Environmental respiratory health and disease

Didier Cataldo

Conflicts of Interest

Speaker fees: AstraZeneca, Boehringer-Ingelheim, Novartis, Chiesi, GSK

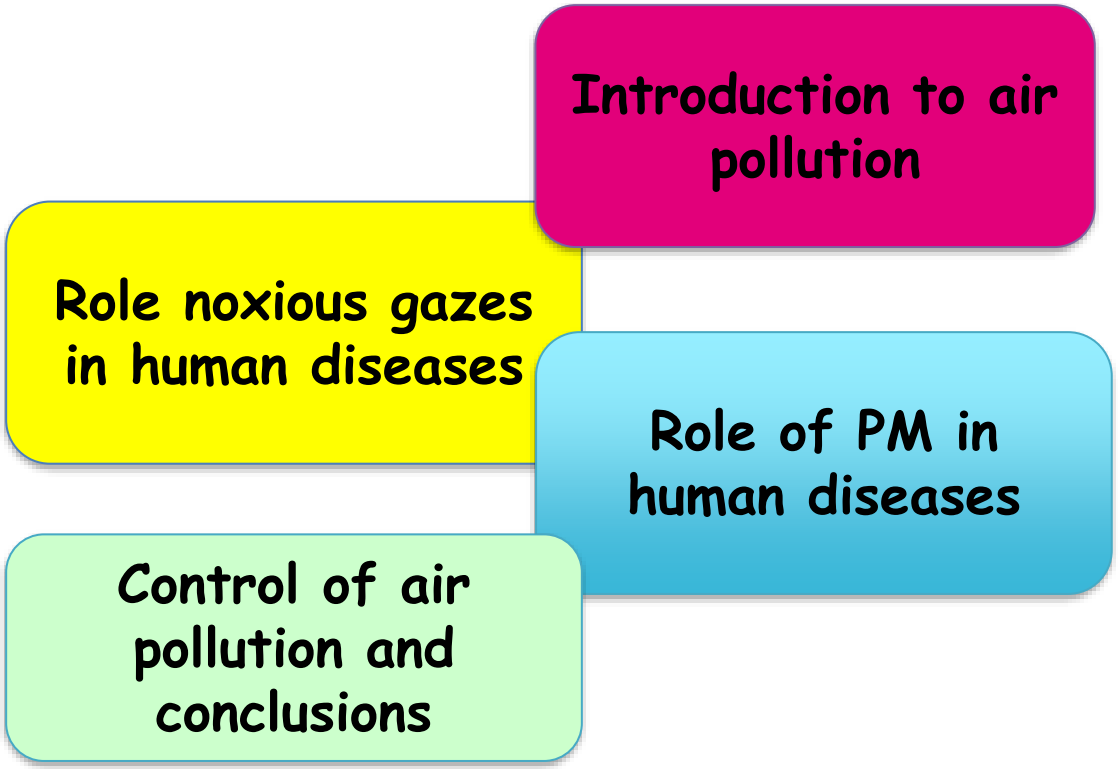
Advisory Boards: AstraZeneca, Boehringer-Ingelheim, Novartis, Sanofi, GSK, Chiesi.

Founder of *Aquilon Pharmaceuticals*

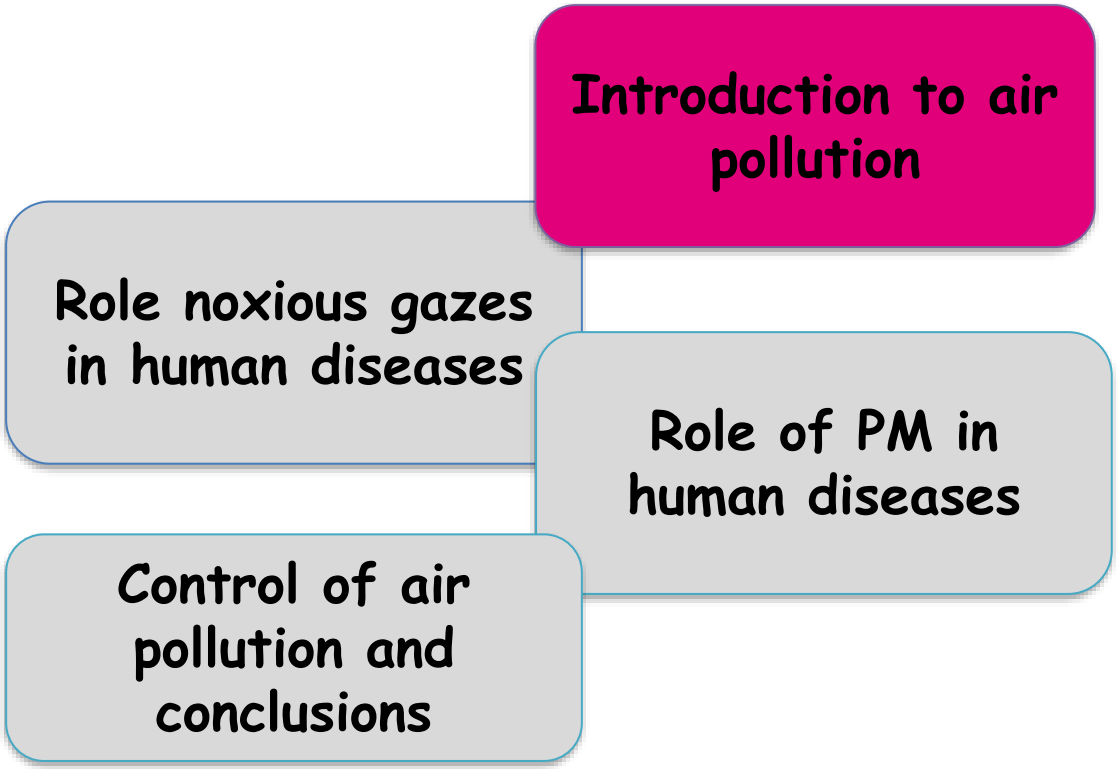
President of the **Belgian Respiratory Society (BeRS)**

None of these activities have any connection with air pollution

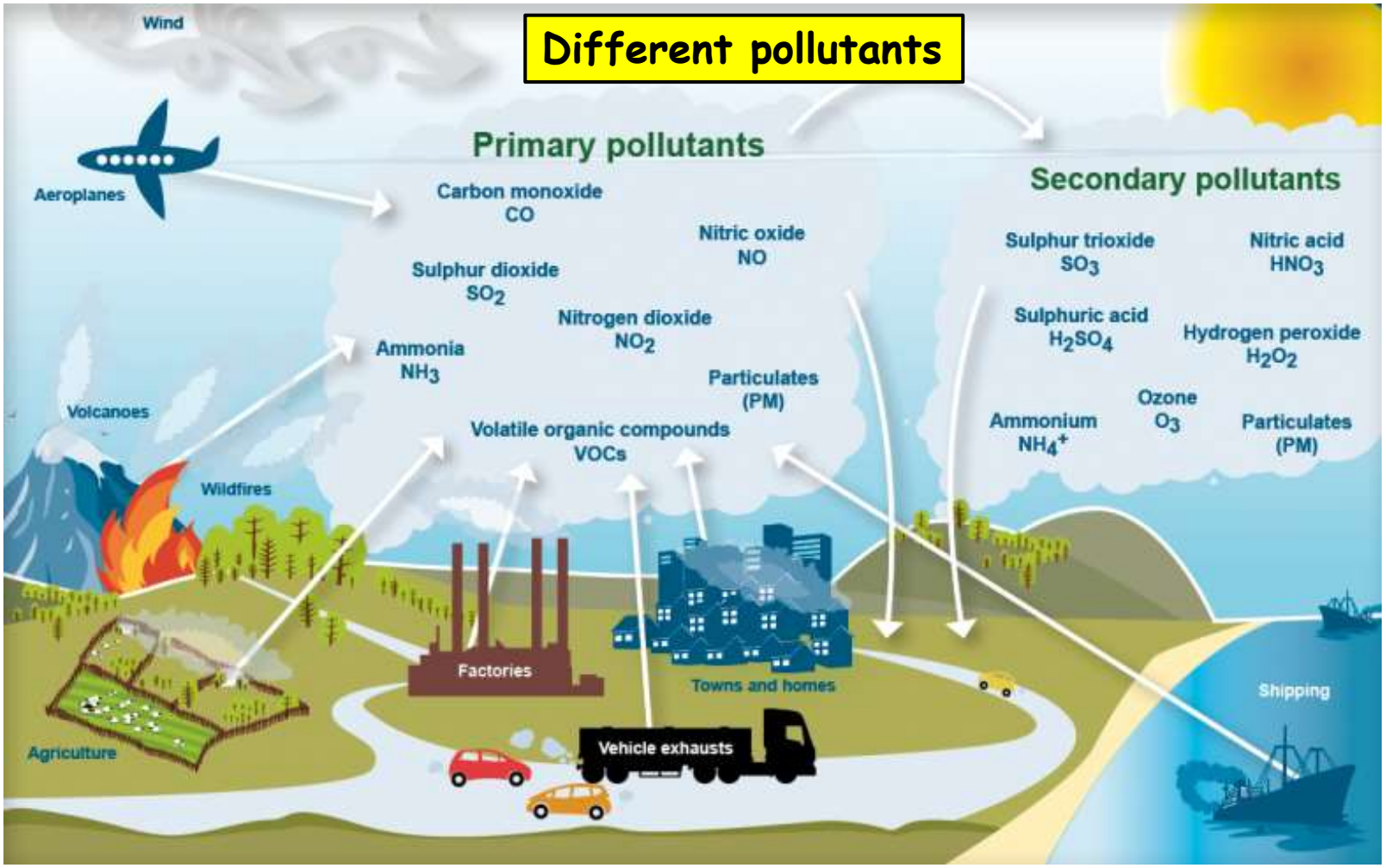
Environmental respiratory health and disease



Environmental respiratory health and disease




SKOLSTREJK
FÖR
KLIMATET



Iasmania.com

World Health Organization

Ambient (outdoor air pollution) in both cities and rural areas was estimated to cause 4.2 million premature deaths worldwide in 2016 (6% due to lung cancer).

World Health Organization

Ambient (outdoor air pollution) in both cities and rural areas was estimated to cause 4.2 million premature deaths worldwide in 2016 (6% due to lung cancer).

In addition to outdoor air pollution, indoor smoke is a serious health risk for some 3 billion people who cook and heat their homes with biomass, kerosene fuels and coal.

Deaths attributable to air pollution by country (yearly)

