Collège National des Cardiologues des Hôpitaux

Cardiovascular effects of Air Pollution

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Disclosure of conflicts of interest:

No competing financial interests.

Member of *Strasbourgrespire*, a non-profit, non-governmental medical organization, helping to inform physicians and public authorities about the health impacts of air pollution

EUROPA ORGANISATION
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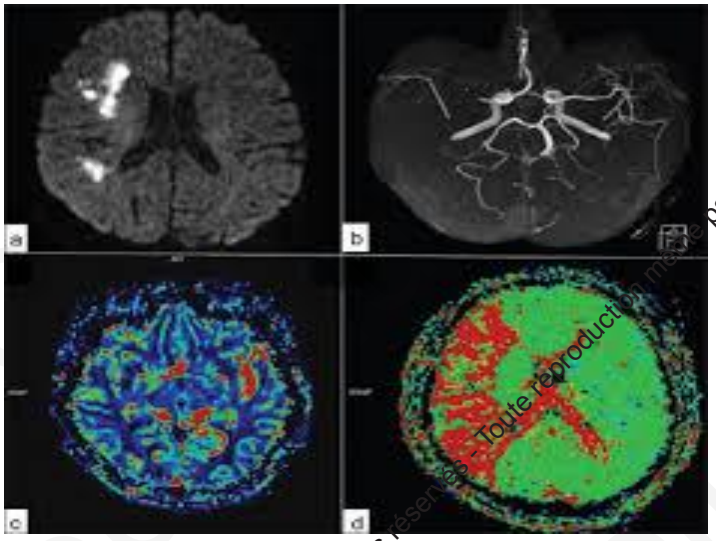
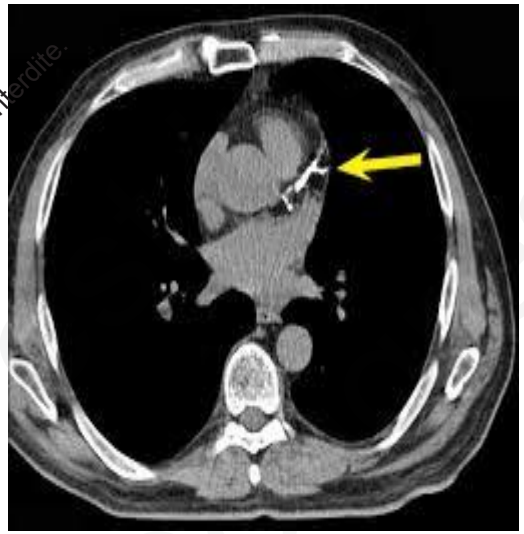
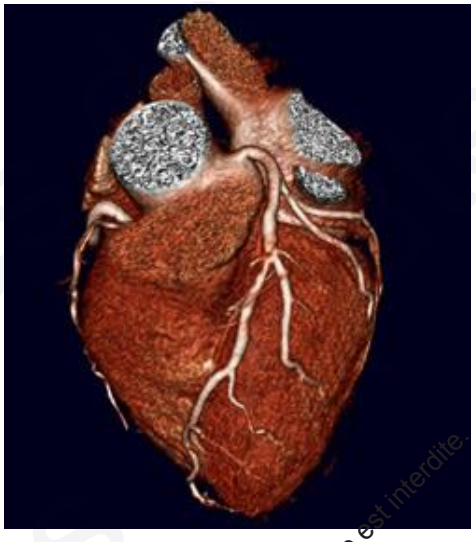


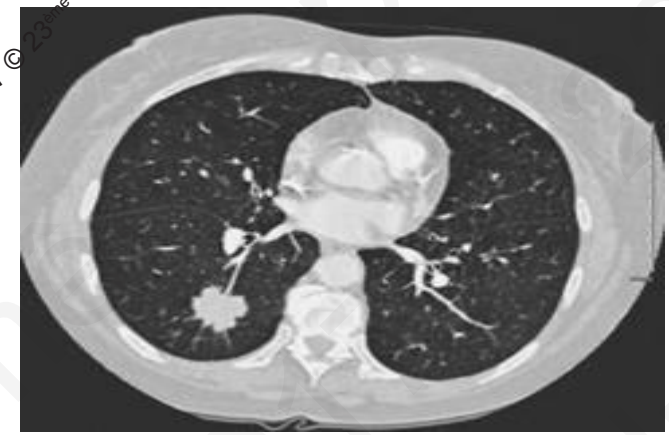
Stroke



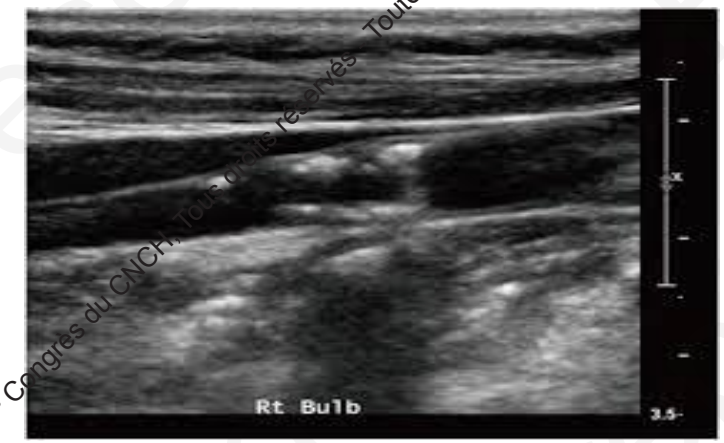


Coronary artery disease

What do Radiologists have to do with air pollution?



Lung cancer (adenocarcinoma)



Carotid atherosclerosis

(Outdoor) Air pollution: definition

Pollution = Particles + Gas

Diameter :
- PM 10 : < 10 µm
- **PM 2,5 : < 2,5 µm**
- **UFP : < 0,1 µm**

NO – **NO_2**
O_3
SO_2
CO, VOCs

and…**Agriculture**, Natural sources

Air pollution : cardiovascular effects

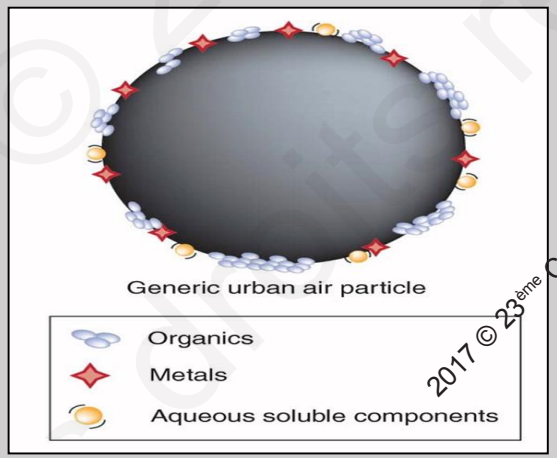
Particulate Matter (PM)

48 000 deaths/year/France

Different toxicity of PM depending on their **size** and **composition**:

1/ PM from **Combustion** sources :Traffic (**diesel**), heating (**wood**, fossil fuels) :

- PM 2,5, UFP > PM 10 (90% of traffic related-PM = UFP)
- Carbon based, contain toxic and carcinogenic organic chemicals (PAH) and reactive metals on their surface



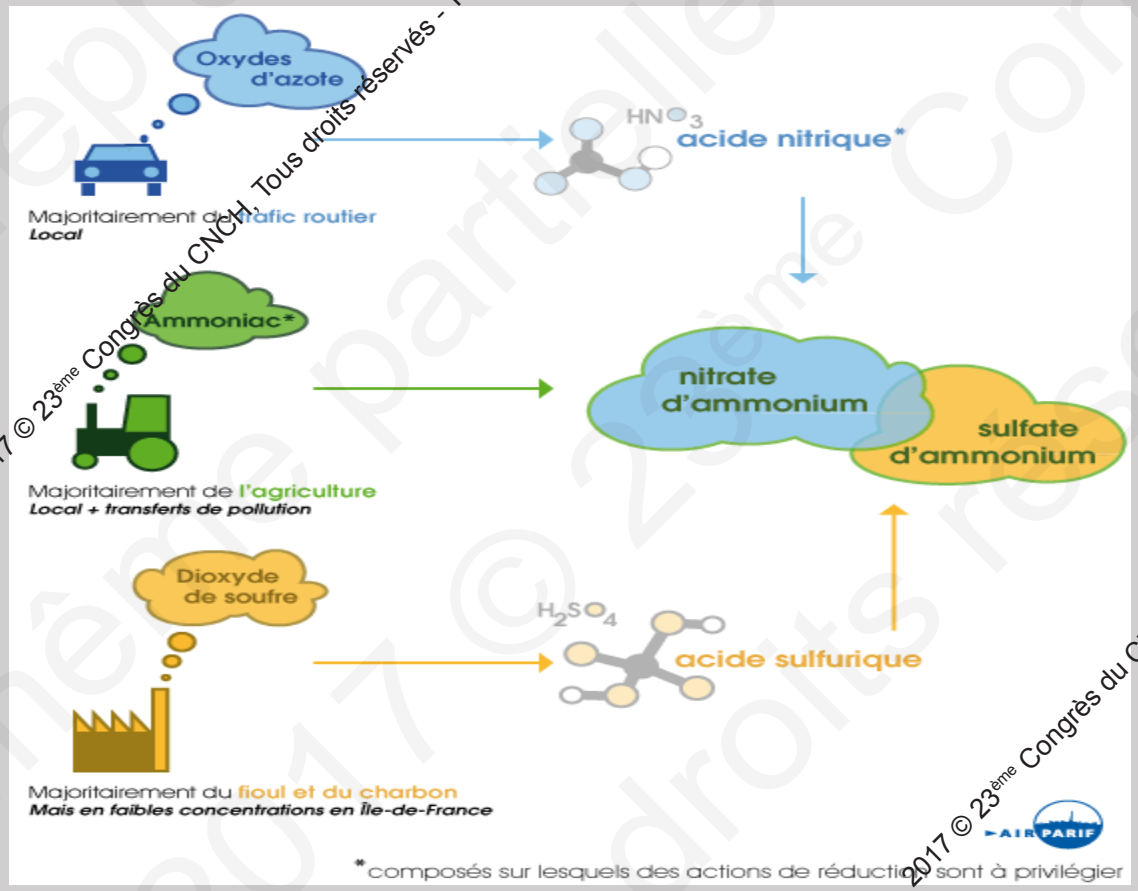
Miller et al. *Future Cardiology.* July 2012

Air pollution : cardiovascular effects

2/ Inorganic PM (agriculture, desert dust,..)

