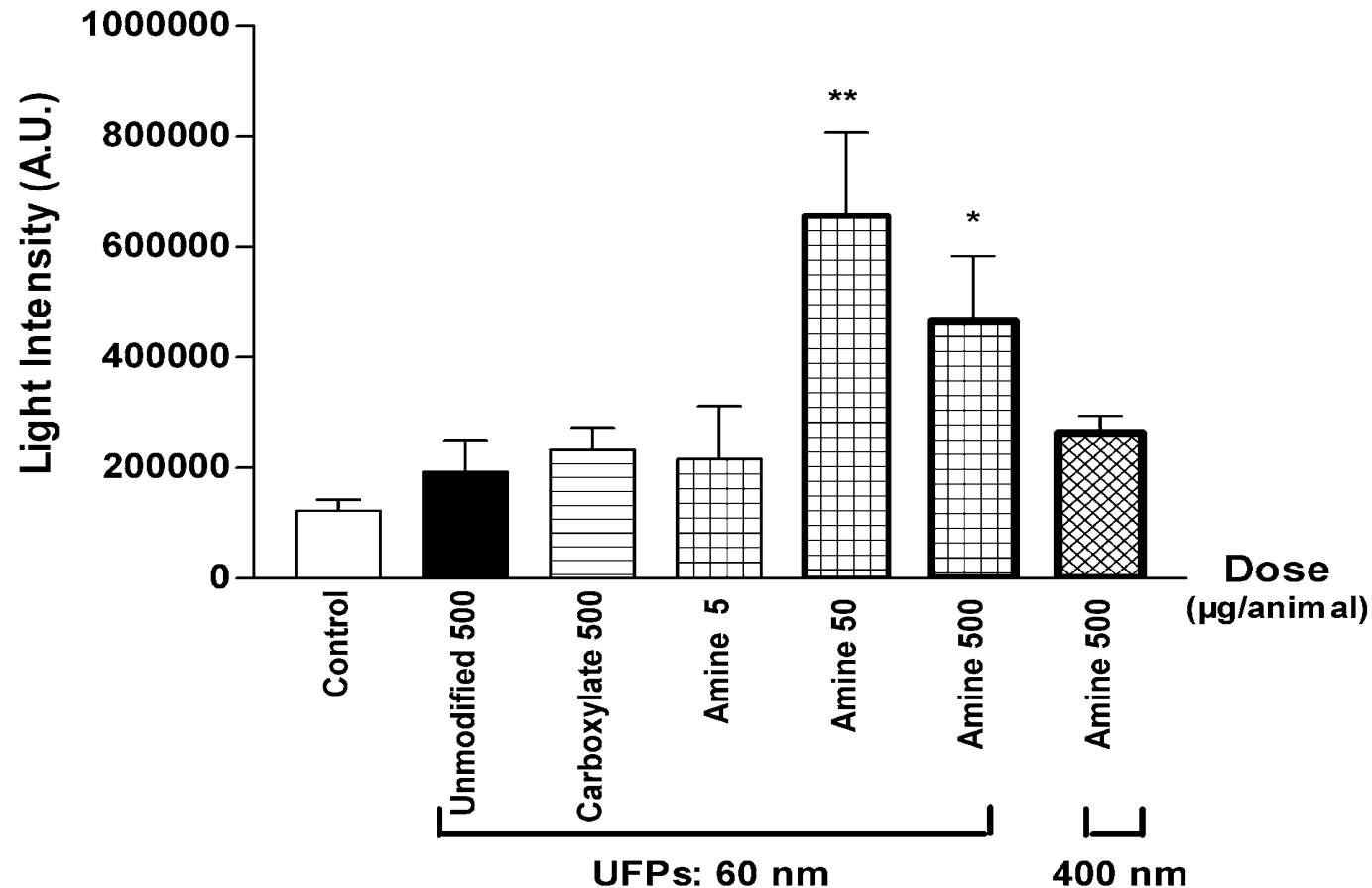
1 h



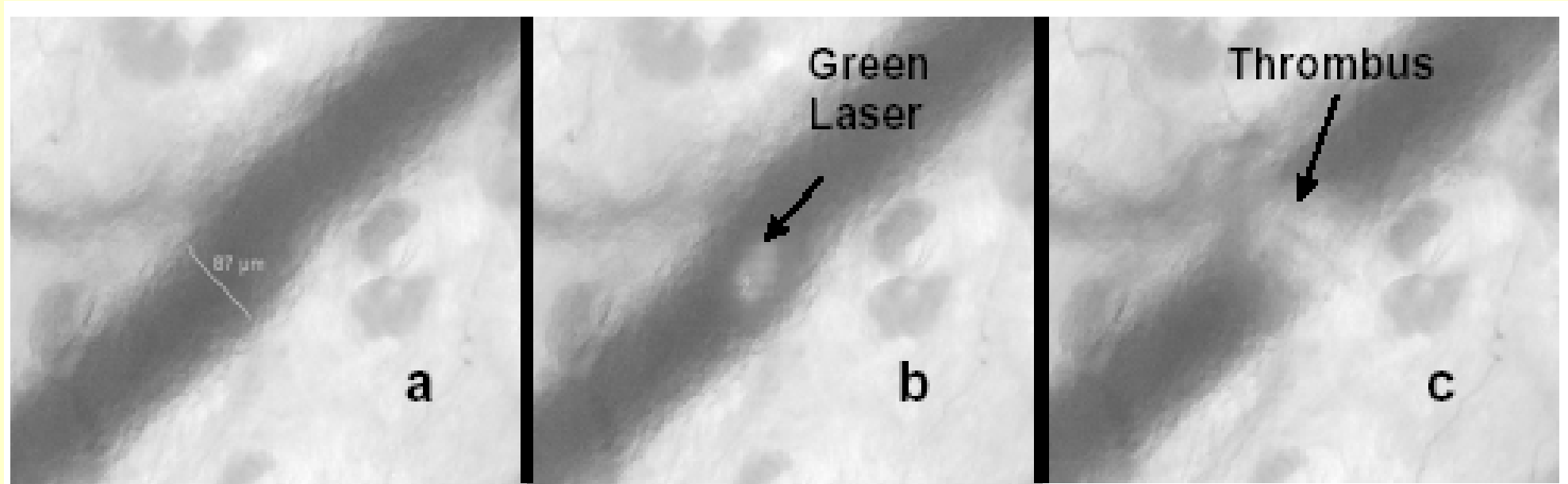
Polystyrene particles i.t.

1 h

Thrombus size in femoral vein

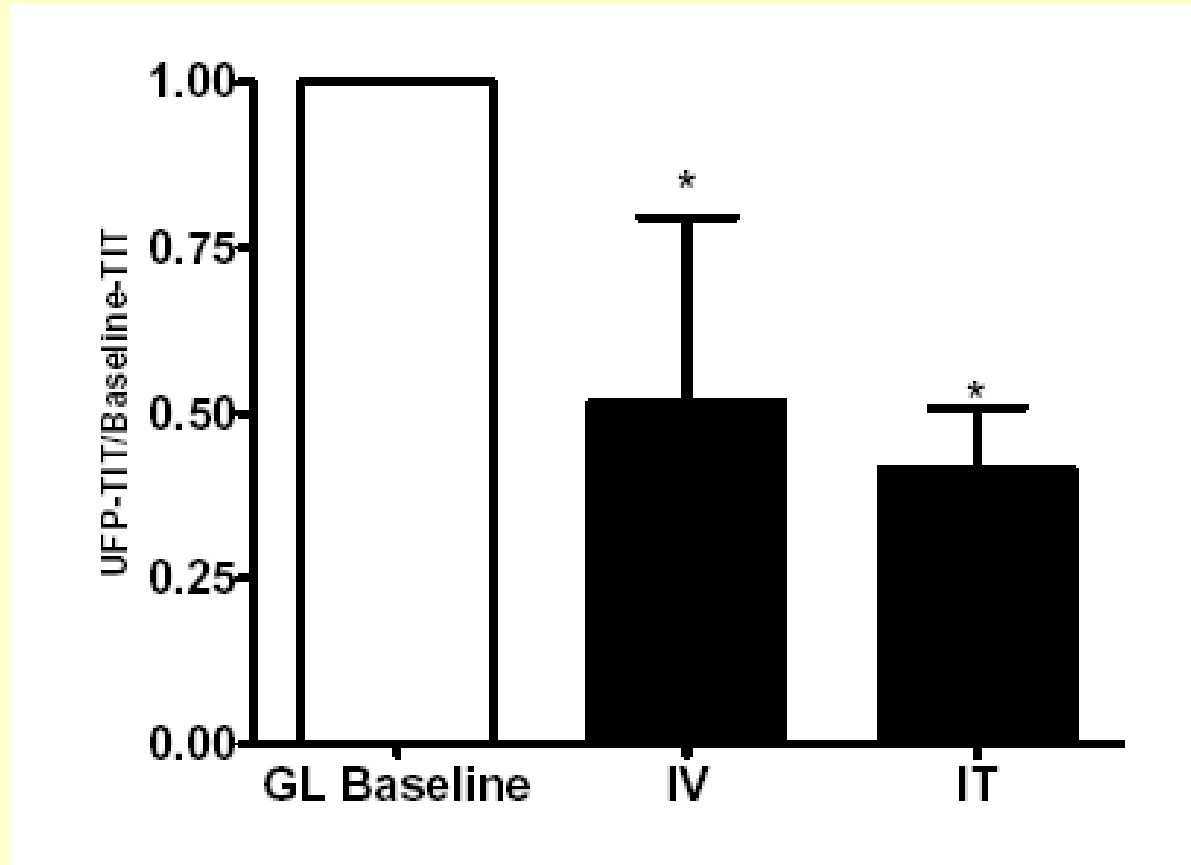


Silva VM, Corson N, Elder A, Oberdörster G. The rat ear vein model for investigating in vivo thrombogenicity of ultrafine particles (UFP). *Tox Sci*, 2005, 85, 983-9