AAP: Ambient air pollution

World Health Organization

Air pollution has effects throughout the whole body

neurodegenerative diseases

impaired cognition
altered behaviour

depression

autoimmune diseases

stem cell alterations

liver toxicity

renal disease

metabolic syndrome
& diabetes

inflammatory bowel disease

osteoperosis

decreased fertility

autoimmune
rheumatic diseases

peripheral artery disease

stroke

olfactory deficits

myocardial infarction
coronary artery disease
arrhythmia

hypertension

rejection of transplants

asthma
COPD
respiratory infection
lung cancer

MRM 2019

pre-eclampsia

spontaneous abortion

premature birth

low birth weights

epigenetic changes

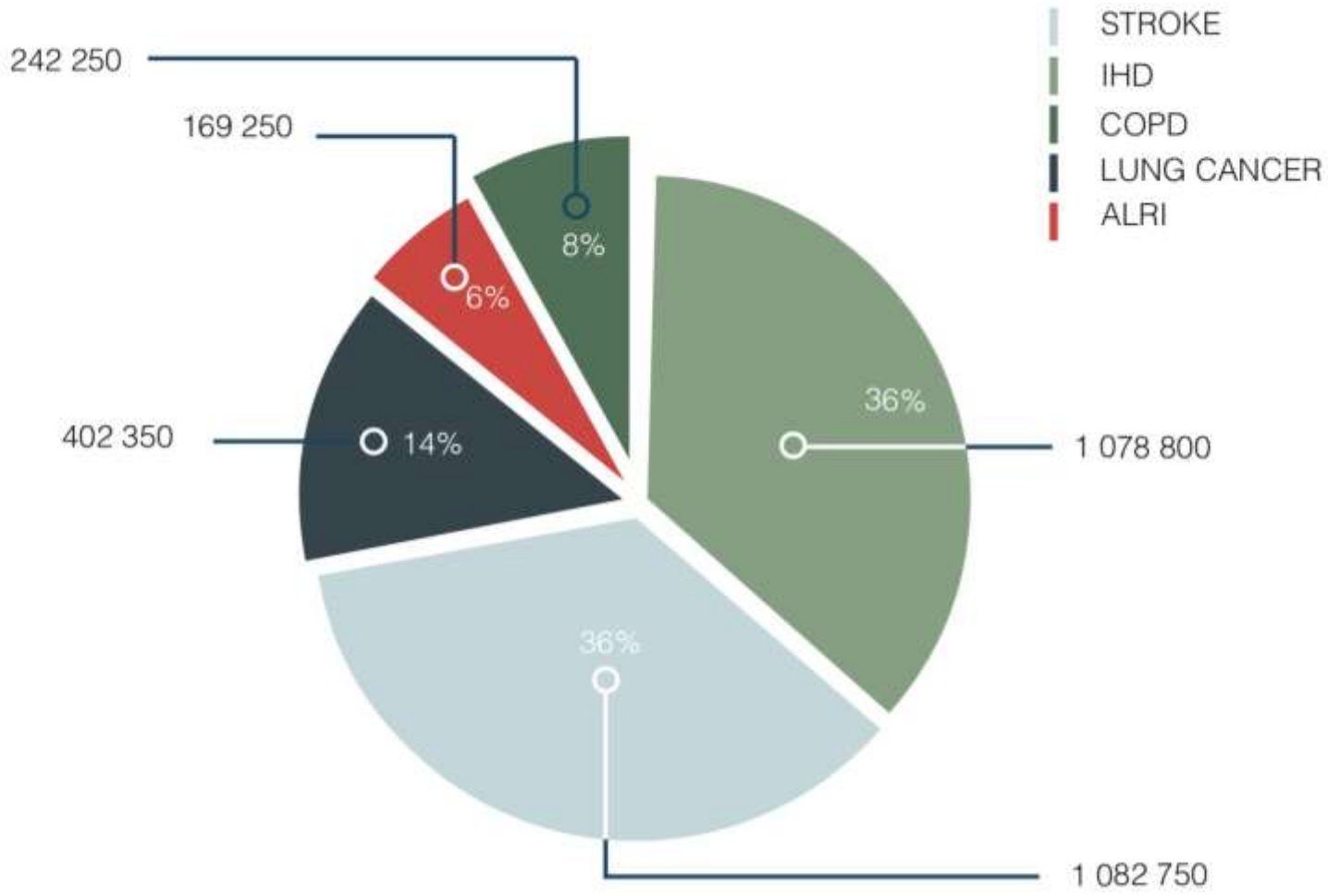
congenital defects

detrimental health effects
in offspring

Miller & Newby, Cardiovasc Res, 2019

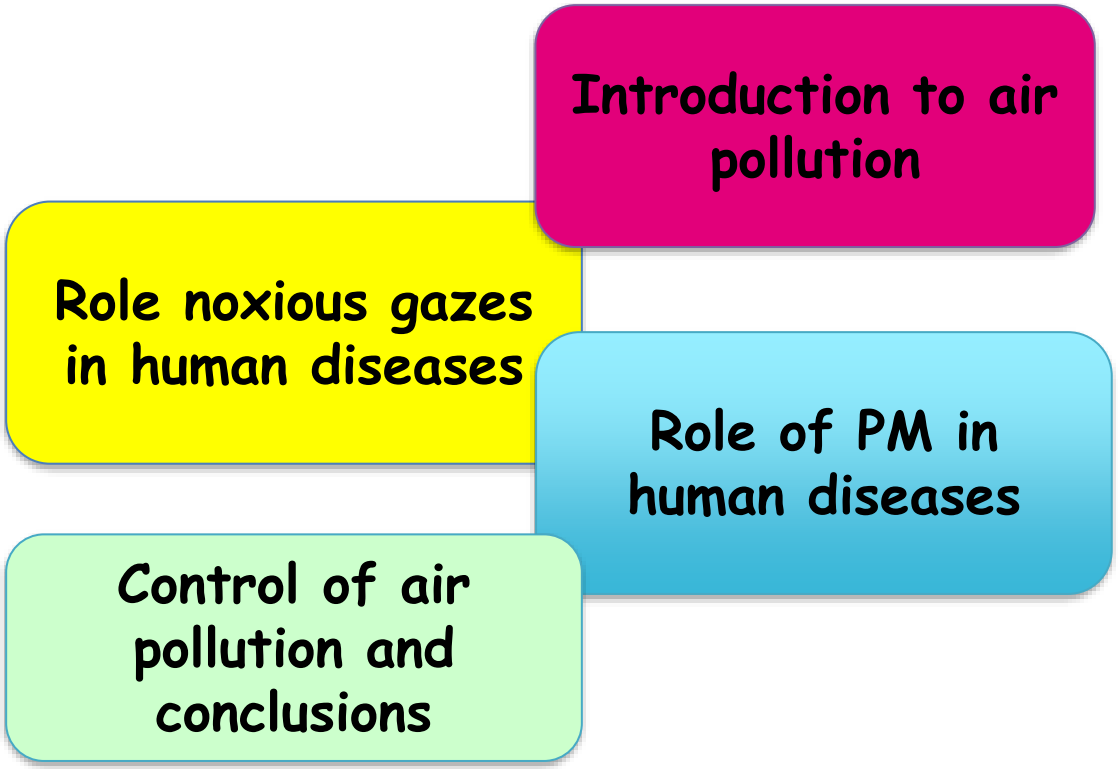
What are the main causes of death after air pollution exposure?

Deaths attributable to air pollution

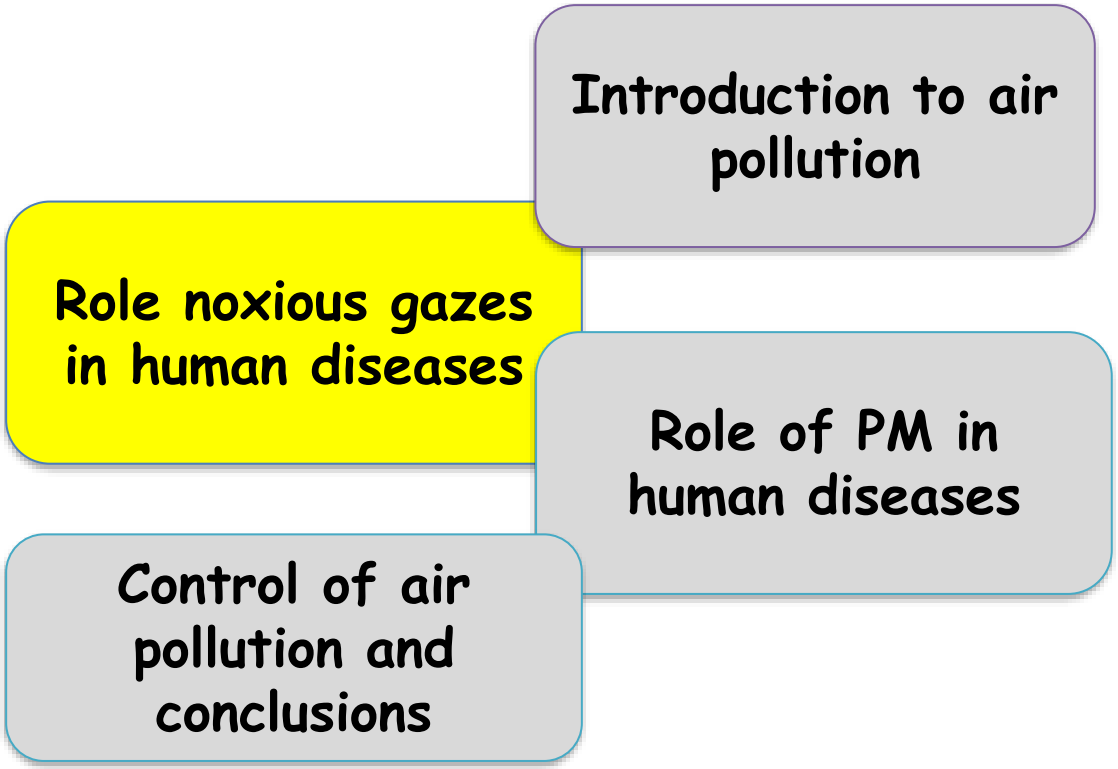


World Health Organization

Environmental respiratory health and disease

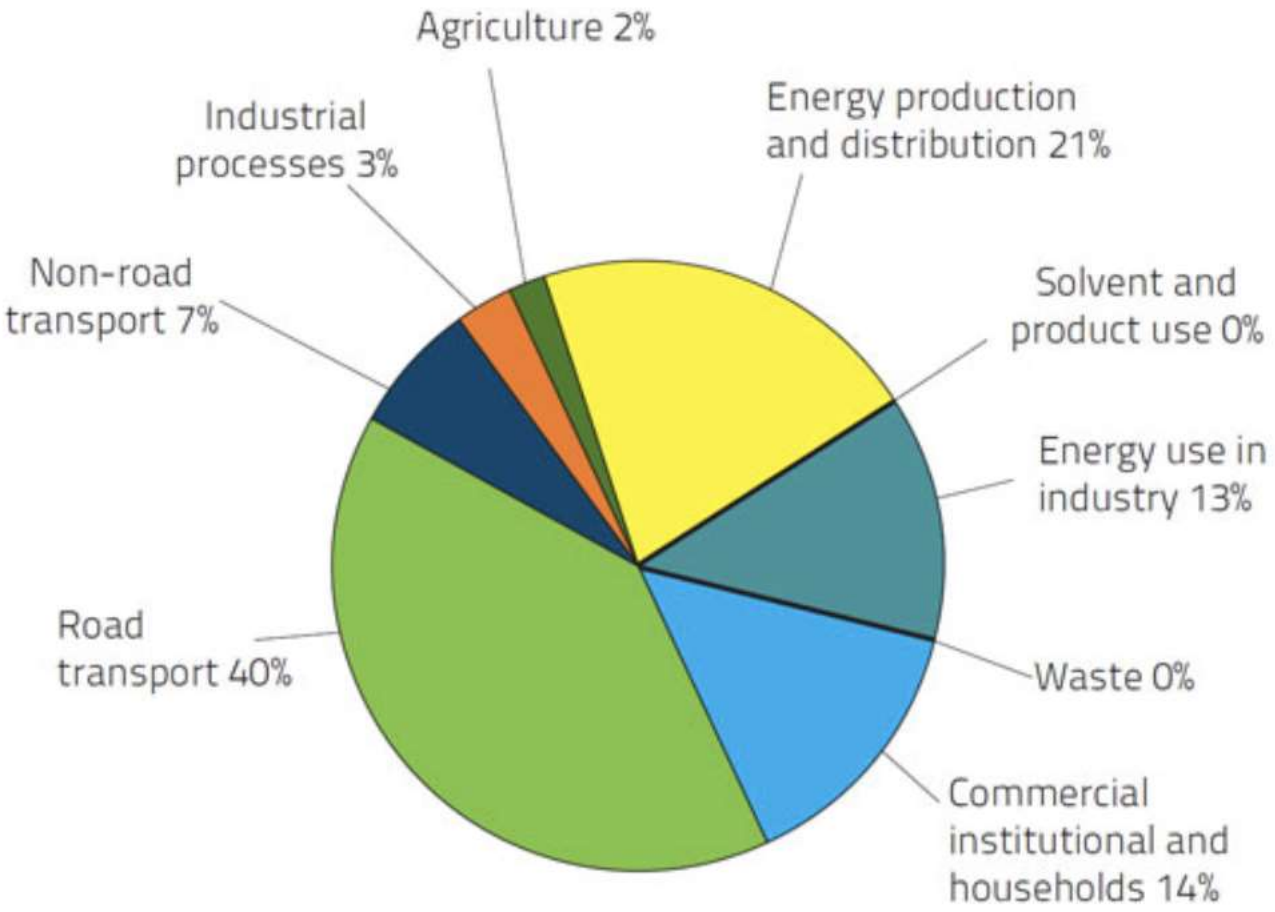


Environmental respiratory health and disease



NO_x (NO - NO_2)

NOx emissions in the EU -share of emissions by sector group, 2011



Source - European Union emission inventory report 1990–2011 under the UNECE Convention on Long-range Trans-boundary Air Pollution (LRTAP)

Annual mean NO_2 concentrations observed at traffic stations, 2015

µg/m³

- ≤ 20
- 20-30
- 30-40
- 40-50
- > 50

No data

Outside coverage

Canary Is.

Azores Is.

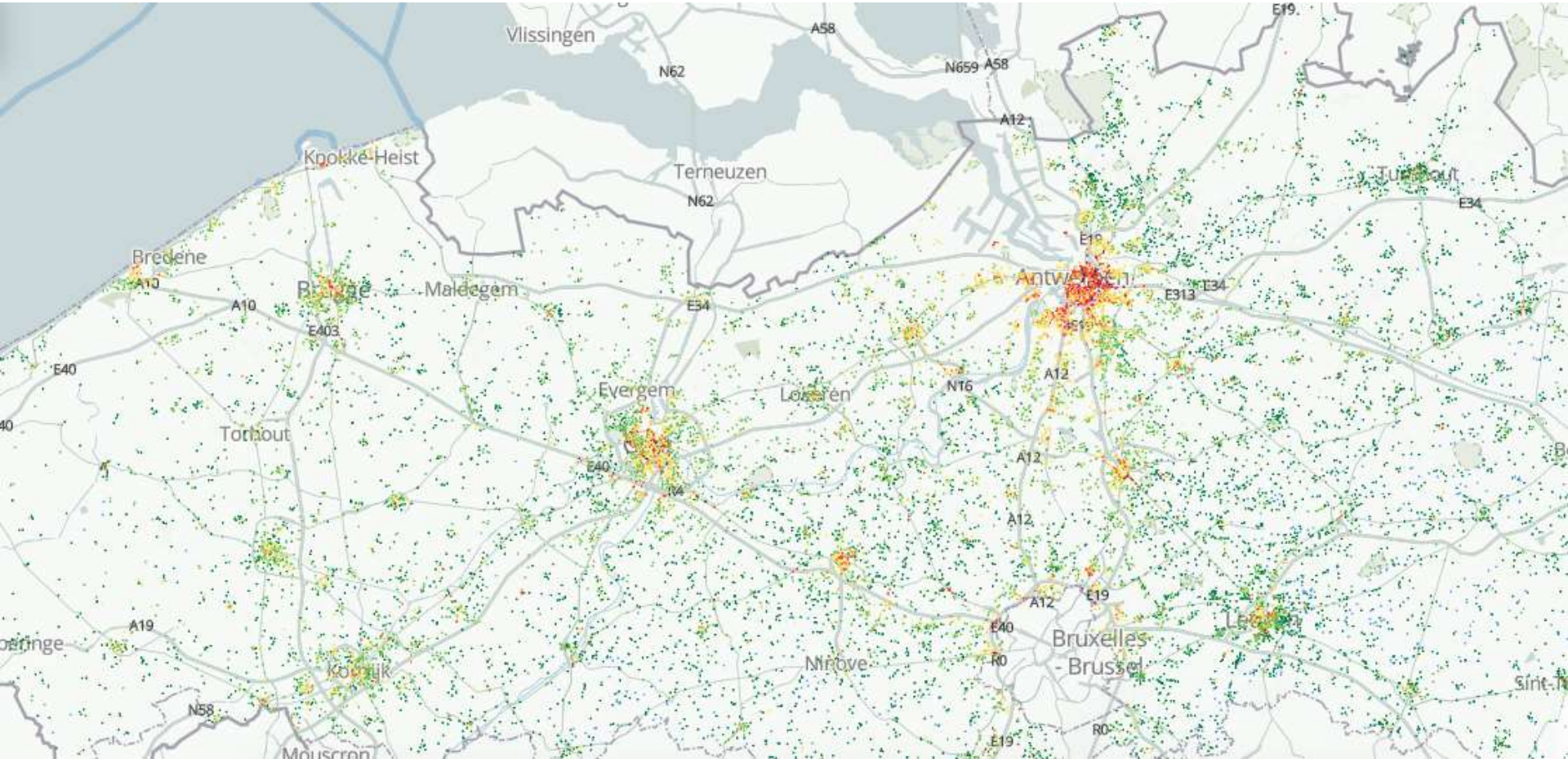
Madeira Is.