Example : Agriculture derived-PM = secondary particles :

atmospheric photochemical reactions between gaz: (NOx + NH_3 + SO2) → particle (sulfate d'ammonium)



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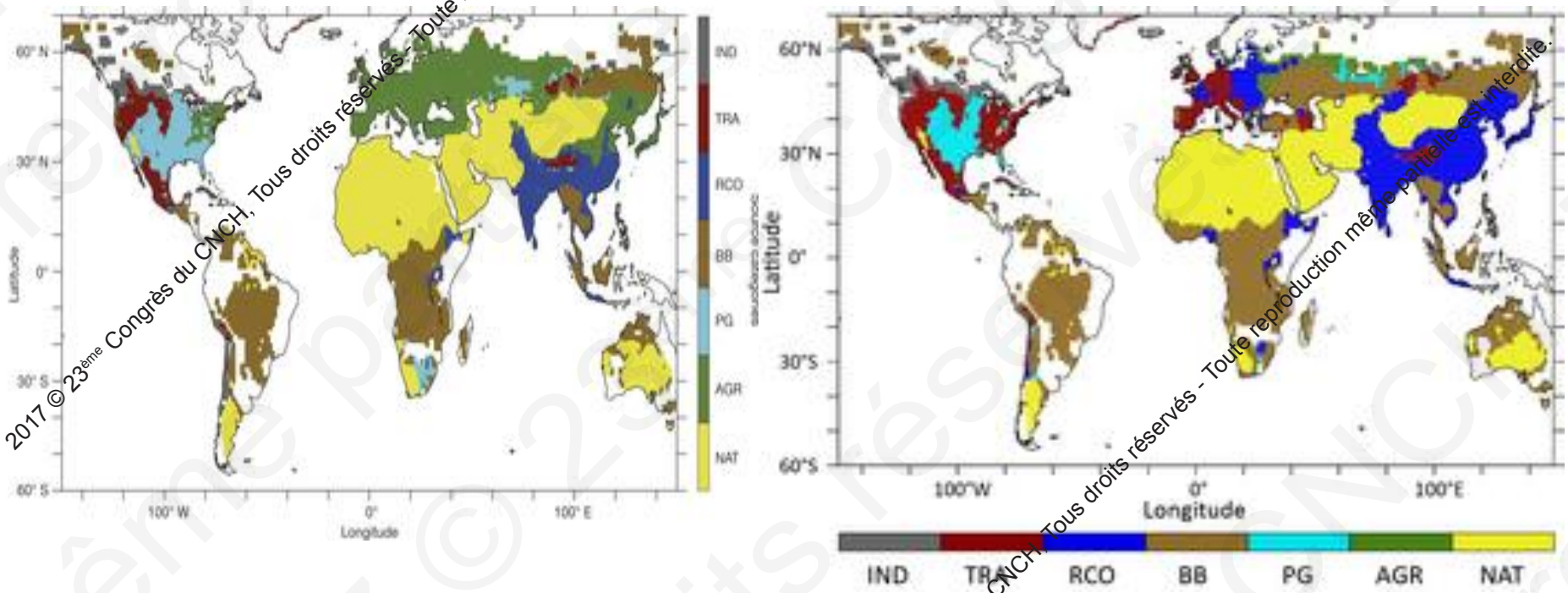
Atkinson et al. *BMJ Open*. 2016 Feb 23;6(2

PM impact on mortality :

Lelieveld et *al*. *Nature 2015*



Source categories responsible for the largest impact on mortality linked to outdoor air pollution in 2010 from a sensitivity calculation with carbonaceous aerosol having a **five times larger impact** than inorganic and crustal compounds.

Air pollution : cardiovascular effects

GASEOUS POLLUTANTS

NOx (urban area: 60% NOx < diesel) : 7700 deaths/year/France

- NO2 direct toxicity
- contribute to **secondary particles formation** (interaction NOx + NH_3)
- precursor of **O_3**

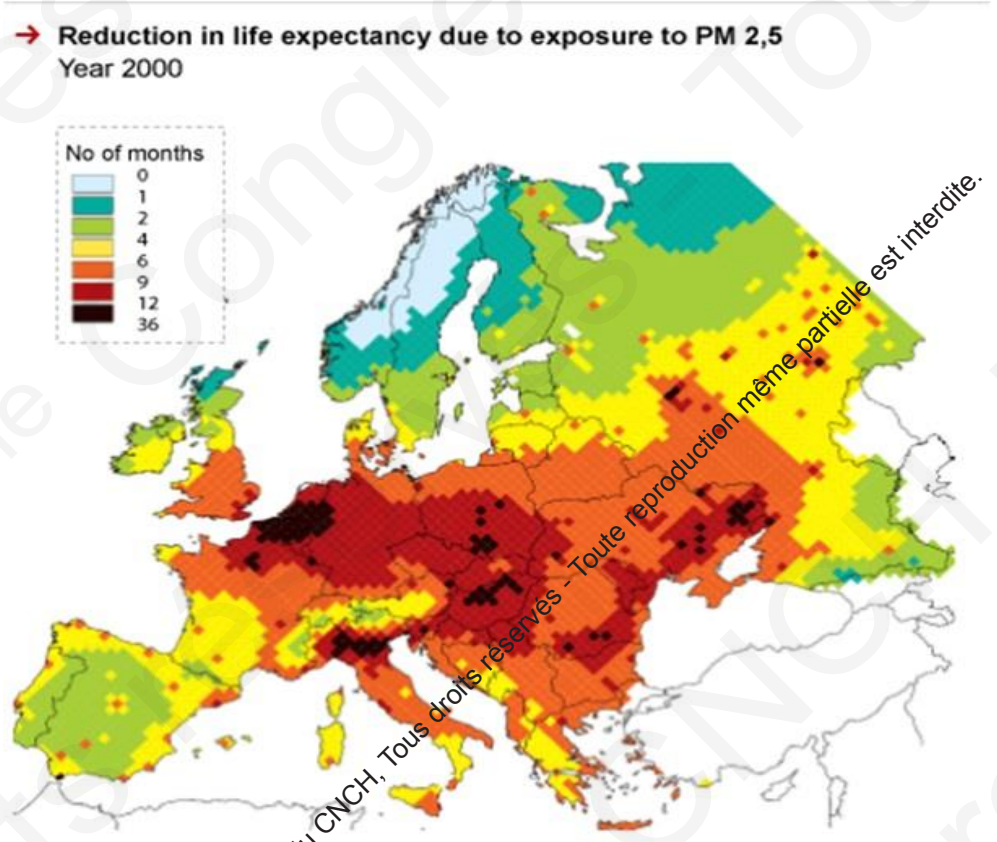
Ozone (O3): secondary pollutant formed by interaction between gaseous precursors (NOx, VOCs) and sunlight (1500 deaths/year/France)

Atkinson et al. *BMJ Open*. 2016 Feb 23;6(2)

Air pollution: health effects

"Urban outdoor air pollution is estimated to cause 3,3 million deaths worldwide per year."

Air quality and health
Fact sheet N°313 W.H.O.
September 2005 (updated 2011)



Markus Amann , Baseline Scenarios for the Clean Air for Europe (CAFE) Programme, International Institute for Applied Systems Analysis, Feb 2005

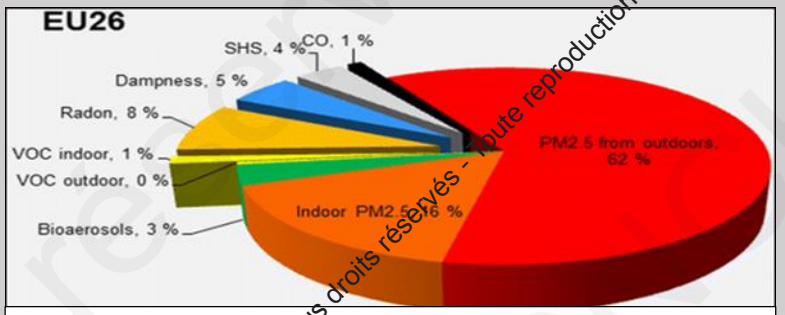
Air pollution : cardiovascular effects

In 2010, outdoor air pollution lead to 3.3 million premature deaths /year worldwide, mostly by PM2.5. The **main causes (80%) are cerebrovascular diseases and ischemic disease.**

Lelieveld et al. *Nature*. 2015 Sep 17;525(7569):367-71

Indoor air pollution : 3.54 million deaths per year : 60 % cerebrovascular disease and ischemic heart disease. WHO. *Household air pollution and health*. Feb 2016

60 % of the total annual **burden of disease** of **indoor** exposures caused by **$PM_{2.5}$** originating **from outdoor** air penetrating indoor



Asikainen. *Environ Health*. 2016 Mar 8;15

Air pollution : cardiovascular effects

Extensive review of medical publications (PubMed) :

1/ Epidemiological studies:

Long-term exposure : yearly-based variations	Short-term exposure: hourly or daily variations example : pollution peak

- Cardiovascular mortality
- Coronary artery ischemic disease
- Heart Failure-Arrhythmia
- Stroke, HTA

Exposure based on background **pollutants concentration** at residential address or **traffic exposure** (distance from traffic at home address , time spent in traffic..)