Illumination with green laser (532 nm): Thrombus Inducing Time (TIT)
Baseline TIT = 60-240 sec
After Rose Bengal: RB-TIT = 30-120 sec

Silva VM, Corson N, Elder A, Oberdörster G. The rat ear vein model for investigating in vivo thrombogenicity of ultrafine particles (UFP). *Tox Sci*, 2005, 85, 983-9



Aminated (+) Polystyrene UFPs (60 nm) injected *iv* or *it* 10-15 min after baseline (without Rose Bengal)

Long-term effects of pollutant particles

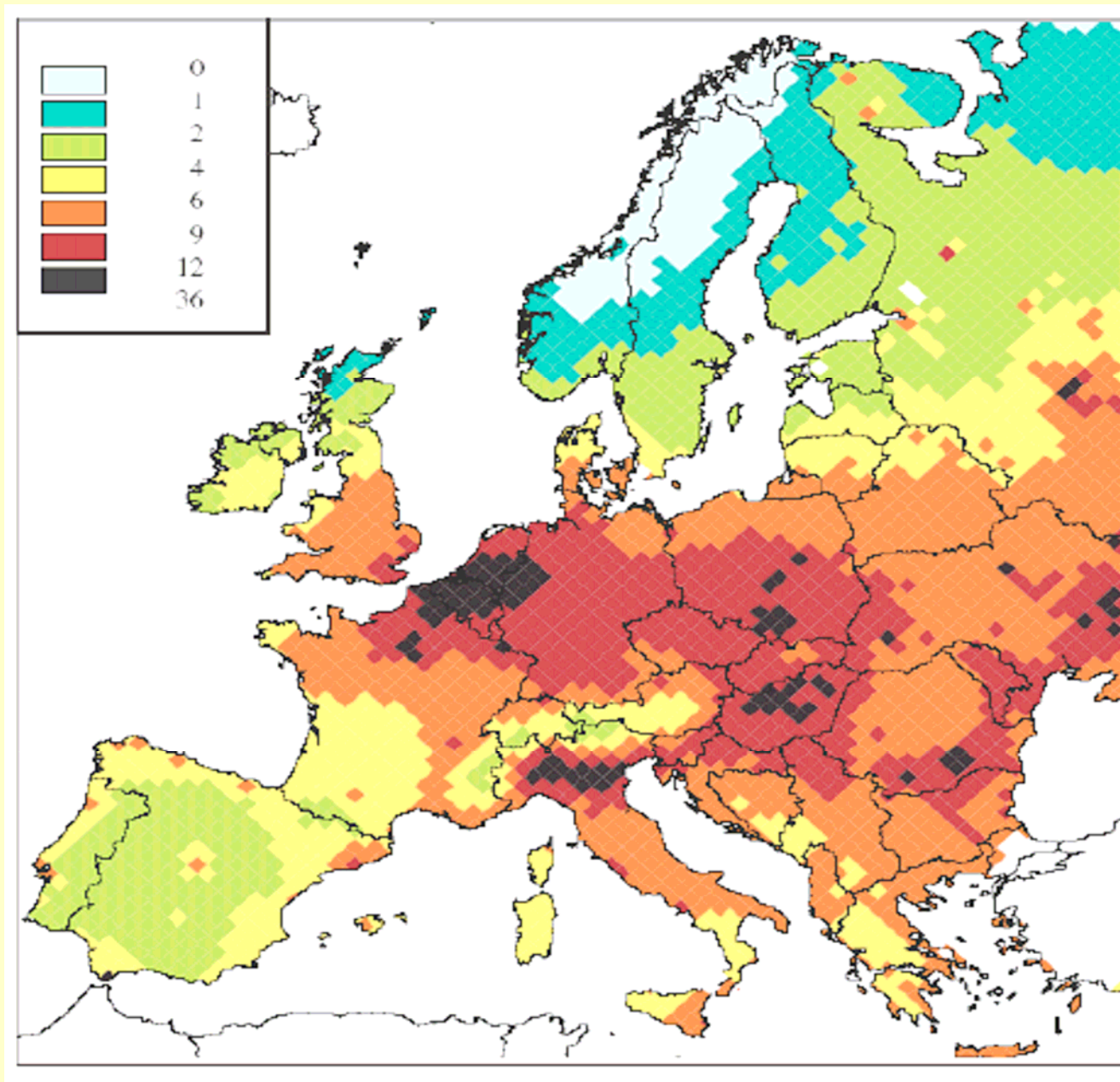


Table 3.17: Losses in statistical life expectancy attributable to the exposure to anthropogenic PM2.5 for the year 2000, the emission ceilings for 2010, the current legislation baseline in 2020 and the optimized scenarios for the three environmental ambition levels (in months)