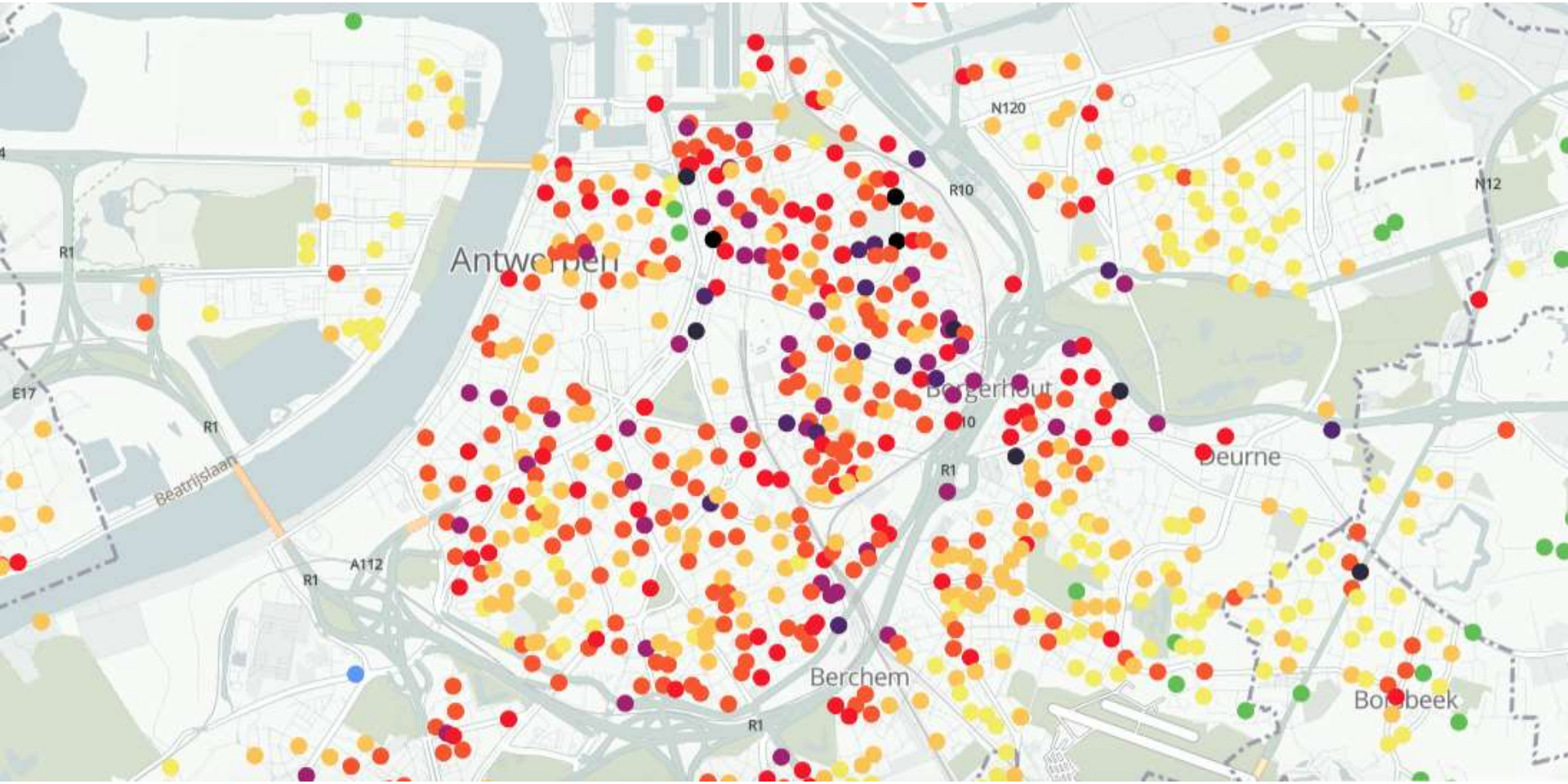
0 500 1 000 1 500 km

dS CURIEUZE NEUZEN VLAANDEREN

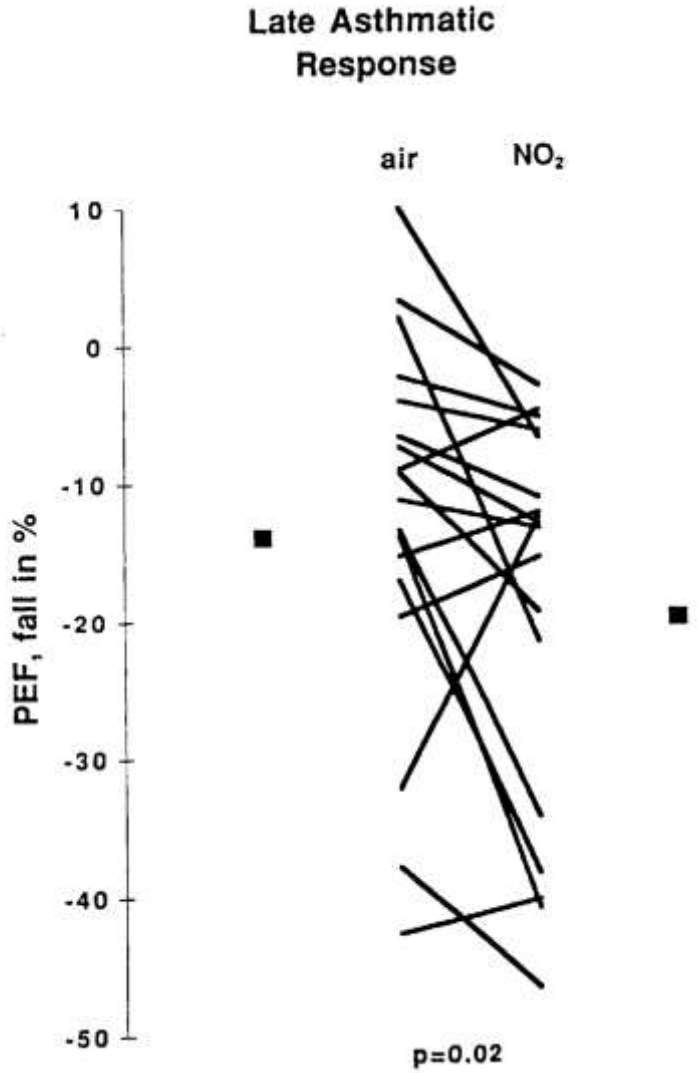
20 000 citizens from Flanders received NO_2 detectors

Levels measured for the first time at an individual scale




N120
R10
N12
R1
Antwerpen
E17
R1
Beatrijslaan
A112
R1
Berchem
R1
Deurne

Nitrogen Dioxide Exposure Enhances Asthmatic Reaction to Inhaled Allergen in Subjects with Asthma



Asthma patients

30 min NO_2 or air exposure

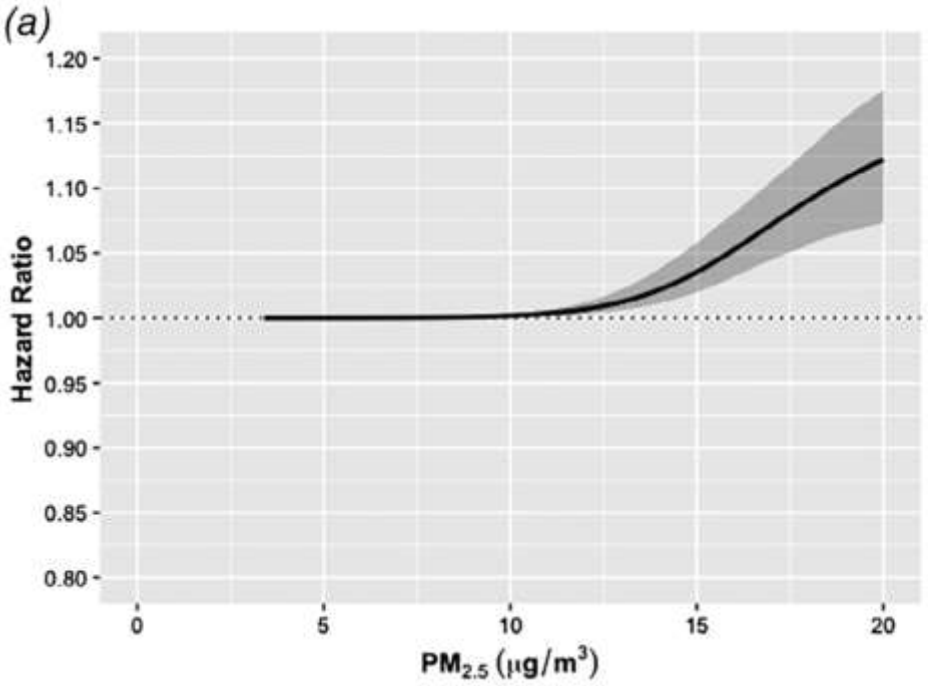
Allergen challenge

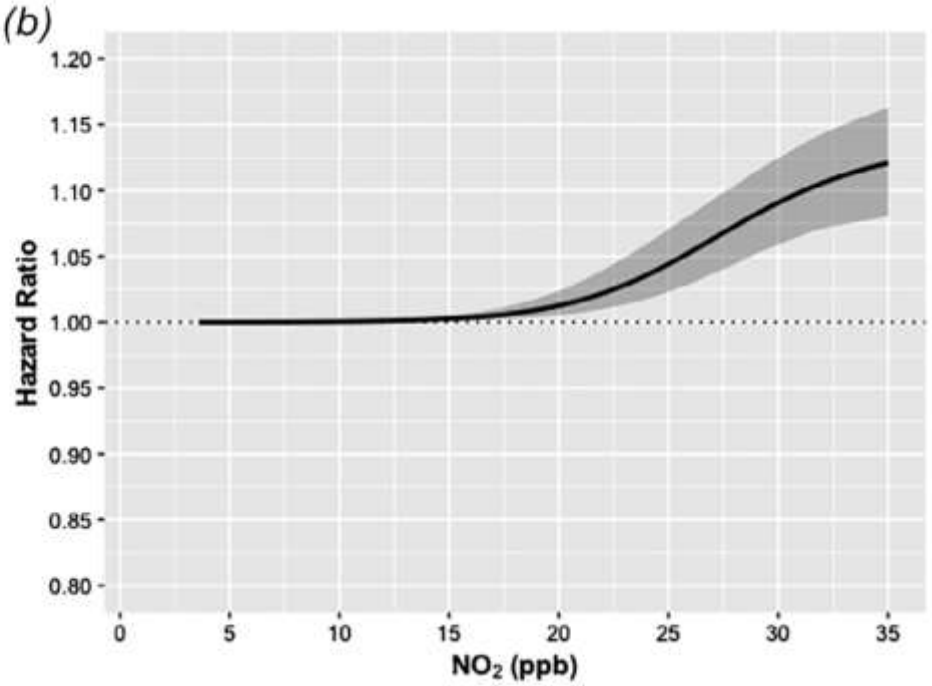
AM J RESPIR CRIT CARE MED 1997;155:881–887.

NO_2 is related to increased cancer incidence

IJC
International Journal of Cancer

Exposure to ambient air pollution and the incidence of lung cancer and breast cancer in the Ontario Population Health and Environment Cohort





Int. J. Cancer: **00**, 00–00 (2019)

Air pollution affects lung cancer survival

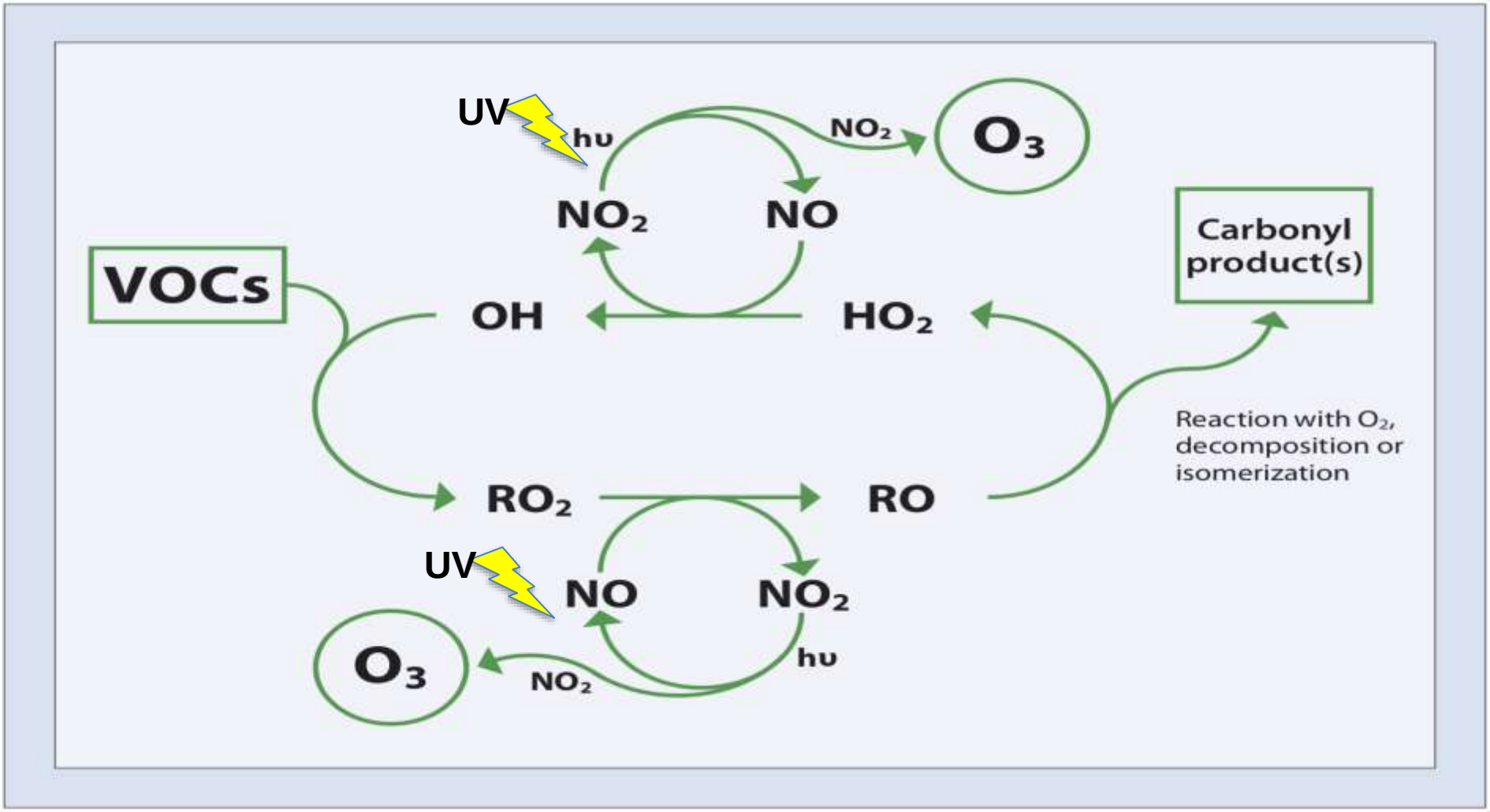
Air pollution affects lung cancer survival