2) Clinical studies :

Interventional controlled studies : performed in humans using an exposition chamber with controlled exposures of air pollutants.

Bourdrel et al. *Arch Cardiovasc Dis*. 2017 Nov;110(11)

Long-term exposure / C.V mortality

<u>Long-term</u> exposure to PM :

Meta-analysis 15 studies : follow up: 5-20 years, adjusted for potential confounders or others C.V risk factors.

↗ 10 µg/m^3 PM 2.5: ↗ **11% cardiovascular mortality** (CI 95% 5-16%)

Hoek et al. *Environ Health Perspect* 2013 12: 43

<u>Long-term</u> exposure to NO2 : 2014 Meta-analysis: follow up : 1–12 years

↗ 10 µg/m^3 in annual NO2 : ↗ 13% cardiovascular mortality (95% CI 1.09–1.18)

Faustini et al. *Eur Respir J* 2014;44:744–753

Long-term exposure to **03** and **SO2** : respiratory ++ , impact on c.v mortality not clearly established.

Atkinson et al. *BMJ Open*. 2016 Feb 23;6(2)

Long-term exposure to Traffic / C.V mortality

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

2014 Oct 21;130(17)

Roadway proximity and the risk of SCD in women

Jaime E. Hart, S.E. Chiuve; F. Laden, C.M. Albert

Prospective study 100 000 middle-aged and older women:

Living within 50 meters of a major roadway ↗ risk of 38 % of sudden cardiac death as compared to women living > 500m.

Even after controlling for potential confounders and other cardiovascular risk factors (HR=1.38; 95%CI: 1.04-1.82).

Long-term exposure/ **Coronary artery disease**

BMJ
British Medical Journal

2014 Jan 21;348

Long term exposure to ambient air pollution and incidence of acute coronary events: the ESCAPE Project

Cesaroni et al.

European prospective study, > 100 000 participants from 11 cohorts :

↗ **10 µg/m3 PM10 :** increased risks of myocardial infarction to **12 %**

↗ **5 µg/m3 PM2.5** : increased risks of myocardial infarction to **13 %** .

Adjustment for confounding (marital and socioeconomic status, diabetes, smoking, BMI, HTA).

Positive associations observed **below** the current recommended annual **European limit** for PM.;

Long-term exposure to traffic / Coronary artery disease

Epidemiology 2013 Sep;24(5):734-42

Changes in Traffic Exposure and the Risk of Incident Myocardial Infarction

Jaime E. Hart, **Eric B. Rimm**, **Kathryn M. Rexrode** and **Francine Laden**

1986-2006, 84 562 women :

- Living close to a roadway (50-150m) : ↗ **11% MI** (95%CI: 1.01 – 1.21) compared with women far from a roadway.

- Adjustment for BMI, physical activity, healthy diet score, alcohol consumption, hypercholesterolemia, high blood pressure, diabetes, family history of MI, smoking status and pack-years, and overall mental health status

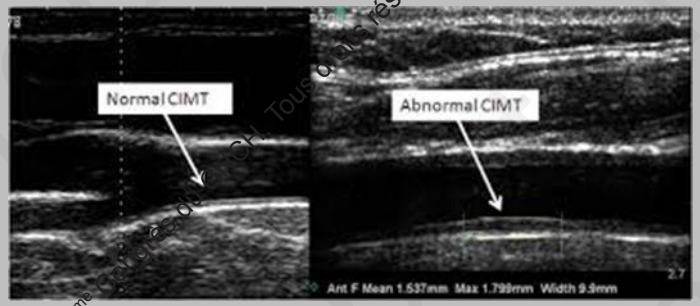
Long-term exposure / Coronary artery disease

Atherosclerosis: using carotid intima-media thickness (CIMT) or coronary artery calcification (CAC) as markers of atherosclerosis :

- Long term exposure to PM2.5 and NOx increases coronary calcification

Kaufman et al. *Lancet.* 2016 Aug 13;388(10045):696-704

Perez et al. *Health Perspect*. 2015 Jun;123(6):597-605

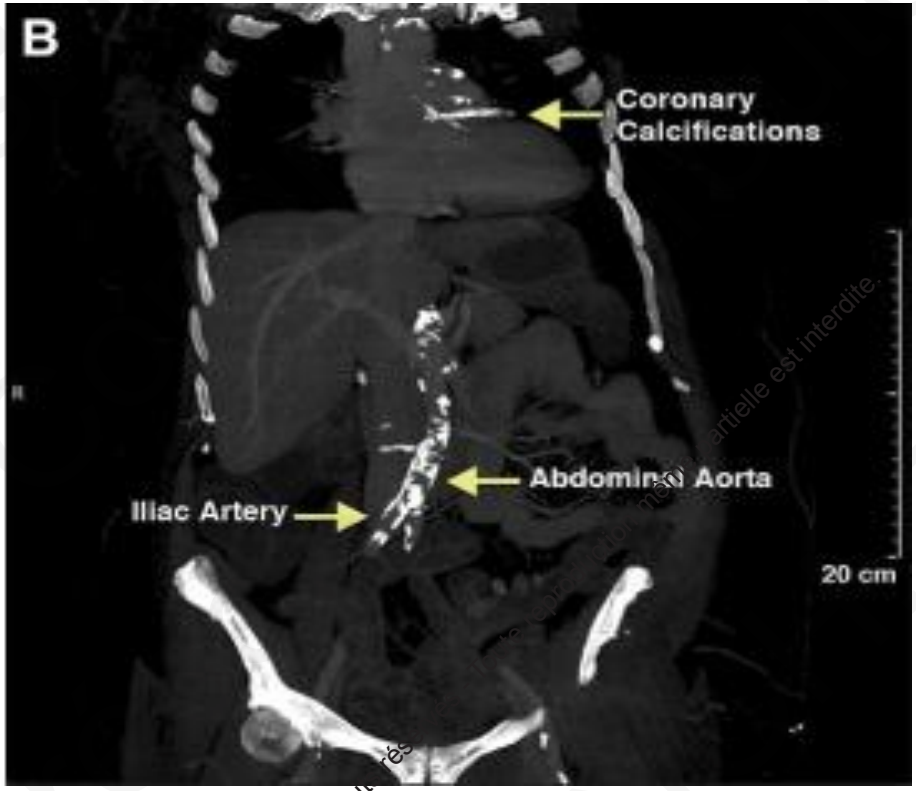


- Long term exposure to traffic :

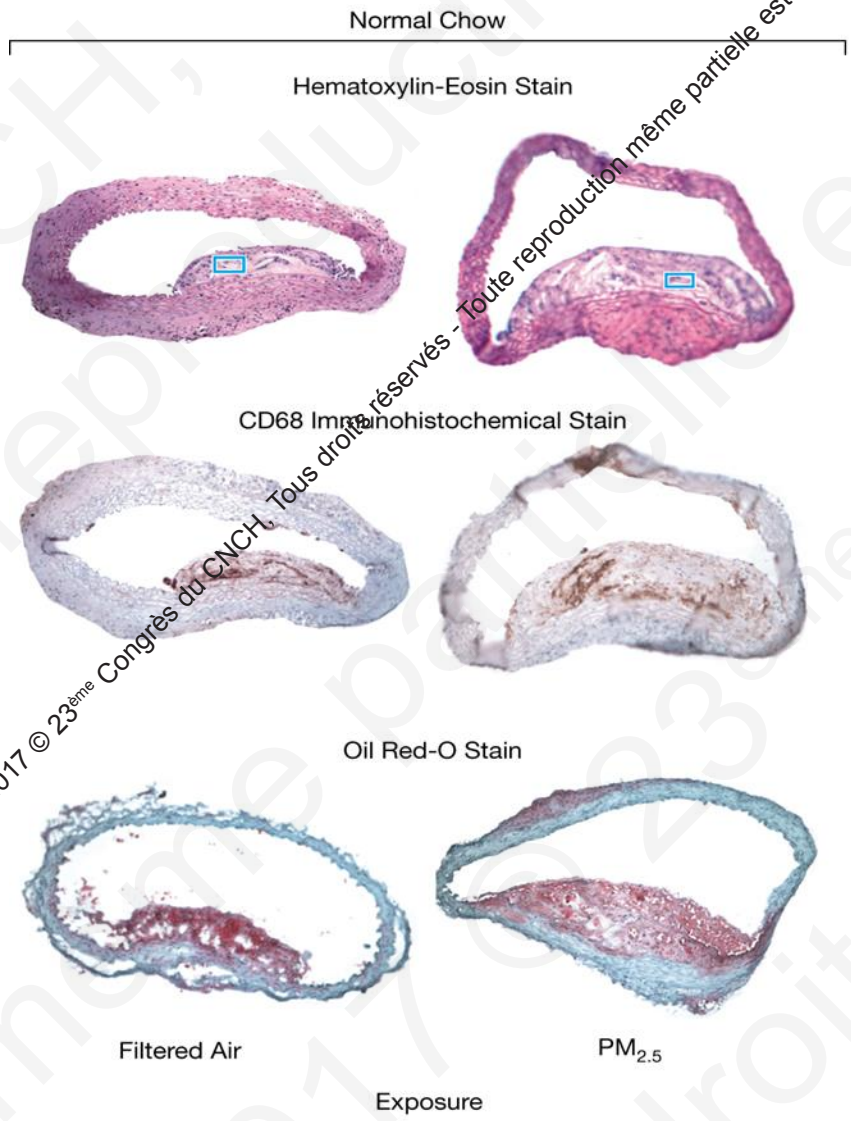
Living within **50 m** from a major road, ↗ **63 %** risk for a high CAC score compared with participants living more than **200 m away** from a major road.