	2000	2010 National emission ceilings	2020 Baseline, Current legislation	Optimized scenarios for 2020			2020 Maximum technically feasible reductions
				Case "A"	Case "B"	Case "C"	
Austria	7.2	5.7	5.4	4.4	4.2	4.0	3.8
Belgium	13.2	9.5	8.9	7.3	7.0	6.7	6.5
Cyprus	4.8	4.3	4.2	4.1	4.1	4.1	4.0
Czech Rep.	8.8	6.5	5.8	4.4	4.1	4.0	3.8
Denmark	5.9	4.7	4.5	3.8	3.6	3.4	3.2
Estonia	3.8	3.2	3.0	2.7	2.6	2.6	2.4
Finland	2.6	2.3	2.2	2.1	2.1	2.1	1.9
France	8.0	6.0	5.5	4.5	4.2	4.1	3.8
Germany	9.2	6.8	6.5	5.1	4.7	4.6	4.4
Greece	6.7	5.5	5.2	4.9	4.8	4.7	4.6
Hungary	10.6	8.3	7.6	5.6	5.3	5.2	4.9
Ireland	4.0	2.9	2.6	2.1	2.0	1.9	1.8
Italy	9.0	6.1	5.3	4.3	4.1	4.0	3.9
Latvia	4.5	4.0	3.8	3.4	3.3	3.2	3.0
Lithuania	6.1	5.4	5.0	4.4	4.3	4.1	3.9
Luxembourg	9.6	7.0	6.8	5.1	4.7	4.4	4.2
Malta	5.6	4.3	4.1	3.8	3.8	3.7	3.6
Netherlands	11.8	8.6	8.3	6.6	6.1	5.9	5.7
Poland	9.6	7.5	6.5	5.2	5.0	4.9	4.7
Portugal	5.1	3.2	3.2	2.8	2.5	2.4	2.2
Slovakia	9.1	7.2	6.4	4.8	4.6	4.4	4.2
Slovenia	8.2	6.5	6.0	4.8	4.6	4.4	4.1
Spain	5.2	3.5	3.2	2.8	2.7	2.6	2.5
Sweden	3.5	2.9	2.7	2.4	2.4	2.2	2.0
UK	6.9	5.0	4.6	3.5	3.2	3.1	3.0
EU-25	8.1	5.9	5.5	4.4	4.1	4.0	3.8

nieuws

hoofdpunten

dossiers

snelnieuws

magazine

weer

Flanderninfo

Flandersnews

Flandreinfo

sporza



(foto: Belga)

Het verkeer is een belangrijke bron van fijn stof, vooral diesels stoten veel erg fijn stof uit.

[terug](#)

video

- Fijn stof meten is nieuw
- "Kostprijs is toch een rem"
- "Fijn stof stopt niet aan de grens"

foto



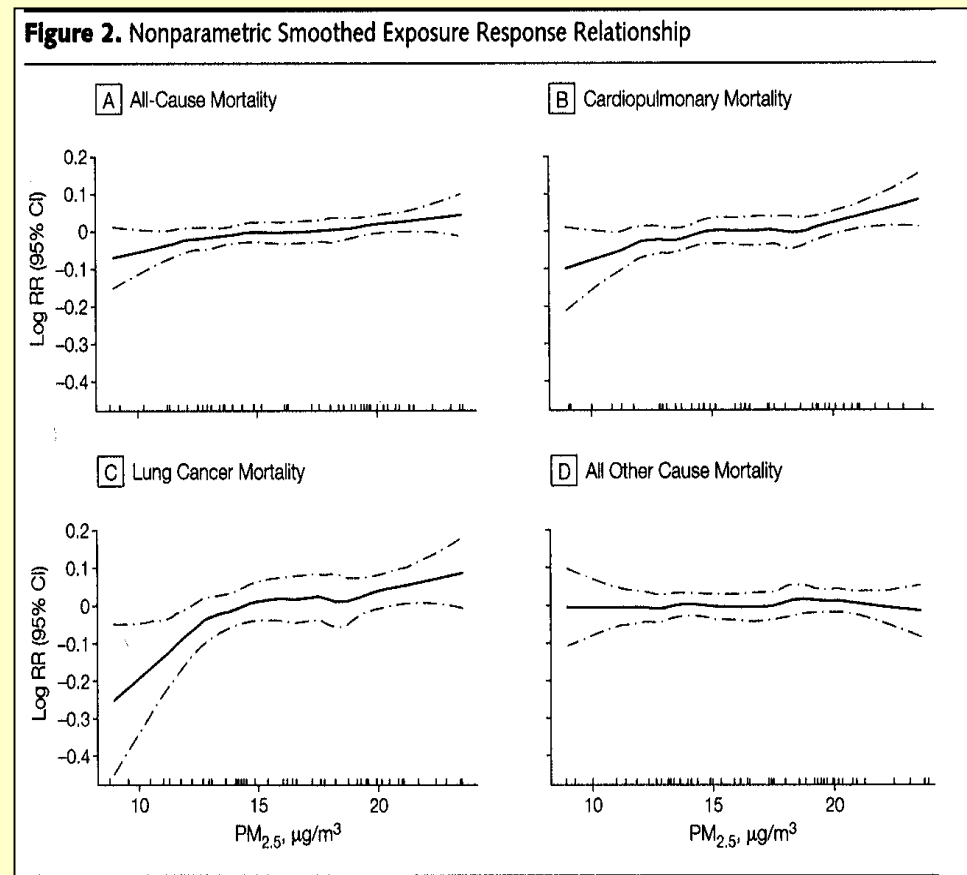
Elk jaar overlijden 13.000 Belgen door fijn stof