Sandrah P Eckel,[1] Myles Cockburn,[1] Yu-Hsiang Shu,[1,2] Huiyu Deng,[1]
Frederick W Lurmann,[3] Lihua Liu,[1] Frank D Gilliland[1]

- **352 053 patients with newly diagnosed lung cancer during 1988–2009 in California**
- **All-cause mortality recorded**
- **Air pollution exposure estimated - half of the study participants (45.4%) lived more than 1500 metres away from a major interstate motorway**
- **Negative association between pollution and survival**
- **For patients with early stage disease, risk of death from any cause was**
    - **30% greater for NO_2**
    - **26% greater for PM_{10}**
    - **38% greater for $PM_{2.5}$**
    - **4% greater for O_3**

Eckel, Thorax 2016

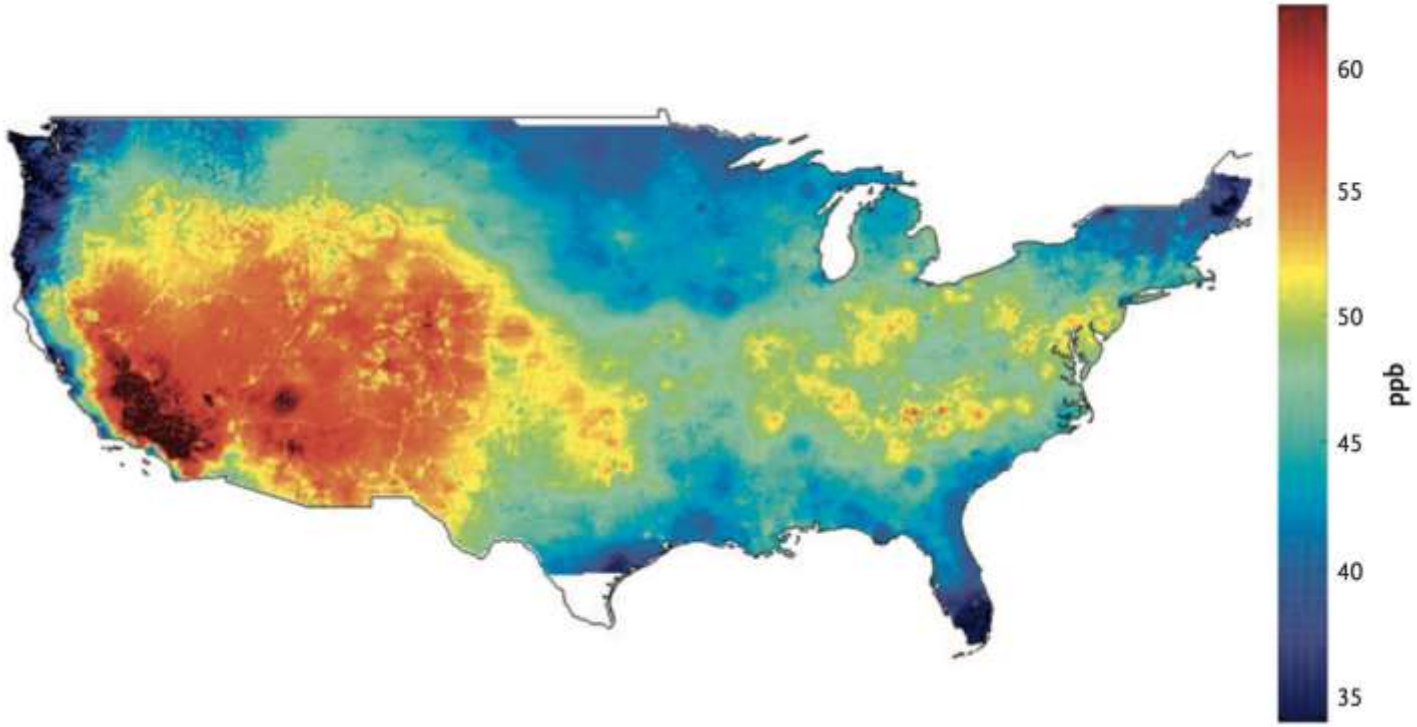
O_3


UV
hυ
NO2
O3
NO2
NO
Carbonyl product(s)
VOCs
OH
HO2
Reaction with O2, decomposition or isomerization
RO2
RO
UV
NO
NO2
hυ
O3
NO2

Great smog 1952

High ozone concentration

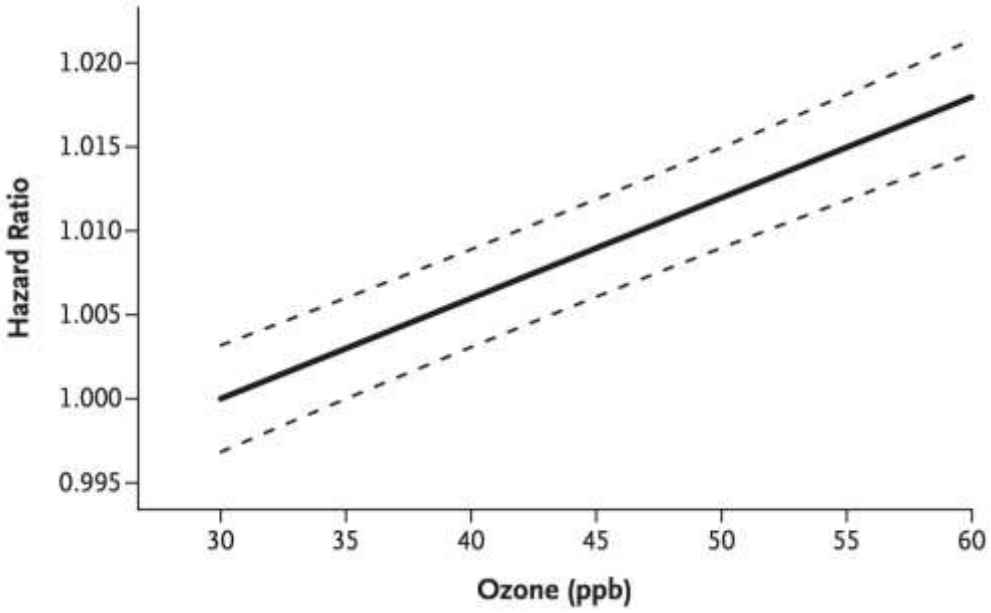
Ozone warm season concentration



Di et al. NEJM 2019

Correlation with all-cause mortality

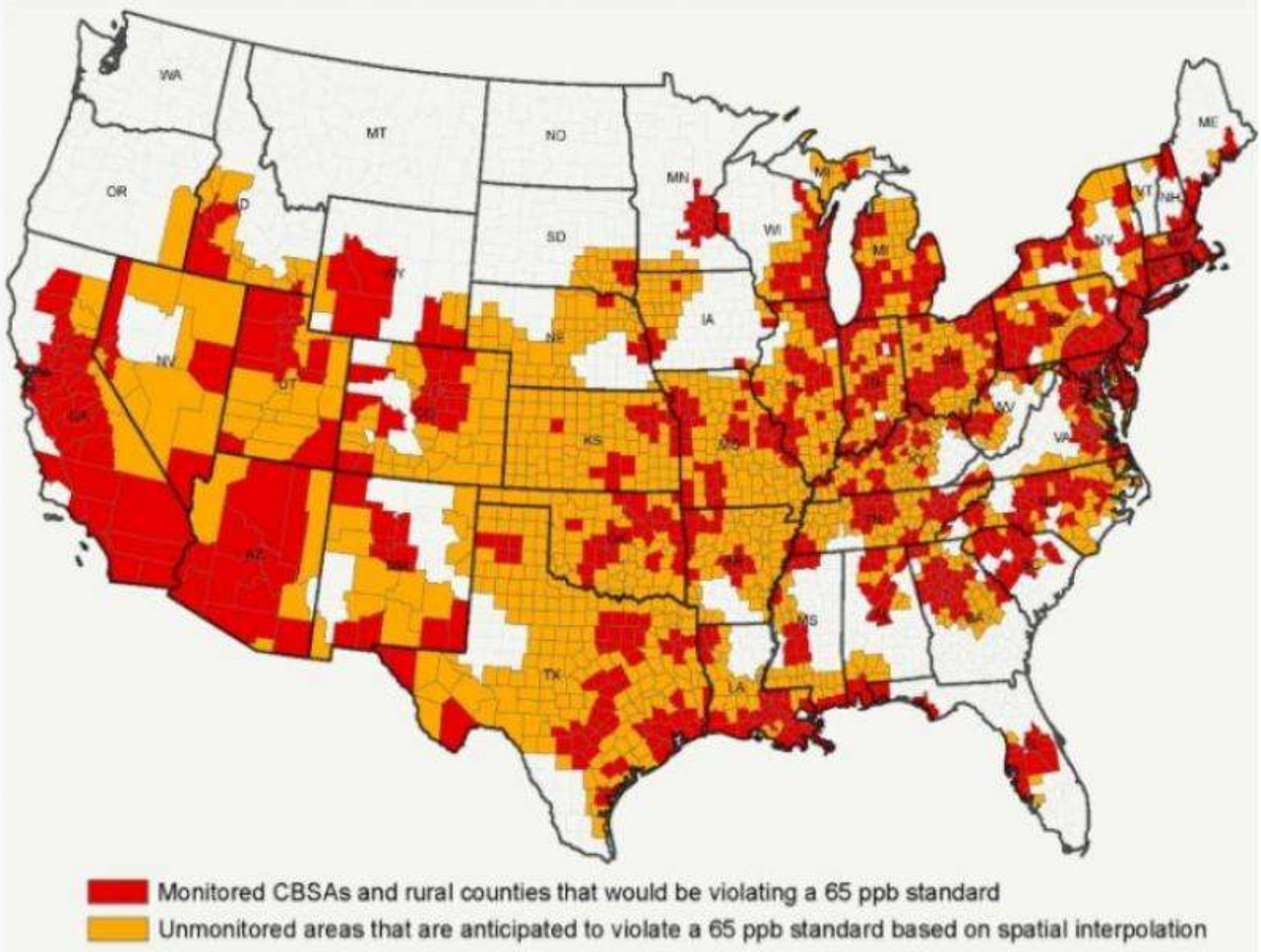
Exposure to ozone



n = 60,925,443
460,310,521 person-year

Di et al. NEJM 2019

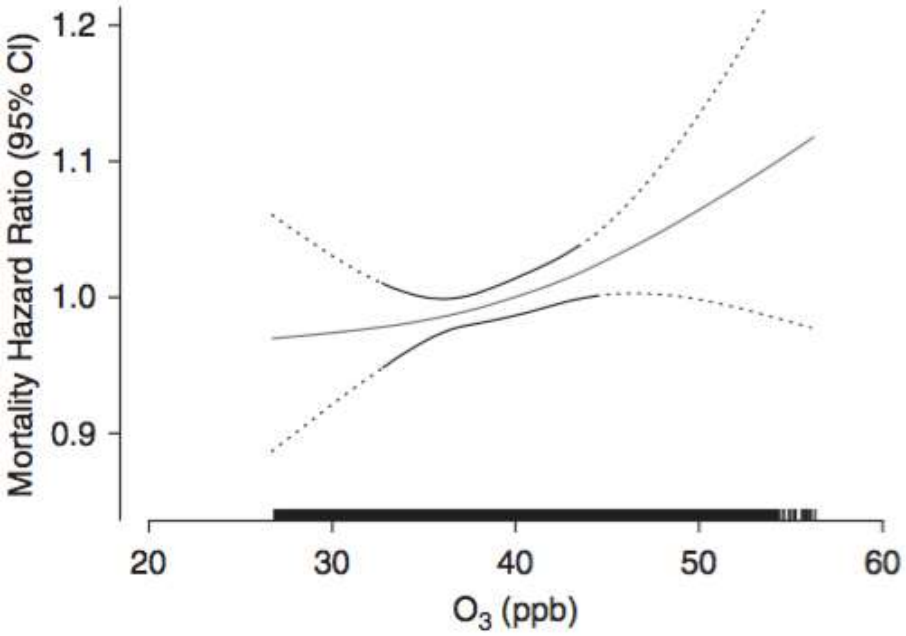
Long-Term Exposure to Ozone and Cause-Specific Mortality Risk in the United States



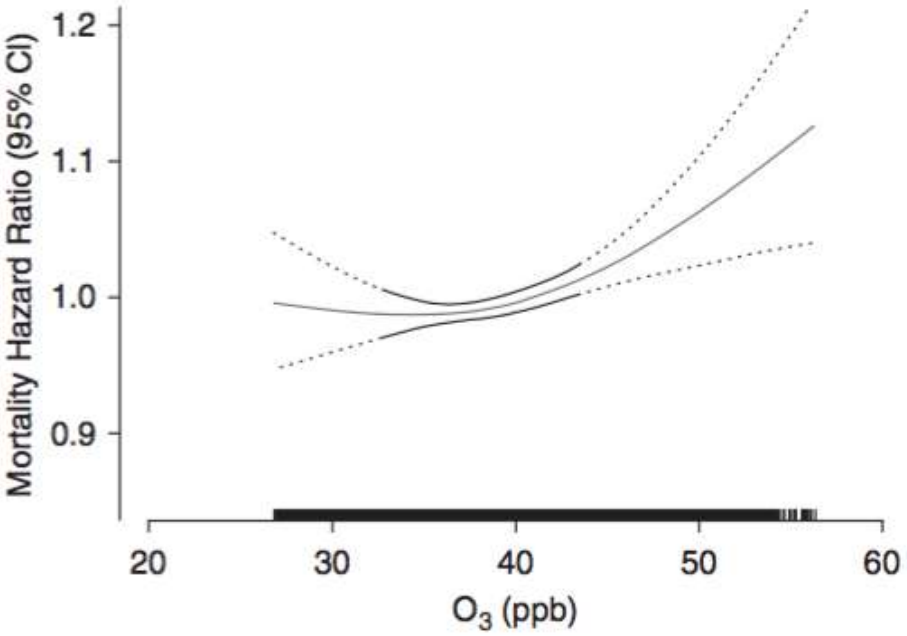
American Journal of Respiratory and Critical Care Medicine Volume 200 Number 8 | October 15 2019