Hoffmann et al.*Circulation.* 2007 Jul 31;116(5):489-96

Long-term exposure : Coronary artery disease



Long-term exposure / Coronary artery disease



Long-term Air Pollution Exposure and Acceleration of Atherosclerosis.

JAMA 2005. 294: 3003-3010

Short-term exposure / Coronary artery disease

<u>Short</u>-Term exposure – Trigger of acute myocardial infarction:

10 µg/m3 increase in **PM2.5** ⇒ **4.5% increase in risk of acute coronary event**.
Strongest associations with same day or average of previous 2 days exposure.

Pope et al. *Circulation* 2006;114:2443-2448
Zhang et al. *J Epidemiol* 2016;26(10):538-545

Short-term increase in **NO2** and **O3** also associated with myocardial infarction

Milojevic et al. *Heart*. 2014 Jul;100(14):1093-8
Argacha et al. *Int J Cardiol.* 2016 Nov 15;223:300-305

Ruidavets, Ferrières et al. *Circulation*. 2005 Feb 8;111

Short-term exposure to Traffic / Coronary artery disease

The NEW ENGLAND JOURNAL of MEDICINE

2004 351:1721-1730

Exposure to Traffic and the Onset of Myocardial Infarction

Annette Peters, Ph.D., Stephanie von Klot, M.P.H., Margit Heier, M.D.,
Ines Trentinaglia, B.S., Allmut Hörmann, M.S., H. Erich Wichmann, M.D., Ph.D., and Hannelore Löwel, M.D.,
for the Cooperative Health Research in the Region of Augsburg Study Group

Germany – 700 Acute myocardial Infarction ⇔ Time spent in traffic (bus, bike, car) before the event :

Risk of myocardial infarction : **x 3** (OR : 2.92; 95 CI, 2.22 to 3.83) for an exposure to traffic one hour before.

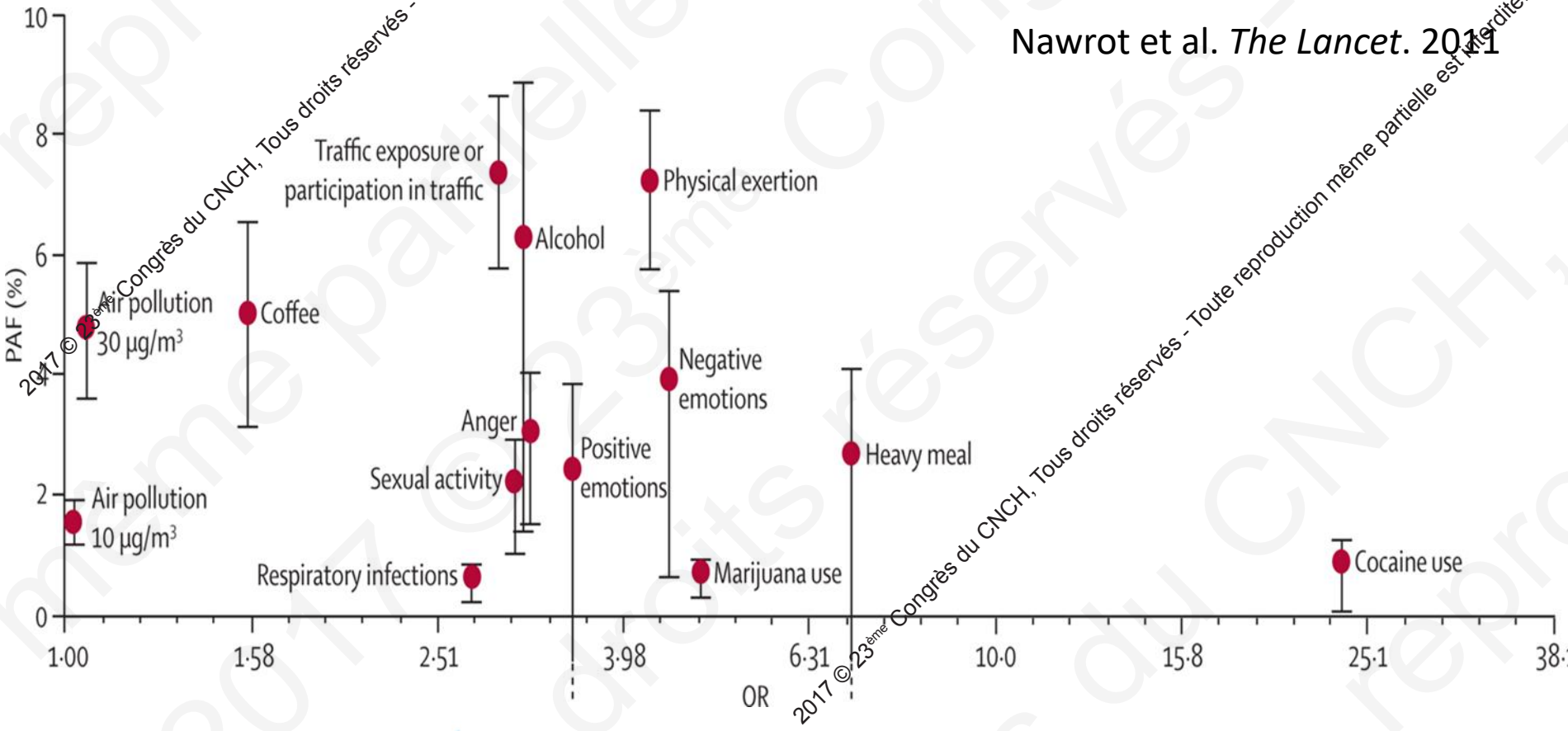
Short-term exposure to Traffic / Coronary artery disease

Meta-analysis of triggers of acute myocardial infaction :

Air pollution and traffic exposure =

the most important triggers of acute coronary syndrome **at the population level**

Nawrot et al. *The Lancet*. 2011



Arrythmia - Heart failure

Arrhythmia :

↘ **Heart Rate Variability** : risk factor for cardiovascular mortality, marker of autonomic nervous system imbalance

Mordukhovich et al. *Environ Health* 2015;14:87

↗ **ventricular arrhythmia** in patients with **implantable defibrillators**

Ljungman et al.*Eur Heart J*. 2008 Dec;29(23):2894-901

Heart Failure : meta-analysis 35 studies:

increased risk of **hospitalization** or **death** from congestive **heart failure** for short term increase in PM and gas (NO2, SO2, CO) .

Shah et al. *Lancet*. 2013 Sep 21;382(9897):1039-48

Stroke

<u>Long</u>-term exposure to PM2.5 : Escape study (**European prospective** study)

100 000 participants

- Risk of stroke was increased of 19% per 5 µg/m3 increase in annual PM2.5 exposure.
- Even with air pollution exposure below the current European recommendations.
- Results robust to adjustment for an extensive list of cardiovascular risk factors and noise coexposure.

Stafoggia et al. *Environ Health Perspect.* 2014 Sep;122(9):919-25.

<u>Long</u>-term exposure to PM2.5 : US study**,** 66 000 postmenopausal women

↗ 10µg/m3 PM2.5 ⇒ 35% increase in the risk of cerebrovascular event.

Miller at al. *N Engl J Med* 2007; 356:447-458

Stroke

<u>Short</u>-term exposure :

- Japan, 11 000 strokes :

↗ 4 % risk of stroke within 6 hours after an increase in pollutants.

Adjusted for ambient temperature, influenza.

Yorifuji et al. *Stroke.* 2014;45:1264-126

- Helsinki. 1998-2004. 3265 deaths from stroke

Interquartile increase in previous-day levels of **UFP** : ↗ 8,5% in stroke mortality (UFP effect > PM2.5)

Kettunen et al. Stroke. 2007;38:918-922

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Stroke

Risks factors of stroke increased by air pollution :

- Atherosclerosis
- Arrythmia

- **<u>Hypertension</u>** :

European prospective study :

Long-term residential exposure to PM 2.5 and high traffic :

↗ incidence of self-reported hypertension (RR :1.22 [95%- CI:1.08; 1.37] per 5 µg/m³ in PM2.5).

Associations are not confounded by road traffic noise.

Fuks et al. *Eur Heart J*. 2016

Meta-analysis: Long-term exposure (PM, NO2) and short-term exposure (SO2, PM) ↗ risk of HTA.

Cai et al. *Hypertension*. 2016;68:62-70

Oxidative Stress - Epigenetic changes

Exposure to PM 2.5 (PAH) ⇒ **oxydative damage** to **DNA**, **lipids** and **proteins** :

Increased levels of : 8-hydroxy-2-deoxyguanosine adducts in DNA (urinary, plasmatic), 15-F(2t)-isoprostane (urinary) and protein carbonyl (plasma) in policemen (Prague), bus drivers and garage men.