wo 14/09/05 - Elk jaar sterven in ons land 13.000 mensen voortijdig door het fijne stof in de lucht. Dat hebben milieuambtenaren van de Europese Commissie becijferd. Het stof veroorzaakt longaandoeningen en hart- en vaatziekten.

PM₁₀ and mortality (long term)

Pope *et al.* Lung cancer, cardio-pulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 2002, 287, 1132-41

- ACS; 1982-98; 500,000 adults; 51 U.S. metropolitan areas
 - average adjusted relative risk per 10 $\mu\text{g}/\text{m}^3$ PM_{2.5}
 - all-cause: 1.06 (1.02-1.11)
 - cardiopulmonary: 1.09 (1.03-1.16)
 - lung cancer: 1.14 (1.04-1.23)
 - all other causes: 1.01 (0.95-1.06)
- controlling for age, sex, race, smoking, education, marital status, BMI, alcohol, occupation, diet
- RR for smoking 2.58, 2.89, 14.80



PM₁₀ and mortality (long term)

Pope *et al.* Cardiovascular mortality and long-term exposure to particulate air pollution. Epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004, 109, 71-77
[+ Editorial p.5-7]

- ACS; 1982-98; 500,000 adults; 51 U.S. metropolitan areas
- average adjusted relative risk per 10 µg/m³ PM_{2.5}
 - All C-V disease + diabetes (45%): 1.12 (1.08-1.15)
 - Ischemic heart disease: 1.18 (1.14-1.23)
 - Dysrhythmias, heart failure, cardiac arrest: 1.13 (1.05-1.21)
 - ...
 - Diseases of respiratory system (8%): 0.92 (0.86-0.98)
 - COPD: 0.84 (0.77-0.93)
 - Pneumonia & influenza: 1.07 (0.95-1.20)

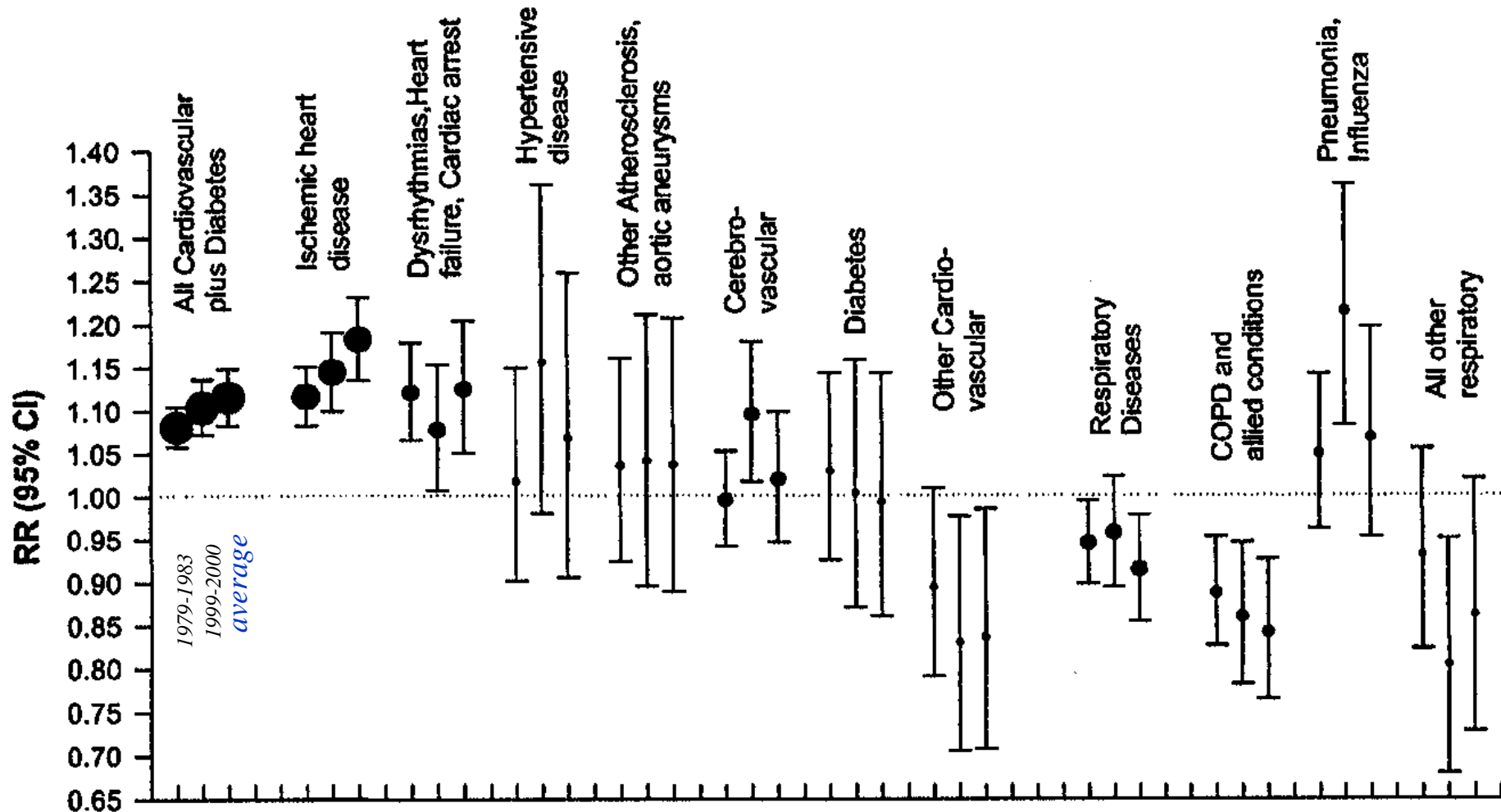
PM₁₀ and mortality (long term)