O_3 dose-response curves

Respiratory diseases mortality

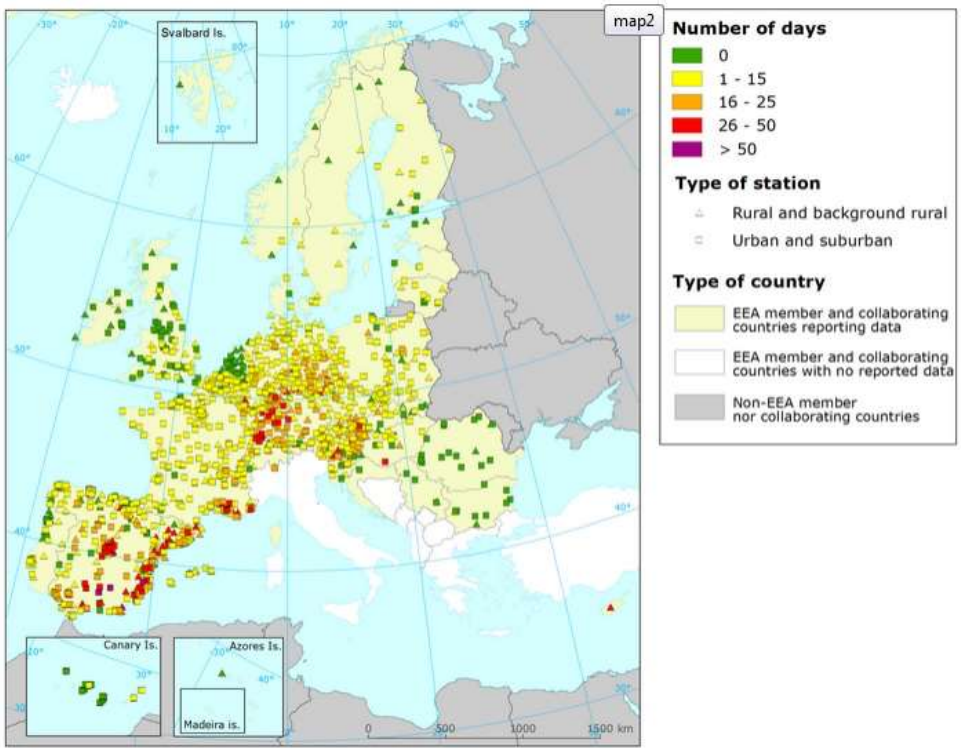


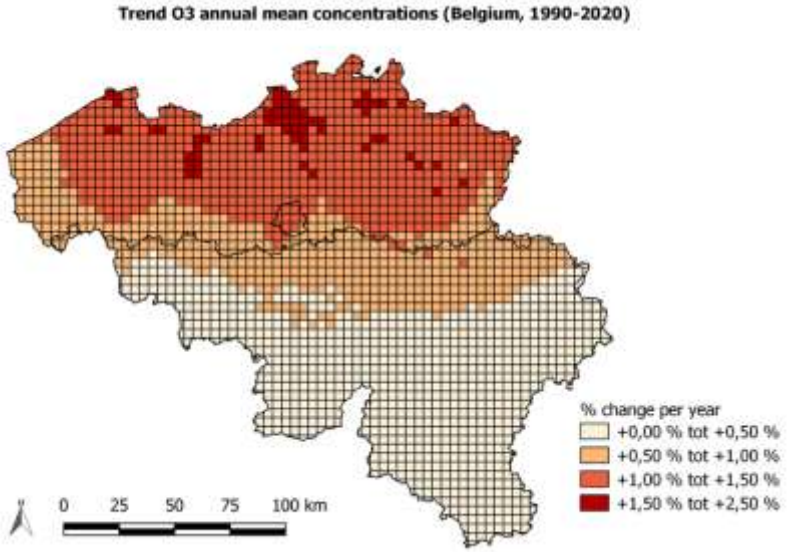
Cardiovascular diseases mortality



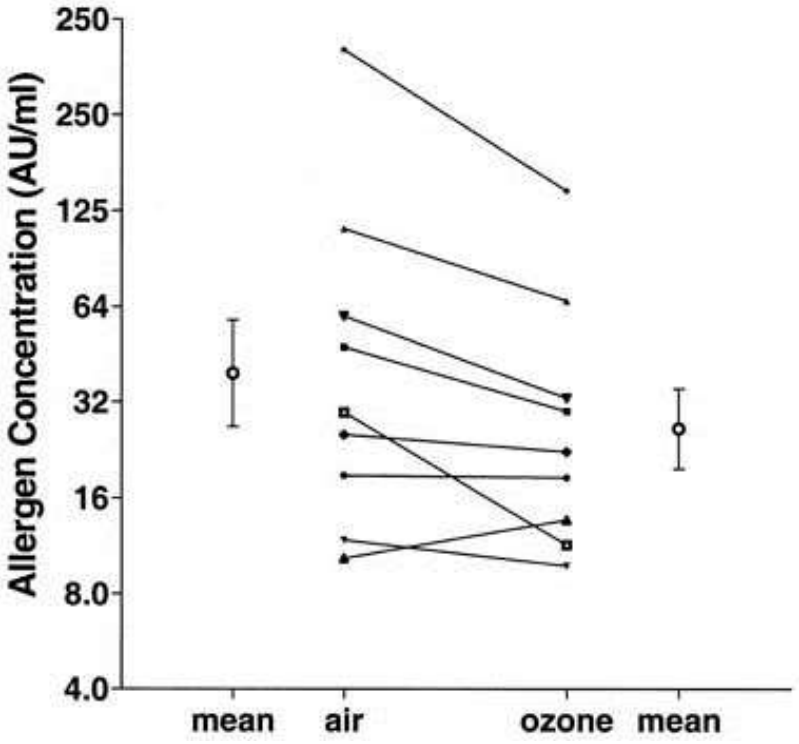
American Journal of Respiratory and Critical Care Medicine Volume 200 Number 8 | October 15 2019

Map 2. Number of days on which ozone concentrations exceeded the long-term objective for the protection of human health during summer 2014 (provisional data)

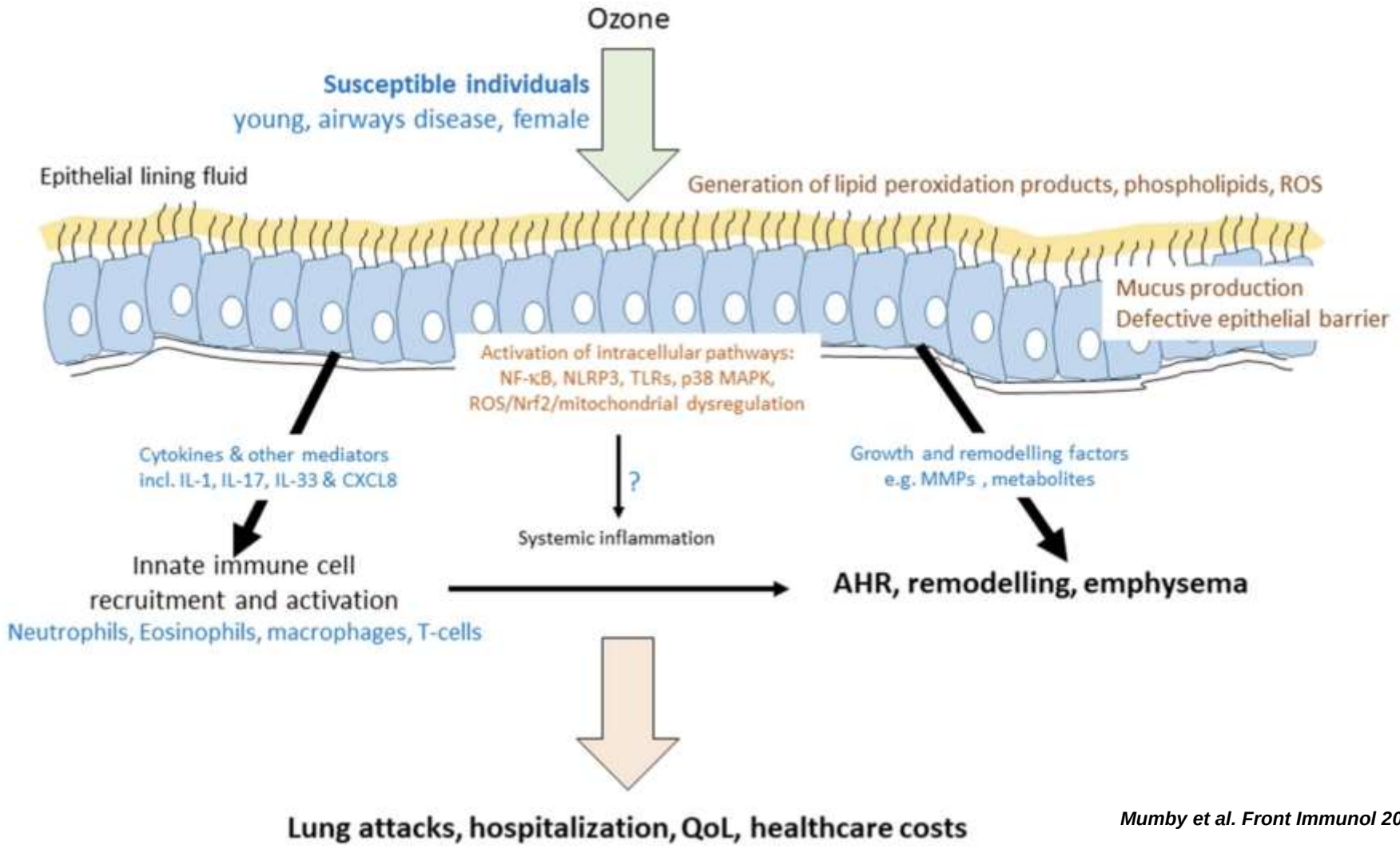




Ozone increases the responsiveness to allergens in asthmatics



Kehl JACI 1999

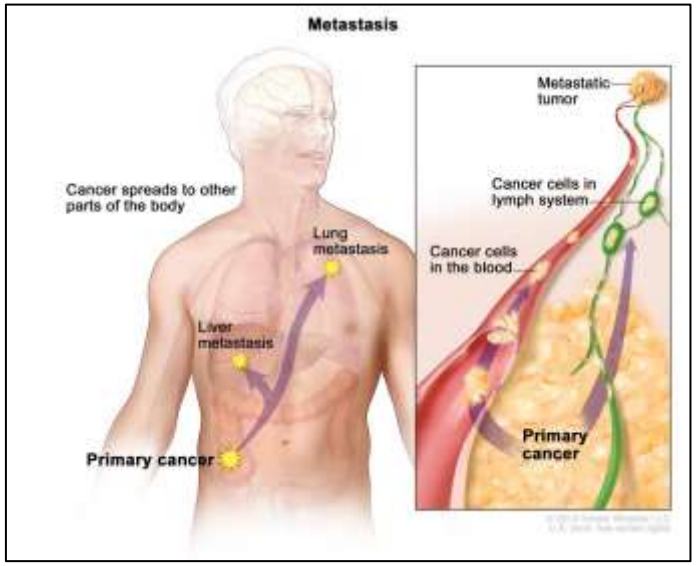


Mumby et al. Front Immunol 2019

Lung metastasis

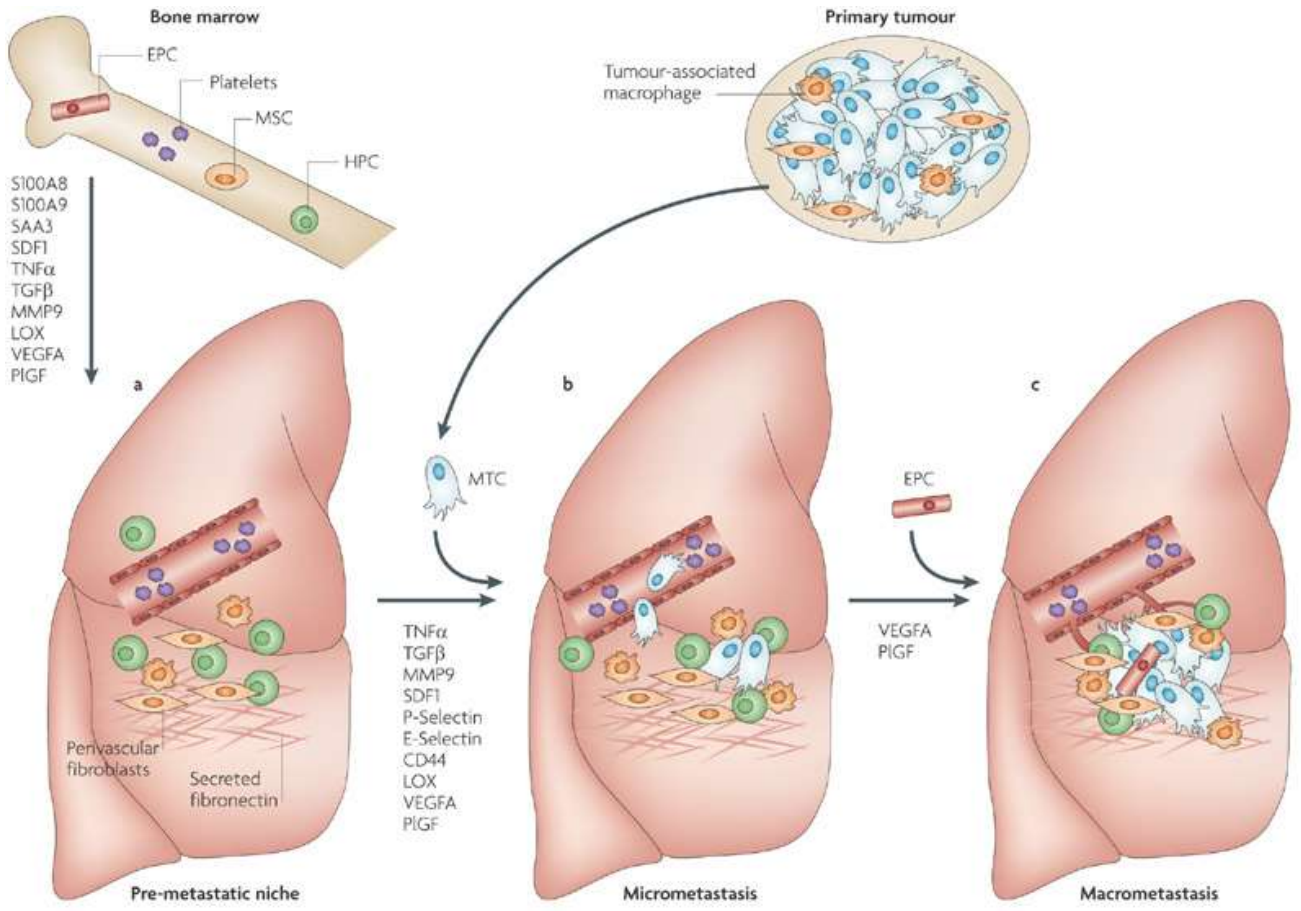
Cancer Type	Main Sites of Metastasis
Bladder	Bone, liver, lung
Breast	Bone, brain, liver, lung
Colon	Liver, lung, peritoneum
Kidney	Adrenal gland, bone, brain, liver, lung
Lung	Adrenal gland, bone, brain, liver, other lung
Melanoma	Bone, brain, liver, lung, skin, muscle
Pancreas	Liver, lung, peritoneum
Prostate	Adrenal gland, bone, liver, lung
Rectal	Liver, lung, peritoneum
Stomach	Liver, lung, peritoneum
Thyroid	Bone, liver, lung
Uterus	Bone, liver, lung, peritoneum, vagina

https://www.cancer.gov



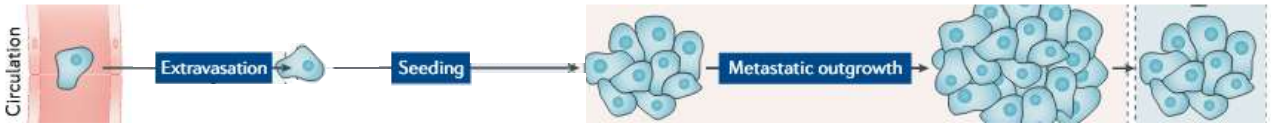
Lungs are among the most frequent sites of metastatic growth from extra-thoracic malignancies