Chuang KJ. *Am J Respir Crit Care Med*. 2007 Aug 15;176(4).

Bagryantseva Y. *Toxicol. Lett.* 2010(1),60–68.

Rossner P Jr. *Mutat Res.* 2011 Feb 10;707(1-2):34-41.

Exposure to PM2.5 : ↗ IL1, IL6, TNFα, CRP.. and decreased "global" DNA methylation

Bind et al. *Epidemiology* 2012;23:332–40.

Vit C, E supplementation: ↘ levels of oxidative stress biomarkers

Vit B6, B12, Folate : ↘ effect on HRV

Péter et al. *Nutrients* 2015;7:10398–416.

Epidemiological studies - Limitations

Usual **exposure assessment** method based on **pollutant outdoor concentration** recorded at the city level or **modeling** at the **individual address** (extrapolation from central site monitoring or the nearest monitor) :

- Can lead to **exposure misclassification.**

- May **not be representative of individual exposure**.

- Does not take into account **time spent** outside, in **traffic** or in the **home** :

There is a need for a new approach to estimate individual exposure (portable air quality monitor ?) and for a better assess in outdoor-indoor air exchange.

Hoek et al. *Environ Health Perspect* 2013 12: 43

Effects of mitigations maneuvers

Effects of the emission control ban:

Diesel emission control ordinance in Japan (Tokyo)introduced in 2003 :

Between 2003-2012:

↘ 44% PM from traffic

↘ 11 % for global cardiovascular mortality

↘ 10 % for ischemic heart disease mortality

Mortality rates adjusted with control town (Osaka).

Yorifuji et al. *Epidemiology.* 2016 Nov;27(6):769-78

Individual level: Face mask?

Limited efficiency : UFP (major part of traffic-related PM) and CO, NOx not stopped by facemask

High efficient face masks : reduce acute cardiovascular effect related to air pollution in CHD patients living in high polluted area (China)

Langrish et al. *Environ Health Perspect* 2012;120:367–72.

Effects of mitigations maneuvers

Association Between Changes in Air Pollution Levels During the Beijing Olympics and Biomarkers of Inflammation and Thrombosis in Healthy Young Adults

125 healthy young adults before, during, and after the 2008 Olympics

Concentrations of particulate and gaseous pollutants decreased substantially (-13% to -60%) from the pre-Olympic period to the during-Olympic period

↓

improvements in sCD62P levels (-34.0%) and von Willebrand (- 13%) factor from pre-Olympic to the during-Olympic period

Rich et al. *JAMA*. 2012 May 16;307(19)

Effects of mitigations maneuvers

Effects of polluted air on cardiovascular and hematological parameters after progressive maximal aerobic exercise.

19 male athletes 21-27 years: multi-stage shuttle run test in either polluted air **or** clean air:

Compared to the clean air environment, progressive incremental exercise in polluted air condition significantly decreased maximal oxygen uptake (VO2max), red blood cell count, and hematocrit.

Mean corpuscular hemoglobin, mean red blood cell volume, white blood cells, and platelets increased significantly when they were exercised in the polluted air ambiance.

Kargarfard et al. *Lung.* 2015 Apr;193(2):275-81

Interventional controlled studies

Randomized double-blind, highly standardized , cross-over studies in exposure chamber :

During 1 or 2 hours, subjects are exposed to controlled amounts of dilute **diesel exhaust** (DE) or **filtered air (**or **ambiant air)** :

2 x 15 min of exercise on a bicycle ergometer separated by 2 x 15 min periods of rest. 300µg/m3 PM

Interventional controlled studies

The NEW ENGLAND JOURNAL of MEDICINE 2007 Sep 13;357(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 to **diesel exhaust** *vs* filtered air:

- **Exacerbation** of exercise-induced **myocardial ischemia** (ST-segment depression) in patients with stable coronary heart disease.

- **Inhibition** of endogenous **fibrinolytic capacity** (reductions in acute tissue activator plasminogen release) in patients with coronary heart disease and also healthy adults.

Interventional controlled studies

2008 Dec;29(24):3043-51

Diesel exhaust inhalation increases thrombus formation in man.

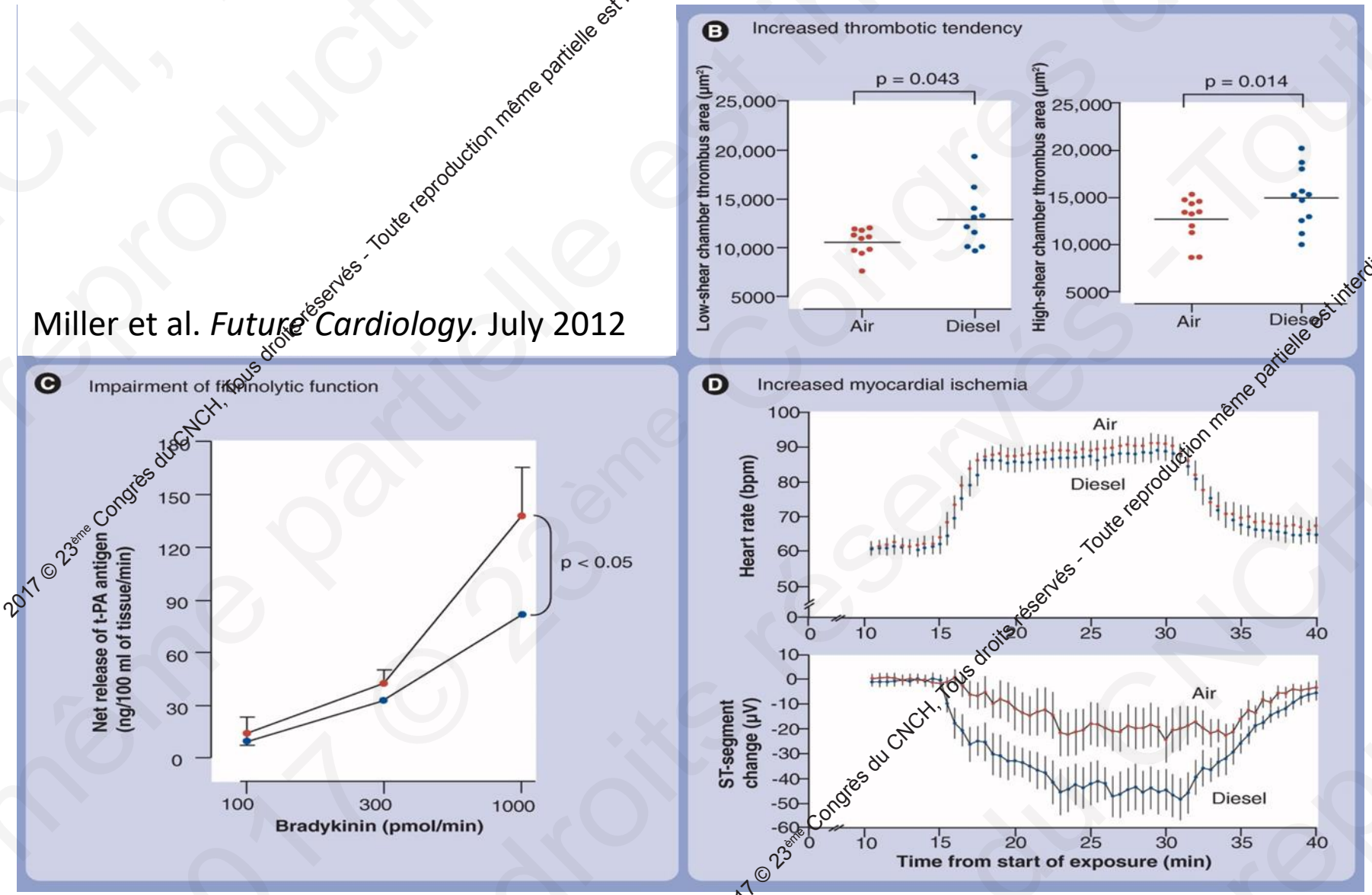
Andrew J. Lucking, Magnus Lundback, Nicholas L. Mills, Dana Faratian, Stefan L. Barath, Jamshid Pourazar, Flemming R. Cassee, Kenneth Donaldson, Nicholas A. Boon, Juan J. Badimon, Thomas Sandstrom, Anders Blomberg, David E. Newby

Exposure to **diesel exhaust** *vs* filtered air :

Increases ex vivo thrombus formation (Badimon chamber) and causes in vivo platelet activation (flow cytometry) in healthy man

Interventional controlled studies

Miller et al. *Future Cardiology.* July 2012



Interventional controlled studies

Exposure to **diesel exhaust** *versus* filtered air :

Acute arterial **vasoconstriction** in healthy adults

Brook et al. *Circulation.* 2002;105:1534–1536

↗**pulmonary vascular resistance** at high cardiac output

Wauters et al. *Am J Physiol Heart Circ Physiol.* 2015 Dec 15;309(12)

Interventional controlled studies

Exposure to **diesel exhaust** *versus* filtered air :

Endothelial vascular dysfunction :

impaired vasodilatation to **nitric oxide**-mediated vasodilators :

endothelium-dependent (acetylcholine) and independent (sodium nitroprusside)

No change after Verapamil infusions (nitric-oxide independent vasodilatators)

Mills at al. *Circulation.* 2005 Dec 20;112(25):3930-6.