Pope *et al.* Cardiovascular mortality and long-term exposure to particulate air pollution. Epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004, 109, 71-77
[+ Editorial p.5-7]

- ACS; 1982-98; 500,000 adults; 51 U.S. metropolitan areas
- average adjusted relative risk per 10 µg/m³ PM_{2.5} smoking
 - All C-V disease + diabetes (45%): 1.12 (1.08-1.15) 1.94 (1.90-1.99)
 - Ischemic heart disease: 1.18 (1.14-1.23) 2.03 (1.96-2.10)
 - Dysrhythmias, heart failure, cardiac arrest: 1.13 (1.05-1.21) 1.72 (1.62-1.83)
 - ...
 - Diseases of respiratory system (8%): 0.92 (0.86-0.98) 3.88 (3.66-4.11)
 - COPD: 0.84 (0.77-0.93) 9.85 (8.95-10.84)
 - Pneumonia & influenza: 1.07 (0.95-1.20) 1.89 (1.70-2.09)

Pope *et al.* Circulation, 2004, 109, 71-77

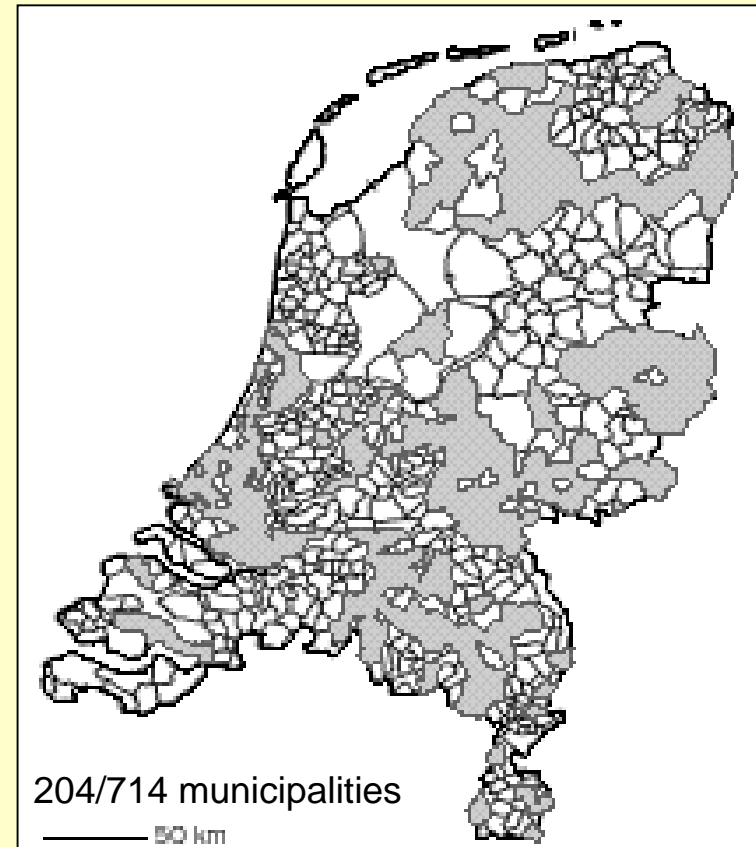
Adjusted RR for mortality associated with $10 \mu\text{g}/\text{m}^3$ change in $\text{PM}_{2.5}$