Pre-metastatic niche



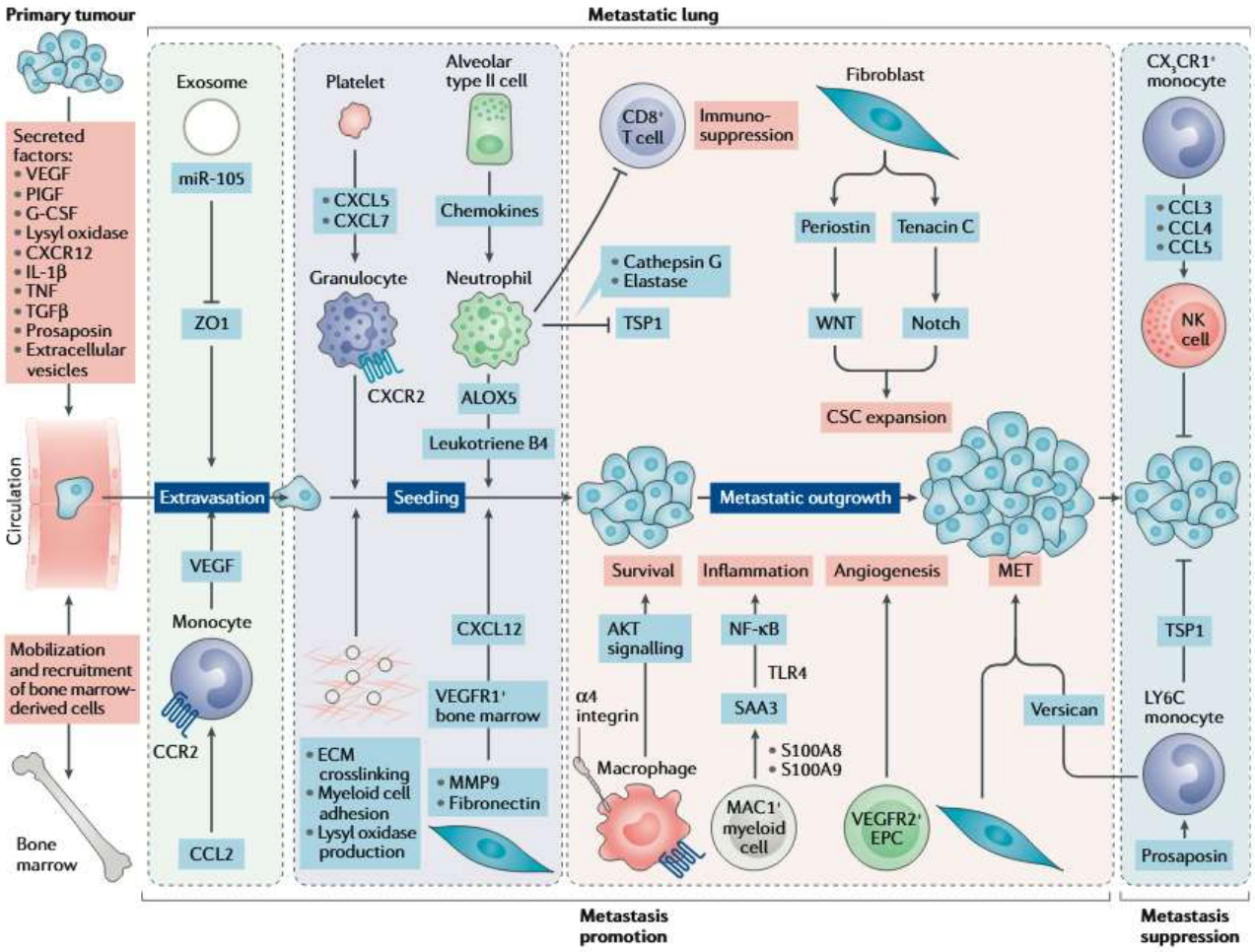
Psaila & Lyden, Nature Reviews 2010

The lung metastatic niche and metastatic cascade



Nasser K. Altorki, 2019, nature reviews

The lung metastatic niche and metastatic cascade



Nasser K. Altorki, 2019, nature reviews

BMJ Journals

Thorax

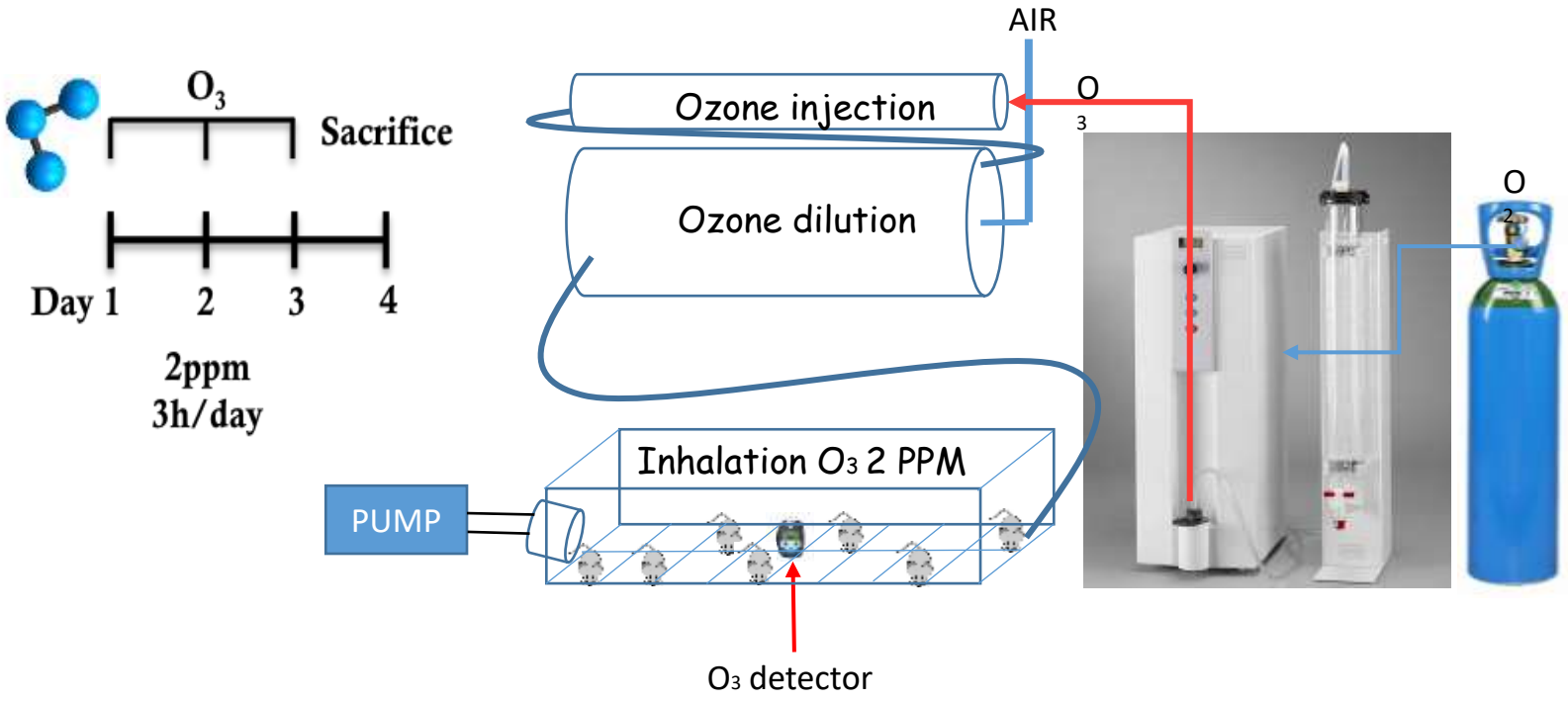
ORIGINAL ARTICLE

Ozone-primed neutrophils promote early steps of tumour cell metastasis to lungs by enhancing their NET production

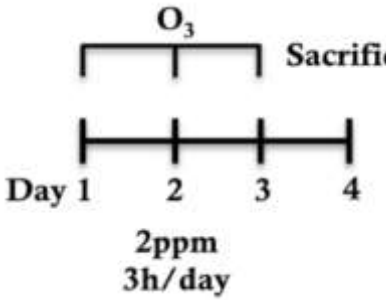
Natacha Rocks,[1] Céline Vanwinge,[1] Coraline Radermecker,[2,3] Silvia Blacher,[1] Christine Gilles,[1] Raphael Marée,[4] Alison Gillard,[1] Brigitte Evrard,[5] Christel Pequeux,[1] Thomas Marichal,[2,3,6] Agnes Noel,[1] Didier Cataldo[1,7]

Rocks et al, Thorax 2019

Development of a mouse model of pulmonary ozone exposure

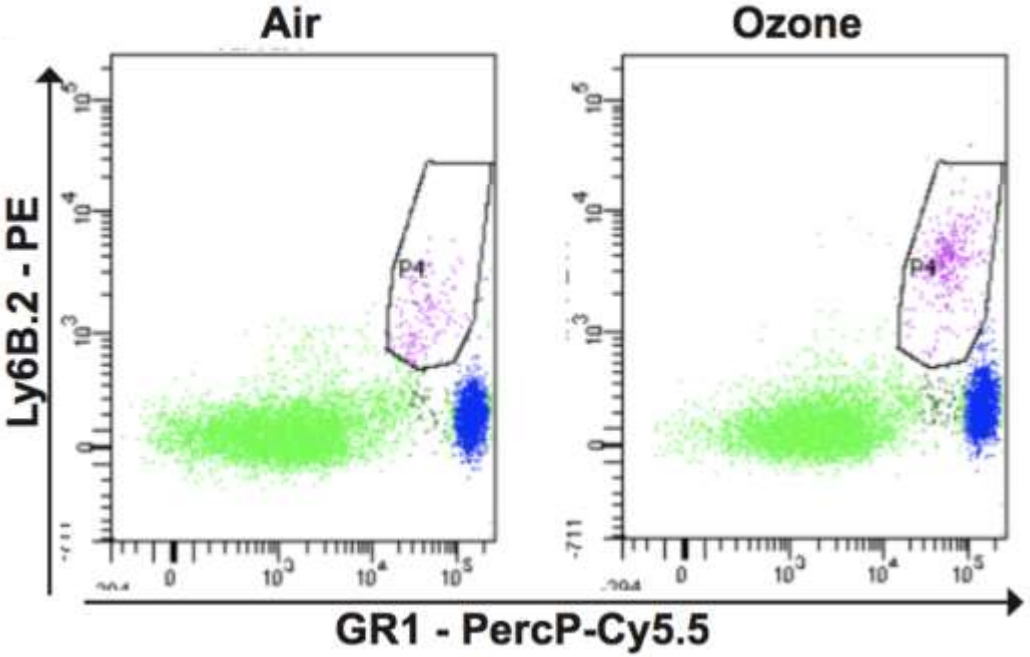


Ozone exposure induces lung neutrophilic inflammation

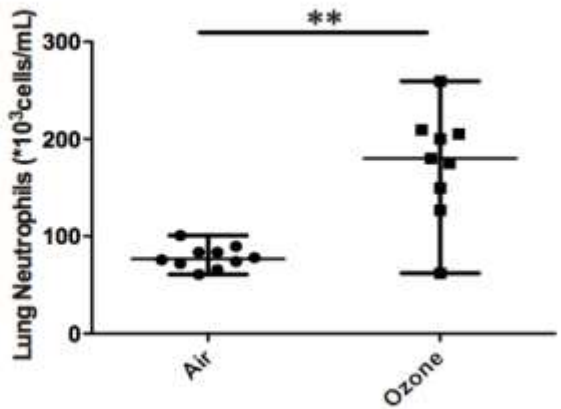


O_3 exposure system

Lung parenchyma neutrophils



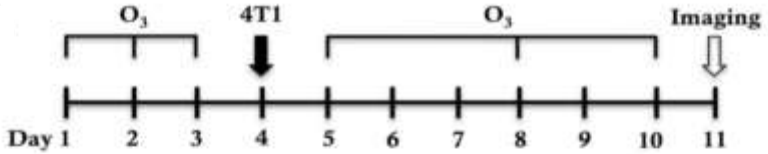
BAL neutrophils

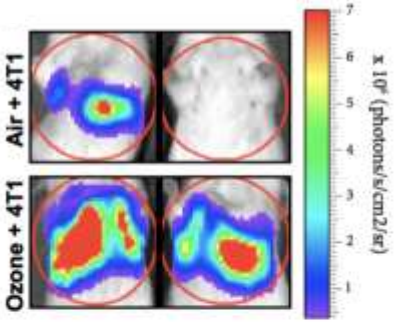


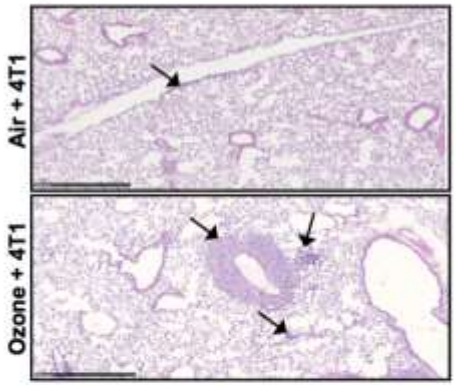
Rocks N, *et al. Thorax* 2019

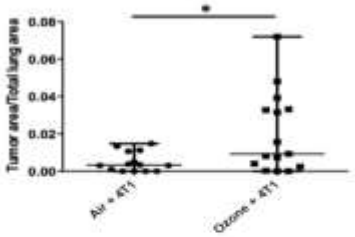
Ozone exposure triggers mouse breast and melanoma cancer cell dissemination