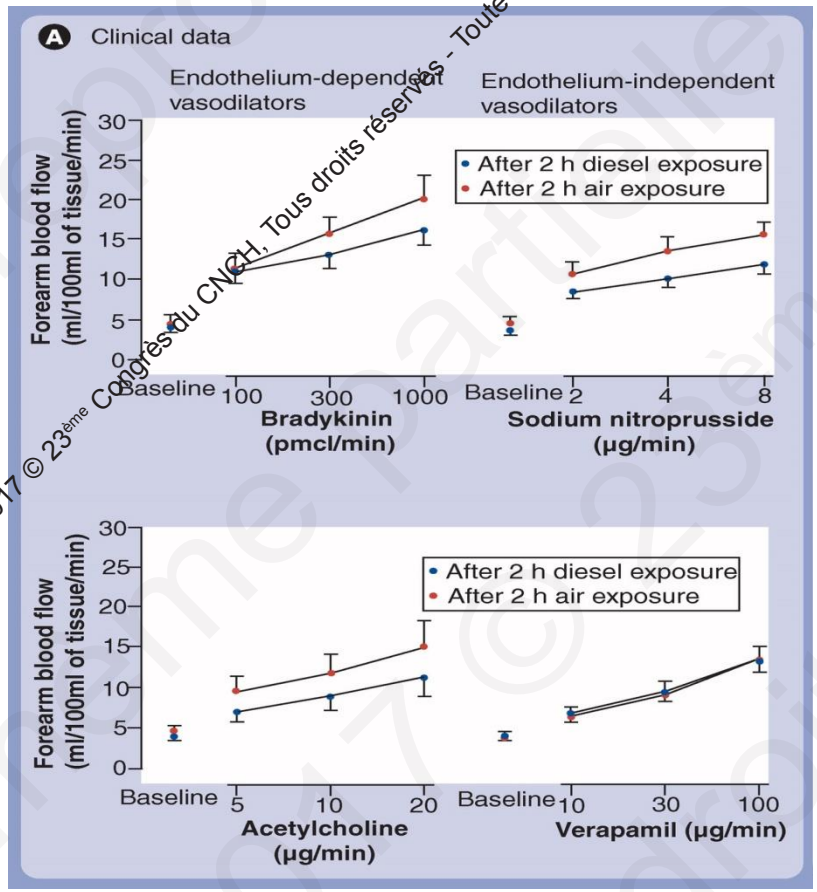
Mills et al. *Eur Heart J*. 2011 Nov;32(21):2660-71

Interventional controlled studies

Exposure to **diesel exhaust** *versus* filtered air: **Endothelial** dysfunction

impaired vasodilatation to **nitric oxide**-mediated vasodilators

No change after Verapamil infusions (nitric-oxide independent vasodilatators)



Mills et al. *Circulation* 2005 Dec 20;112(25)

Endothelial dysfunction → ↘NO bioavailability

one of the earliest signs of atherosclerosis and an independent predictor of future C.V event

Davignon, Ganz. *Circulation* 2004 Jun 15;109

Interventional controlled studies

Exposure to **diesel exhaust** *versus* ambiant air :

Endothelial **oxidative stress** :

↗ biological markers of oxidative stress

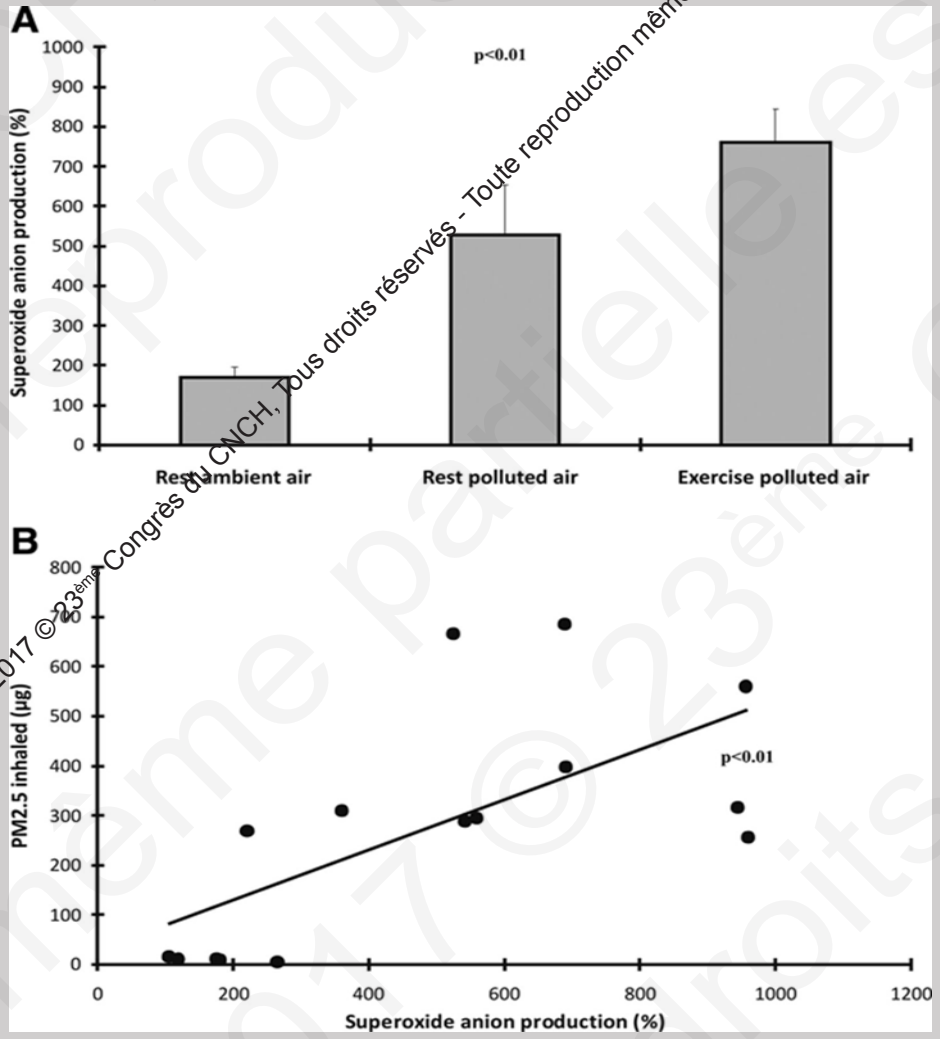
(IL 1, 6, TNFα, oxydative damage to protein, lipids and DNA)

↗ ROS: **superoxide anion** production by human umbilical vein endothelial cells (HUVECs) incubated with sera from subjects

Wauters et al. *Hypertension.* 2013 Aug;62(2):352-8

Interventional controlled studies

Exposure to **diesel exhaust** *versus* ambiant air :



Superoxide anion production
(by human umbilical vein endothelial cells (HUVECs) incubated with sera from subjects)

Air Pollution (DE)
↓
↗ ROS
↓
↘ NO availability

Wauters. *Hypertension.* 2013 Aug;62(2):352-8

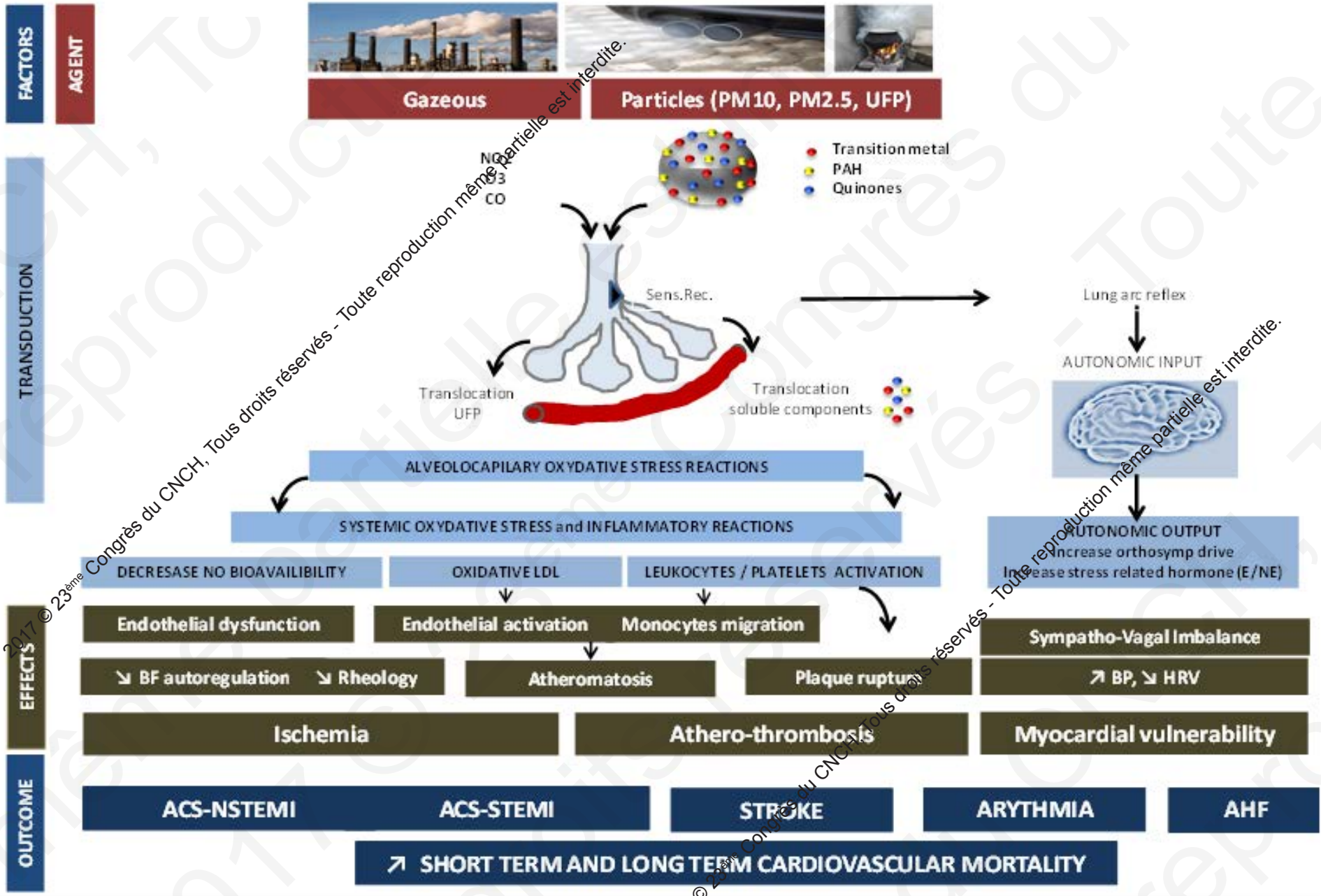
Interventional controlled studies: Limitations