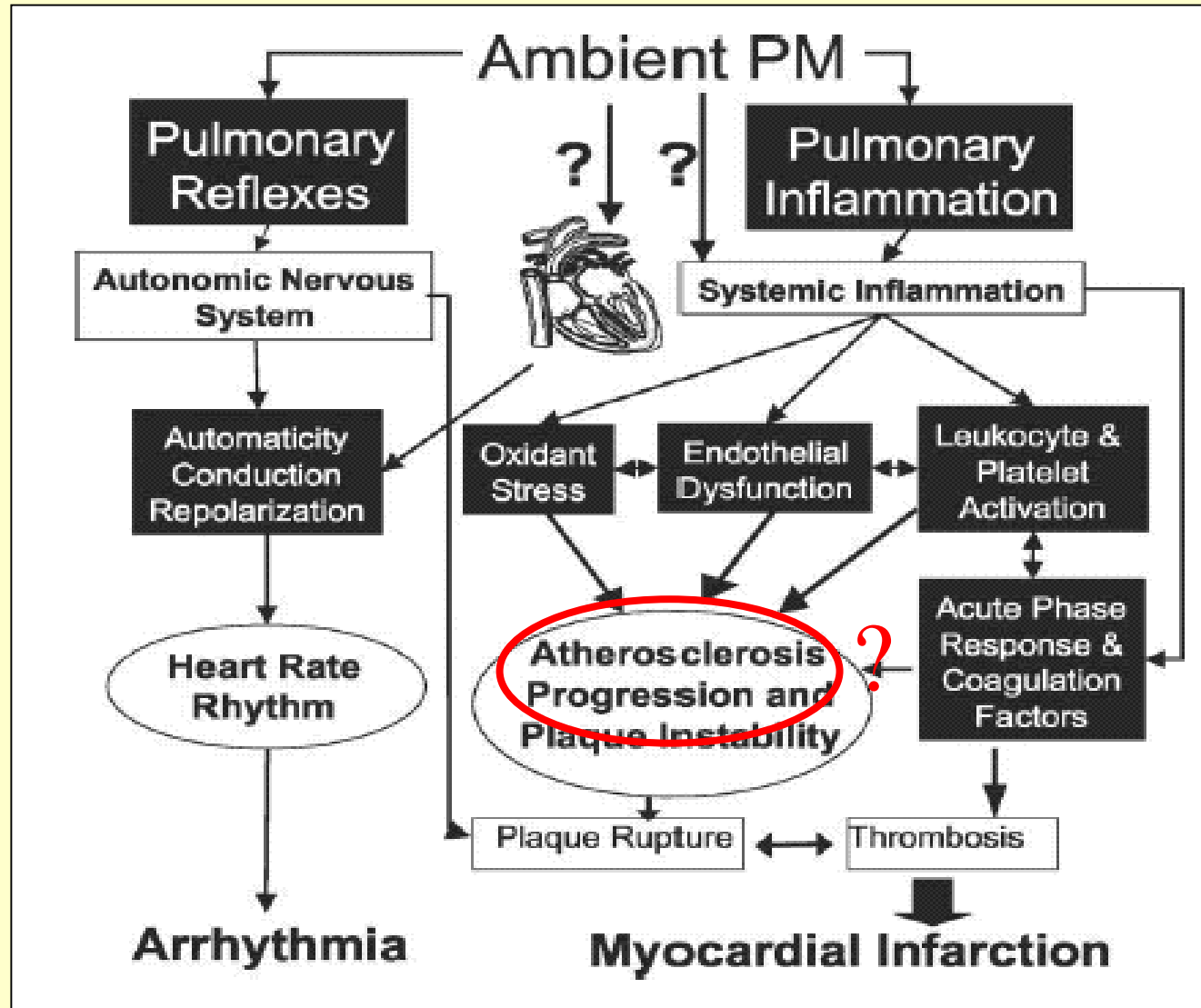
PM₁₀ and mortality (long term)

Hoek *et al.* Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet* 2002, 360, 1203-9

- NCLS: 1986-94; n = 4,492 (55-69 y); 489 †
- *estimation* of long-term pollution (BS & NO₂): regional + urban background + local
- exposed to traffic = home (GIS) :
 - < 100 m of freeway (n=132)
 - < 50 m of major urban road (n=77)
- adj.RR of cardiopulmonary death
 - background BS (/10 µg/m³): 1.34 (0.68-2.64)
 - living near major road: **1.95** (1.09-3.51)adjusted for age, sex, education, BMI, occupation, active & passive smoking, neighbourhood SES



Brook RD *et al.* Air pollution and cardiovascular disease. A statement for health-care professionals from the expert panel on population and prevention science of the American Heart Association. *Circulation* 2004 (June 1); 109: 2655-71



Ambient Air Pollution and Atherosclerosis in Los Angeles

Nino Künzli, Michael Jerrett, Wendy J. Mack, Bernardo Beckerman, Laurie LaBree, Frank Gilliland, Duncan Thomas, John Peters, and Howard N. Hodis