4T1 Breast

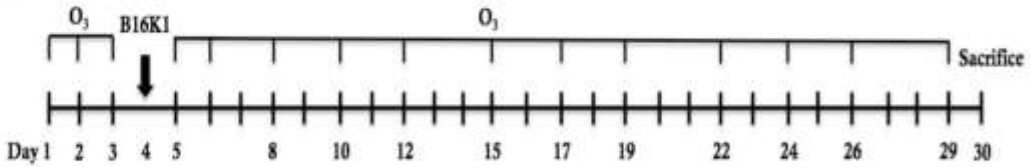


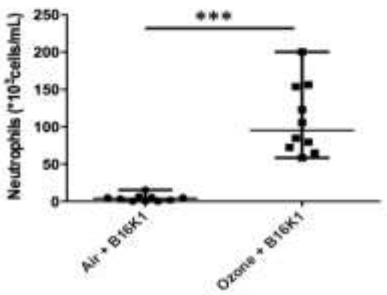


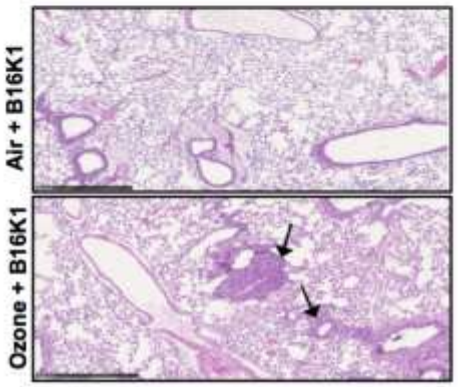


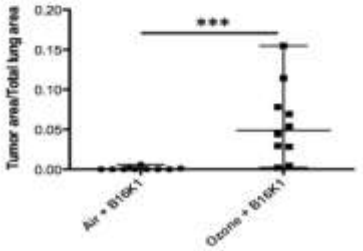


B16K1 Melanoma





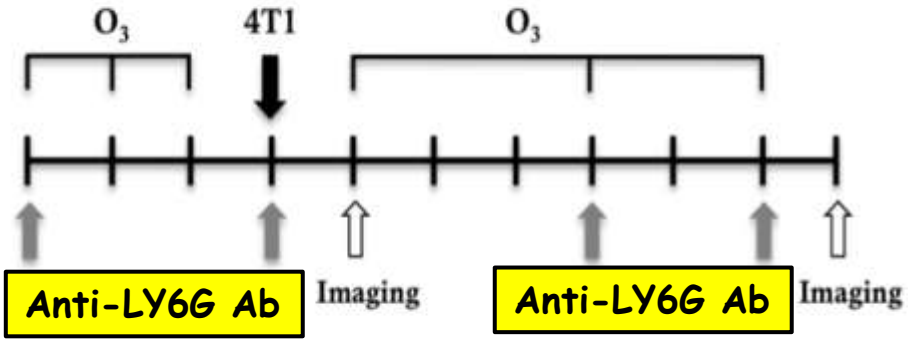




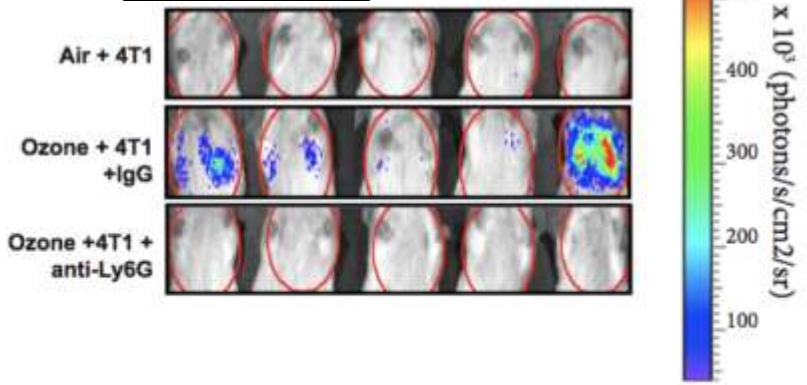
Rocks N, *et al. Thorax* 2019

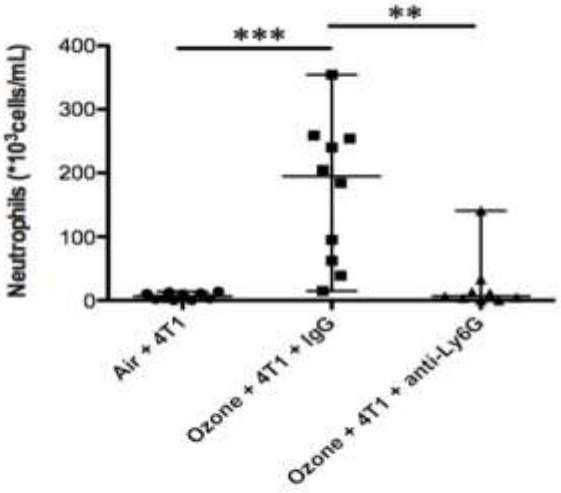
Neutrophils depletion blocks breast cancer cell dissemination in O_3-exposed animals

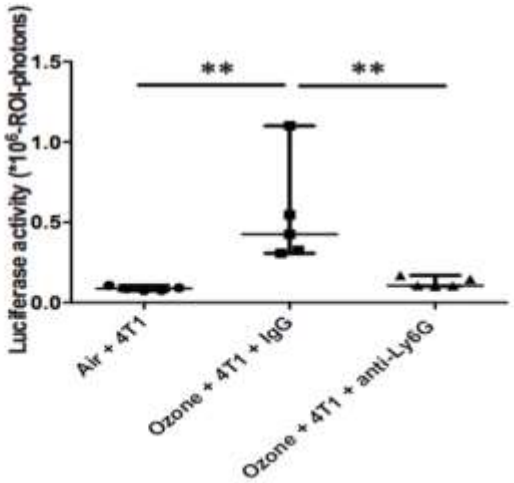
4T1 Breast



24 hours

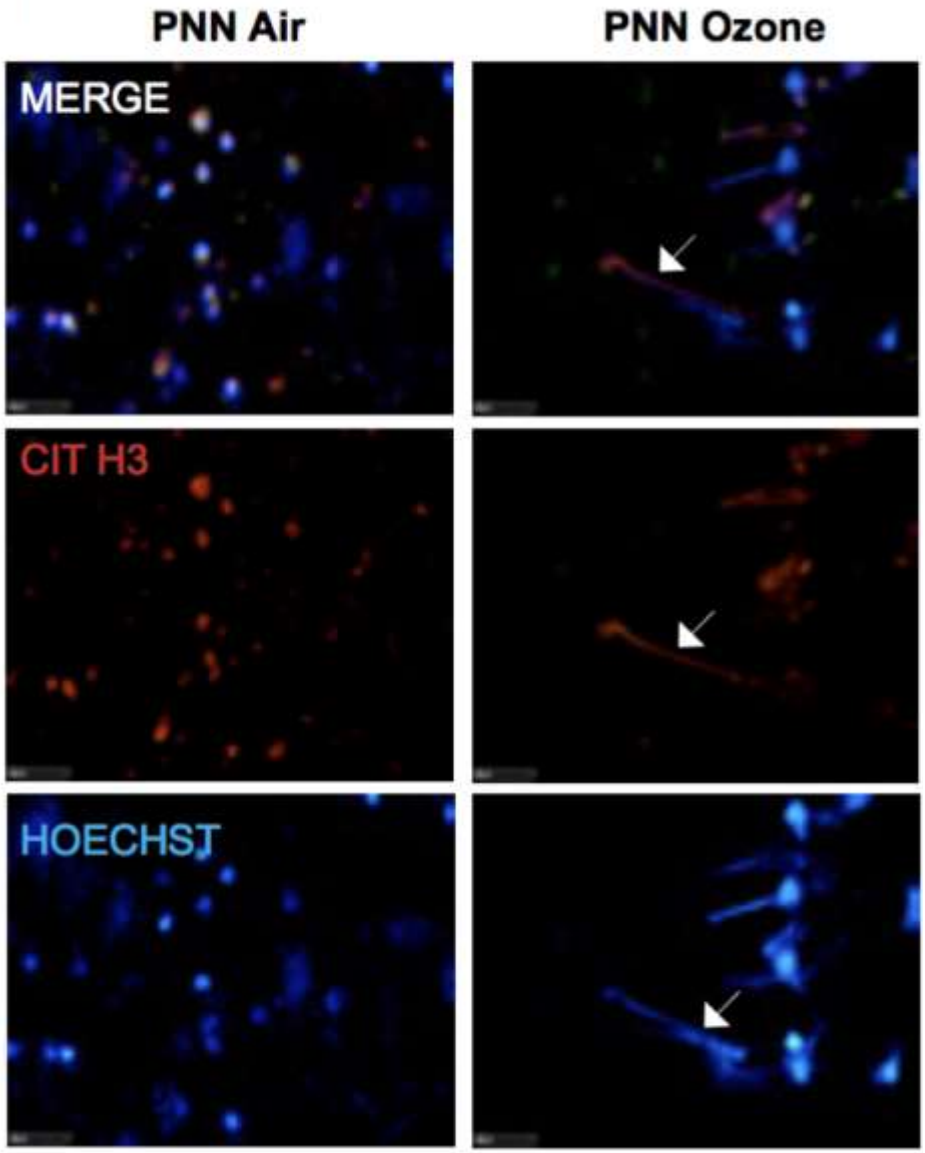


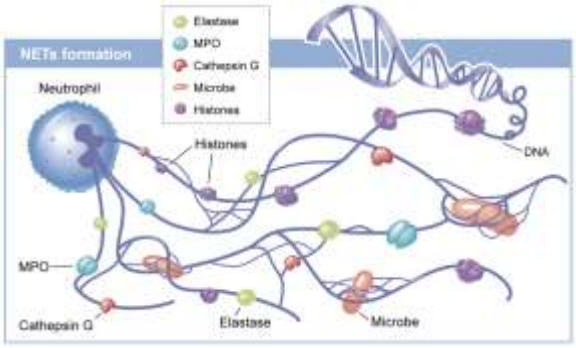




Rocks N, *et al. Thorax* 2019

O_3-exposed animals display NETs in vitro and in lung parenchyma

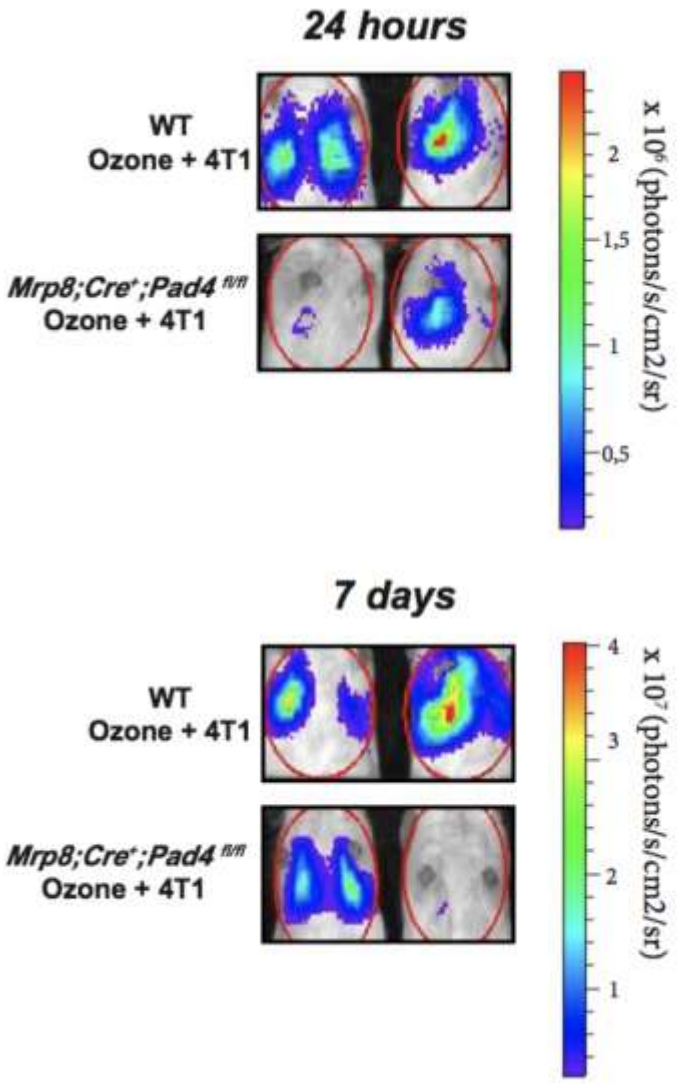


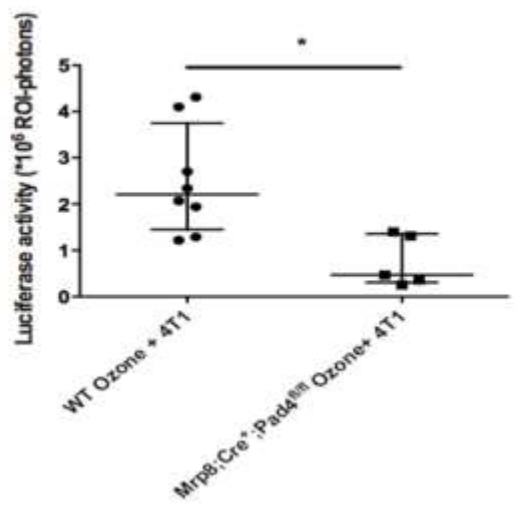


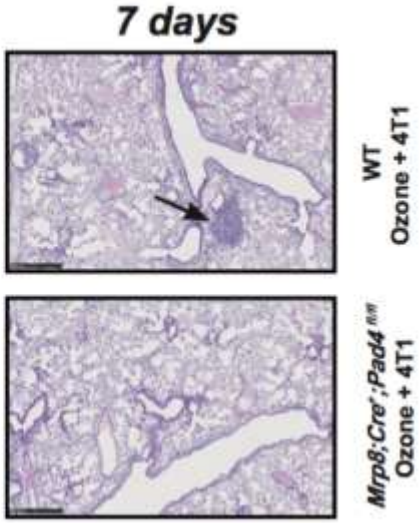
Rocks N, *et al*. *Thorax* 2019

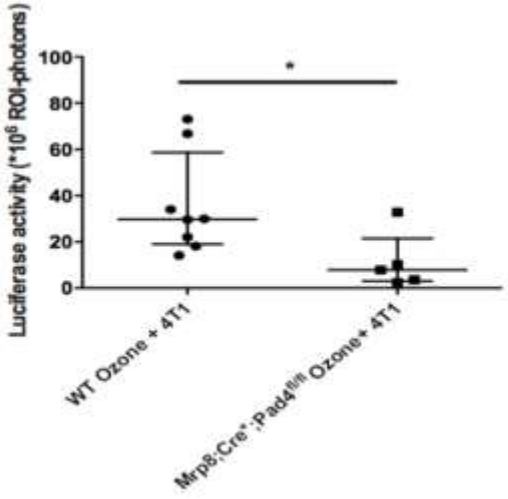
NETs inhibition decreases lung metastasis in O_3-exposed animals