- Only short-term exposure (1h-2h)

- Gasoline exhaust not tested

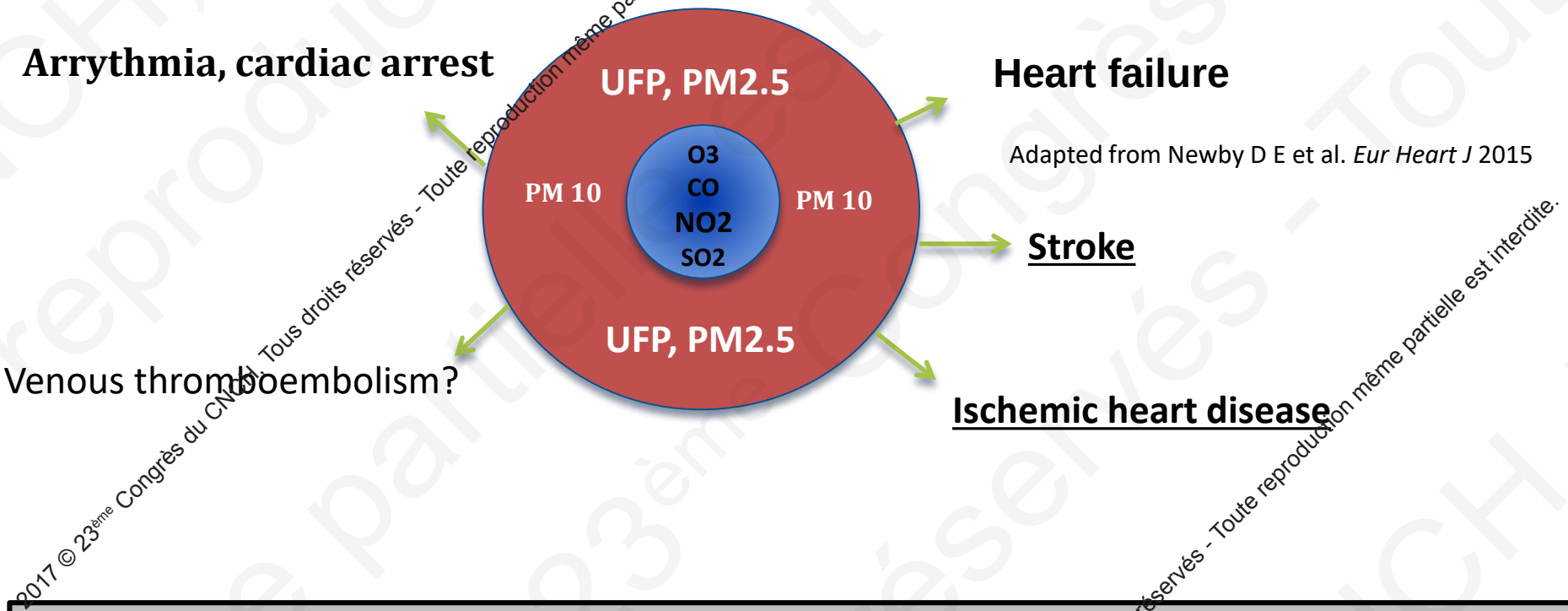
- Diesel car filters not tested

- But provide valuable informations on physiological effects and **reproduce the effect of physical exercise during a pollution peak!**



Bourdrel et al. *Arch Cardiovasc Dis*. 2017 Nov;110(11)
Argacha, Bourdrel et al. *Trends Cardiovasc Med*. 2017 Aug 4

Conclusions



Adapted from Newby D E et al. *Eur Heart J* 2015

Impact of road traffic exposure, Diesel (UFP, NO2)

Oxidative stress

No threshold of exposure below which there is not an effect

Healthy peoples also!

Take Home Message

"There is now **abundant evidence** that air pollution contributes to the risk of cardiovascular disease and associated mortality..

Air pollution should be viewed as one of several **major <u>modifiable</u> risk factors** in the prevention and management of cardiovascular disease.

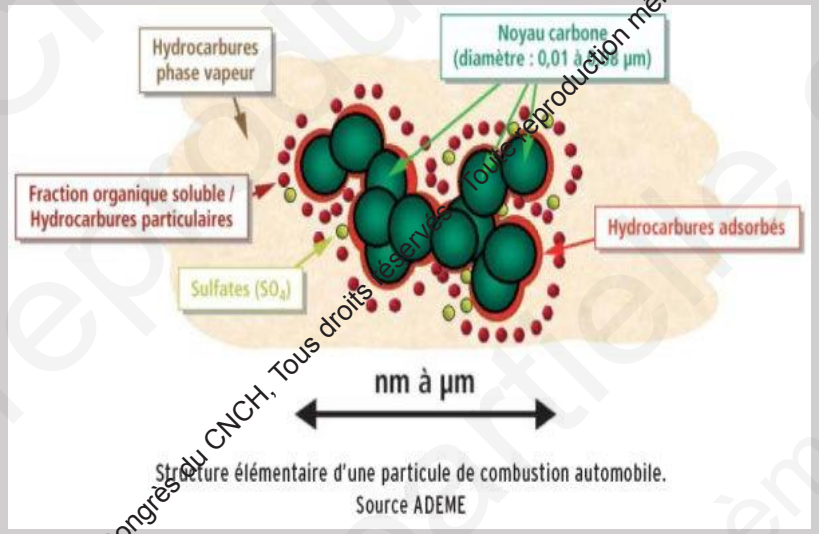
In light of this evidence, efforts to reduce exposure to air pollution should **urgently be intensified** "

Experts conference from the European Society of Cardiology, *Eur Heart J* (2015)

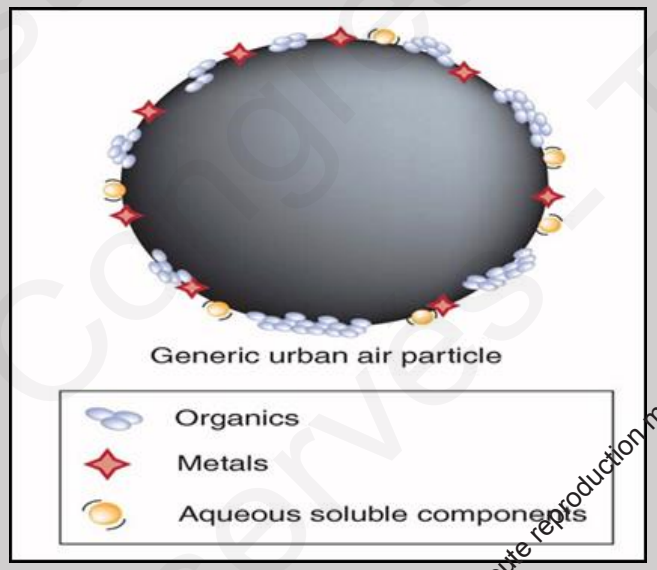
US environmental Protection agency and **American Heart Association** :
"short and long-term exposure to PM2.5 are **<u>causally</u>** related to cardiovascular disease"

Interventional controlled studies

Effects of Diesel Particles:



Structure élémentaire d'une particule de combustion automobile.
Source ADEME



Adverse vascular effects of diesel exhaust predominantly mediated by **surface** compounds of combustion-derived nanoparticulate (metals and hydrocarbons: PAH, quinones..)
while exposure to **pure** carbon had no effect.