Divisions of Environmental Health and Biostatistics, Department of Preventive Medicine, and Atherosclerosis Research Unit, Division of Cardiovascular Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

Associations have been found between long-term exposure to ambient air pollution and cardiovascular morbidity and mortality. The contribution of air pollution to atherosclerosis that underlies many cardiovascular diseases has not been investigated. Animal data suggest that ambient particulate matter (PM) may contribute to atherogenesis. We used data on 798 participants from two clinical trials to investigate the association between atherosclerosis and long-term exposure to ambient PM up to 2.5 μm in aerodynamic diameter ($\text{PM}_{2.5}$). Baseline data included assessment of the carotid intima-media thickness (CIMT), a measure of subclinical atherosclerosis. We geocoded subjects' residential areas to assign annual mean concentrations of ambient $\text{PM}_{2.5}$. Exposure values were assigned from a $\text{PM}_{2.5}$ surface derived from a geostatistical model. Individually assigned annual mean $\text{PM}_{2.5}$ concentrations ranged from 5.2 to 26.9 $\mu\text{g}/\text{m}^3$ (mean, 20.3). For a cross-sectional exposure contrast of 10 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$, CIMT increased by 5.9% (95% confidence interval, 1–11%). Adjustment for age reduced the coefficients, but further adjustment for covariates indicated robust estimates in the range of 3.9–4.3% (p -values, 0.05–0.1). Among older subjects (≥ 60 years of age), women, never smokers, and those reporting lipid-lowering treatment at baseline, the associations of $\text{PM}_{2.5}$ and CIMT were larger with the strongest associations in women ≥ 60 years of age (15.7%, 5.7–26.6%). These results represent the first epidemiologic evidence of an association between atherosclerosis and ambient air pollution. Given the leading role of cardiovascular disease as a cause of death and the large populations exposed to ambient $\text{PM}_{2.5}$, these findings may be important and need further confirmation. *Key words:* air pollution, atherosclerosis, particulate matter. *Environ Health Perspect* 113:201–206 (2005). doi:10.1289/ehp.7523 available via <http://dx.doi.org/> [Online 22 November 2004]

Carotid intima-media thickness CIMT

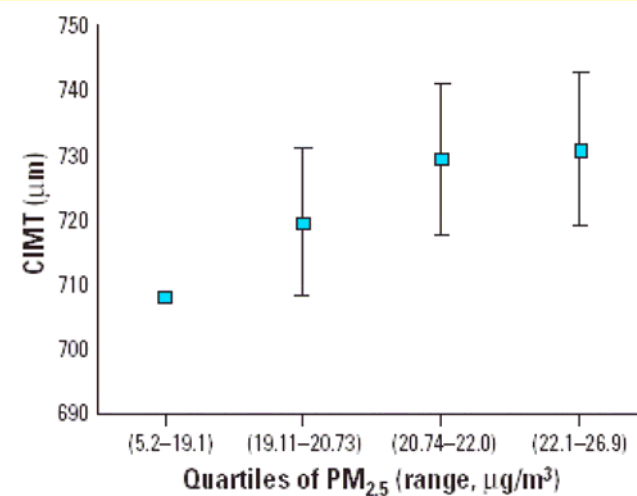


Figure 2. Mean CIMT ± 1 SE among quartiles of the $\text{PM}_{2.5}$ distribution. The y-axis shows mean CIMT levels at the population average of the adjustment covariates (age, sex, education, and income). The first quartile is the reference group.

PM and atherosclerosis

- Pro-inflammatory effects of PM
- Few experimental data
 - Sakai *et al.* Effect of relocating to areas of reduced atmospheric particulate matter levels on the human circulating leukocyte count. *J Appl Physiol* 2004, 97, 1774-80
 - Suwa *et al.* Particulate air pollution induces progression of atherosclerosis. *J Am Coll Cardiol* 2002, 39, 935-42

PM and inflammation

- Sakai *et al.* Effect of relocating to areas of reduced atmospheric particulate matter levels on the human circulating leukocyte count. *J Appl Physiol* 2004, 97, 1774-80
 - Japanese Antarctic Research Expedition 1999-2001
 - 39 men, 24-57 y, 16 smokers
 - 1999-2001: 516 days, 336 days in Antarctica
 - PM number densities: ↓↓ to < 1% of levels in Japan
 - Blood: total WBC ↓, PMN ↓, monocytes ↓

PM and atherosclerosis

- Suwa *et al.* Particulate air pollution induces progression of atherosclerosis. *J Am Coll Cardiol* 2002, 39, 935-42
 - Watanabe heritable hyperlipidemic rabbits
 - R/ Ottawa PM₁₀ (5 mg by intrapharyngeal instillation) 2x/week, 4 weeks
 - Blood: ↑ PMN (bone marrow stimulation)
 - Coronary (and aortic) atherosclerotic lesions: ↑
+ ↑ plaque cell turnover

Thank you for your attention



ben.nemery@med.kuleuven.be