Mills et al. *Eur Heart J*. 2011 Nov;32(21):2660-71

Human cells studies

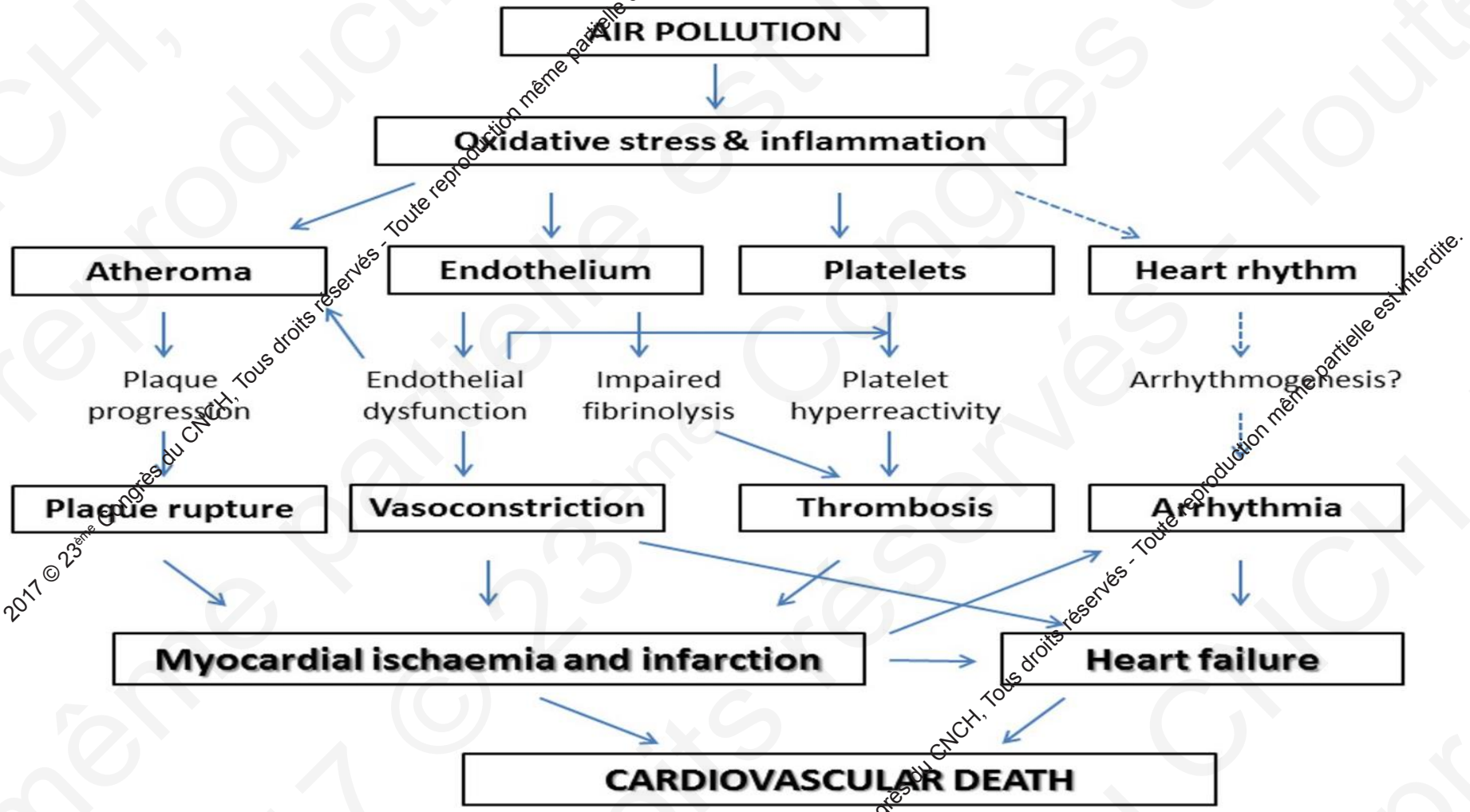
Experimental studies on human bronchial epithelial exposed to diesel exhaust with a diesel car particulate filter show persistant oxidative stress reactions and tumorigenic potential, due to gaseous compounds (NO2 , CO, the gas-phase PAHs) and nanoparticulate PAHs unfiltered exhaust .

Hawley et al . *Toxicol Sci.* 2014 Oct;141(2):505-14

Induction of **superoxide-dismutase gene expression** by filtered diesel exhaust in human respiratory epithelium cells, implies that the gazeous exhaust components are also involved in air pollution related oxidative stress reactions

Steiner et al. *Atmospheric Environment* 81 (2013) 117

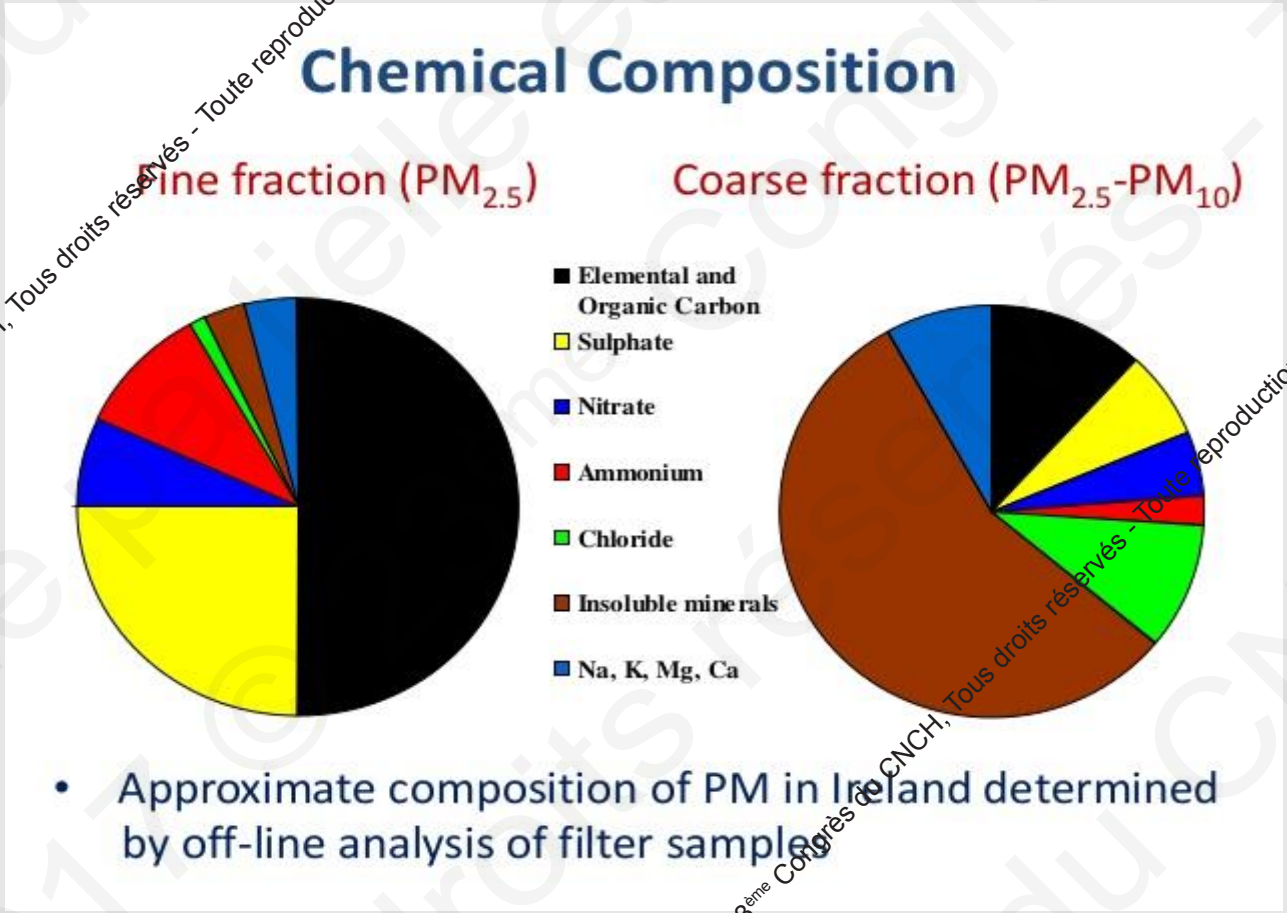
Conclusions



Newby et al. *Eur Heart J.* 2015 Jan 7;36(2)

Air pollution : cardiovascular effect

PM size *and* composition / Toxicity:



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Air quality standards

	Averaging period	EU 2008	WHO 2005	Unit
Fine particle PM 2.5	24 hours	NA	25	µg/m³
	1 year	25	10	µg/m³
Particle PM10	24 hours	50	50	µg/m³
	1 year	40	20	µg/m³
Ozone (O3)	max 8 hour mean	120	100	µg/m³
Nitrogen dioxide	1 hour	200	200	µg/m³
	1 year	40	40	µg/m³
Sulphur dioxide (SO2)	1 hour	350	NA	µg/m³
	24 hours	125	20	µg/m³
	10 minutes mean	NA	500	µg/m³

Epidemiological studies: Cardiovascular Mortality

Authors	All causes	Cardiovascular	Cardiopulmonary	IHD
Ostro et al. (this report)	1.06 (0.96–1.16)[a]		1.19 (1.05–1.36)[a]	1.55 (1.24–1.93)[a]
Ostro et al. (2010)	1.84 (1.66–2.05)[a]		2.05 (1.80–2.36)[a]	2.89 (2.27–3.67)[a]
Pope et al. (2002, 2004)	1.06 (1.02–1.11)	1.12 (1.08–1.15)	1.09 (1.03–1.16)	
Laden et al. (2006)	1.16 (1.07–1.26)	1.28 (1.13–1.44)		
Miller et al. (2007)		1.76 (1.25–2.47)[a]		2.21 (1.17–4.16)[a]
Jerrett et al. (2005)	1.15 (1.03–1.29)		1.10 (0.94–1.28)	1.32 (1.05–1.66)
Eftim et al. (2008)	1.21 (1.15–1.27)			
Chen et al. (2005)				1.42 (1.06–1.90)[a]
Puett et al (2009)	1.26 (1.02–1.54)[a]			2.02 (1.07–3.78)[a]

Comparative HRs (95% CIs) associated with a 10-µg/m^3 change in long-term exposure to $PM_{2.5}$ in several cohort studies conducted in the **United States**.
Ostro et al. *Environ Health Perspect* 118:363–369

Interventional controlled studies