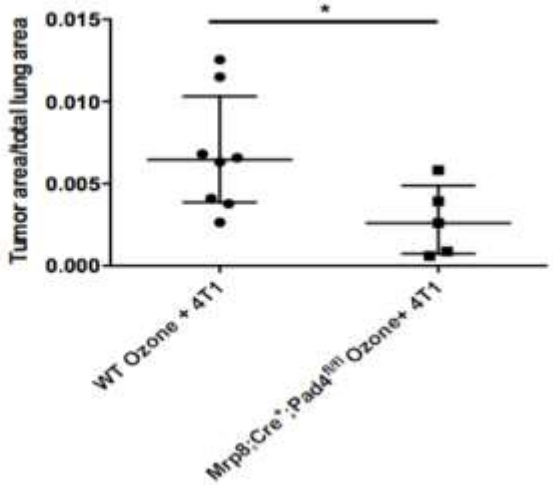
Pad4 KO animals







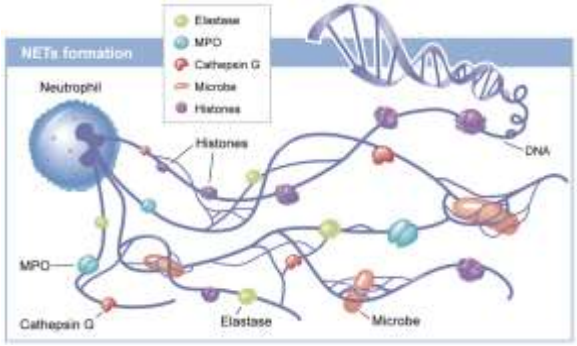




Similar results with Pad4 inhibitors or DNAse

Ozone increases lung metastasis by NETs formation

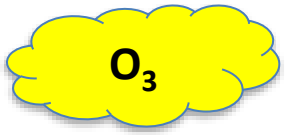
O_3

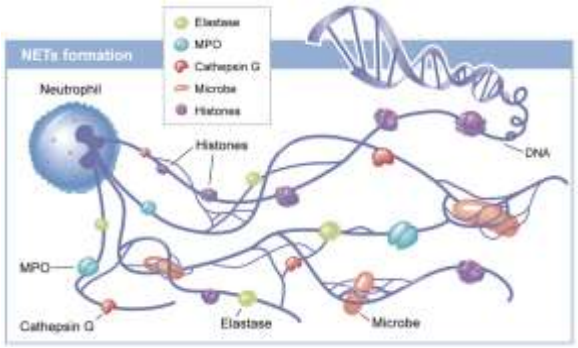


Metastasis

Thorax 2019 (IF 9.65)

Ozone increases lung metastasis by NETs formation



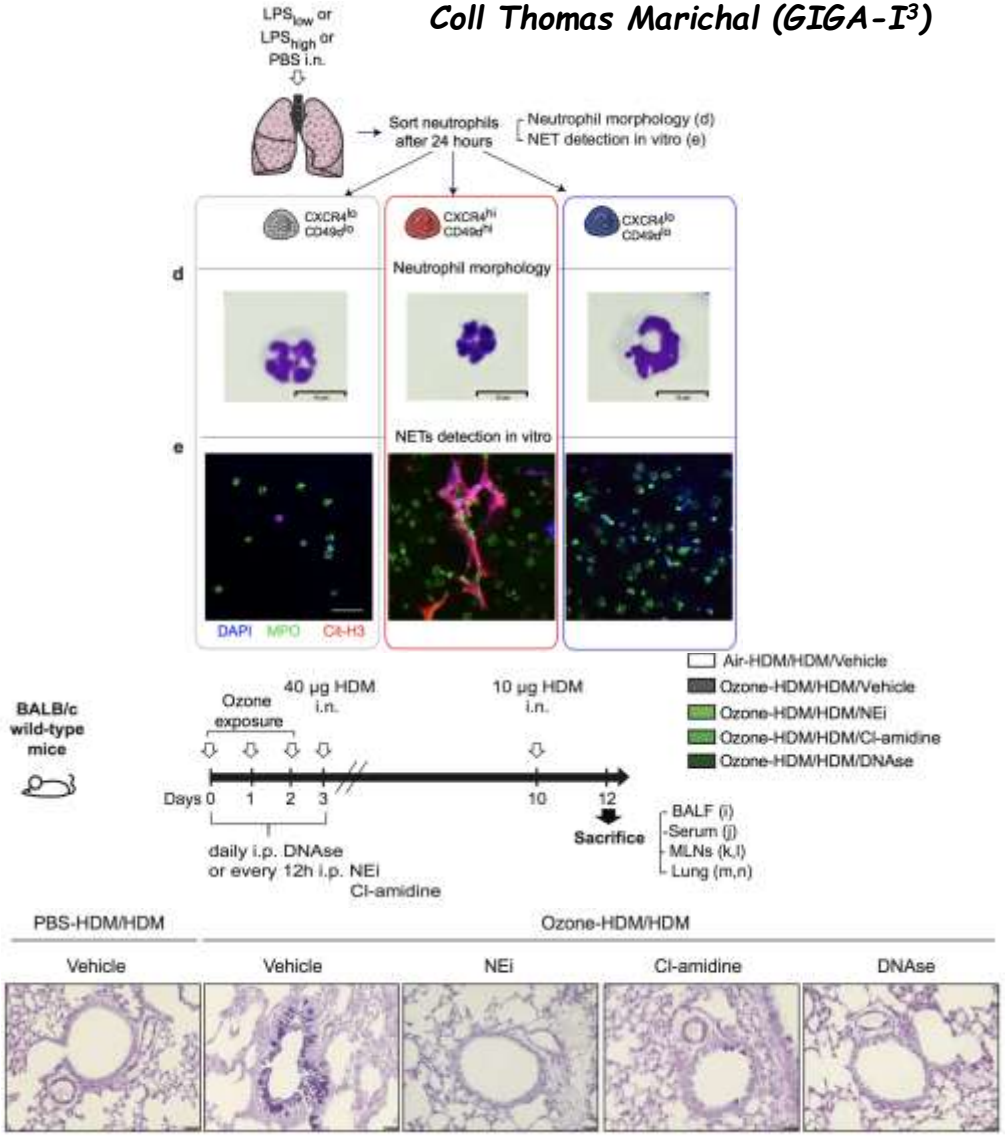


Metastasis

Thorax 2019 (IF 9.65)

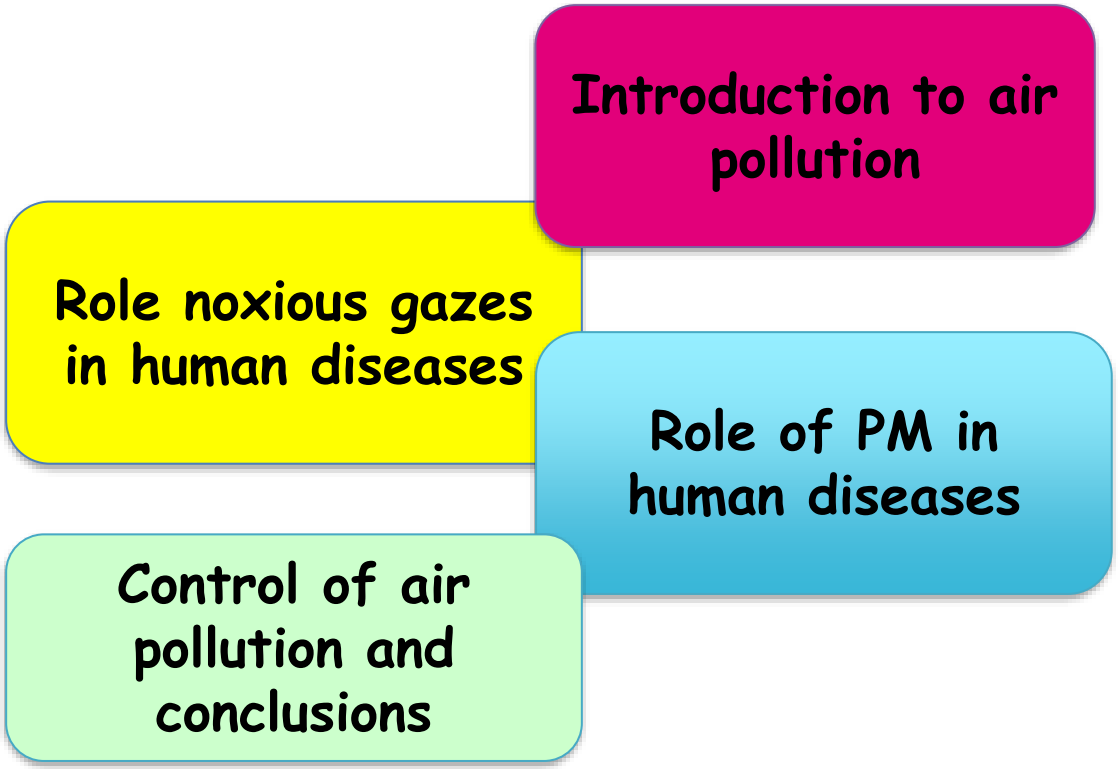
Ozone-induced NETs contribue to sensitization to airborne allergens

Coll Thomas Marichal (GIGA-I³)

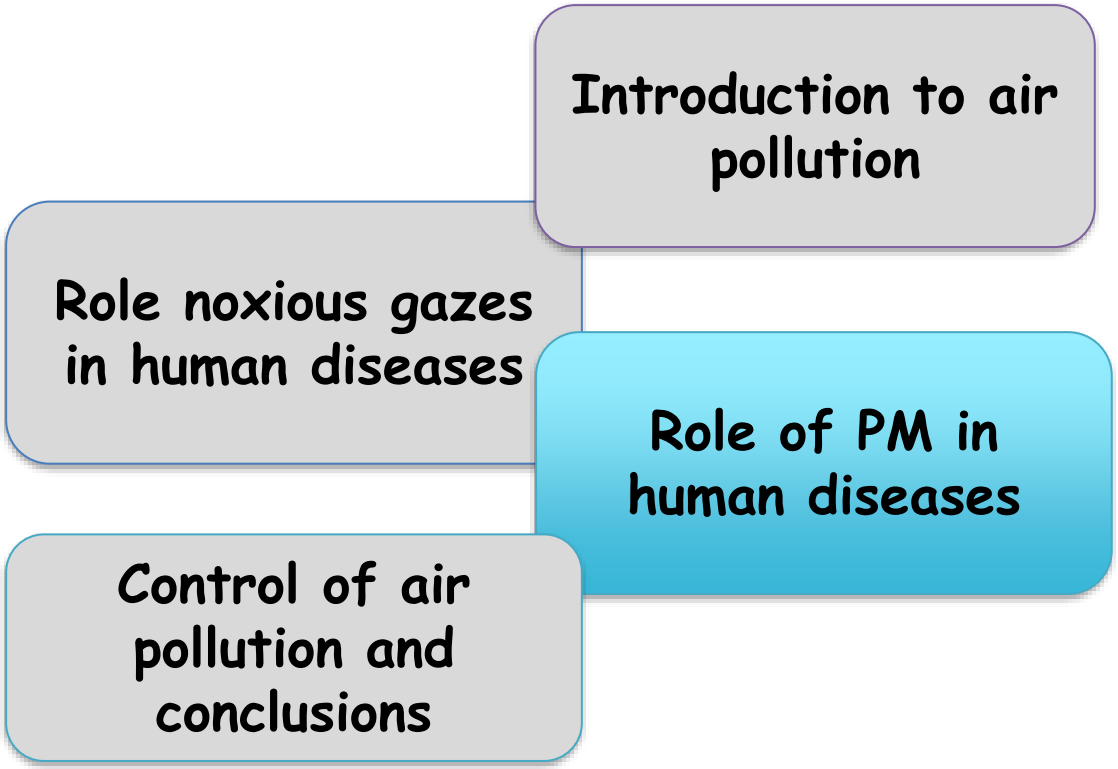


Nature Immunology 2019 (IF 21.81)

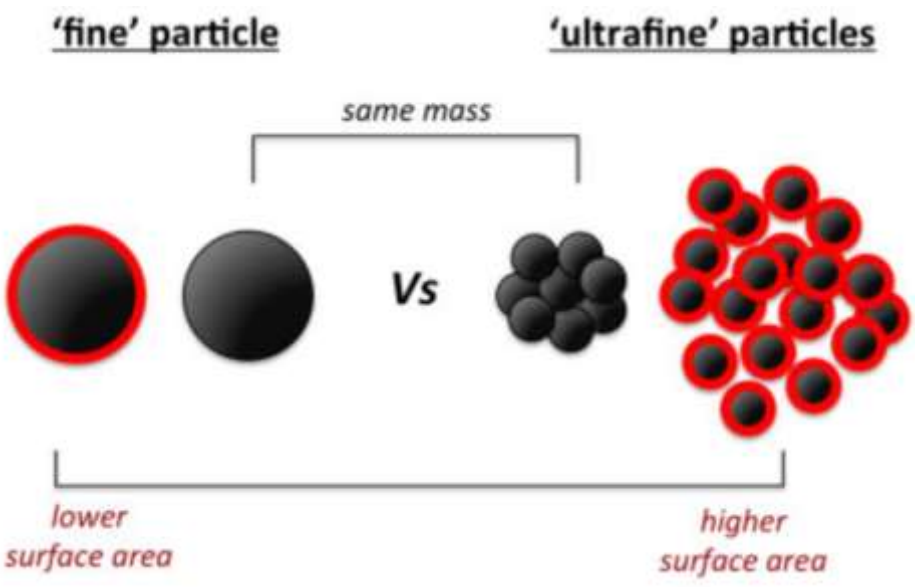
Environmental respiratory health and disease

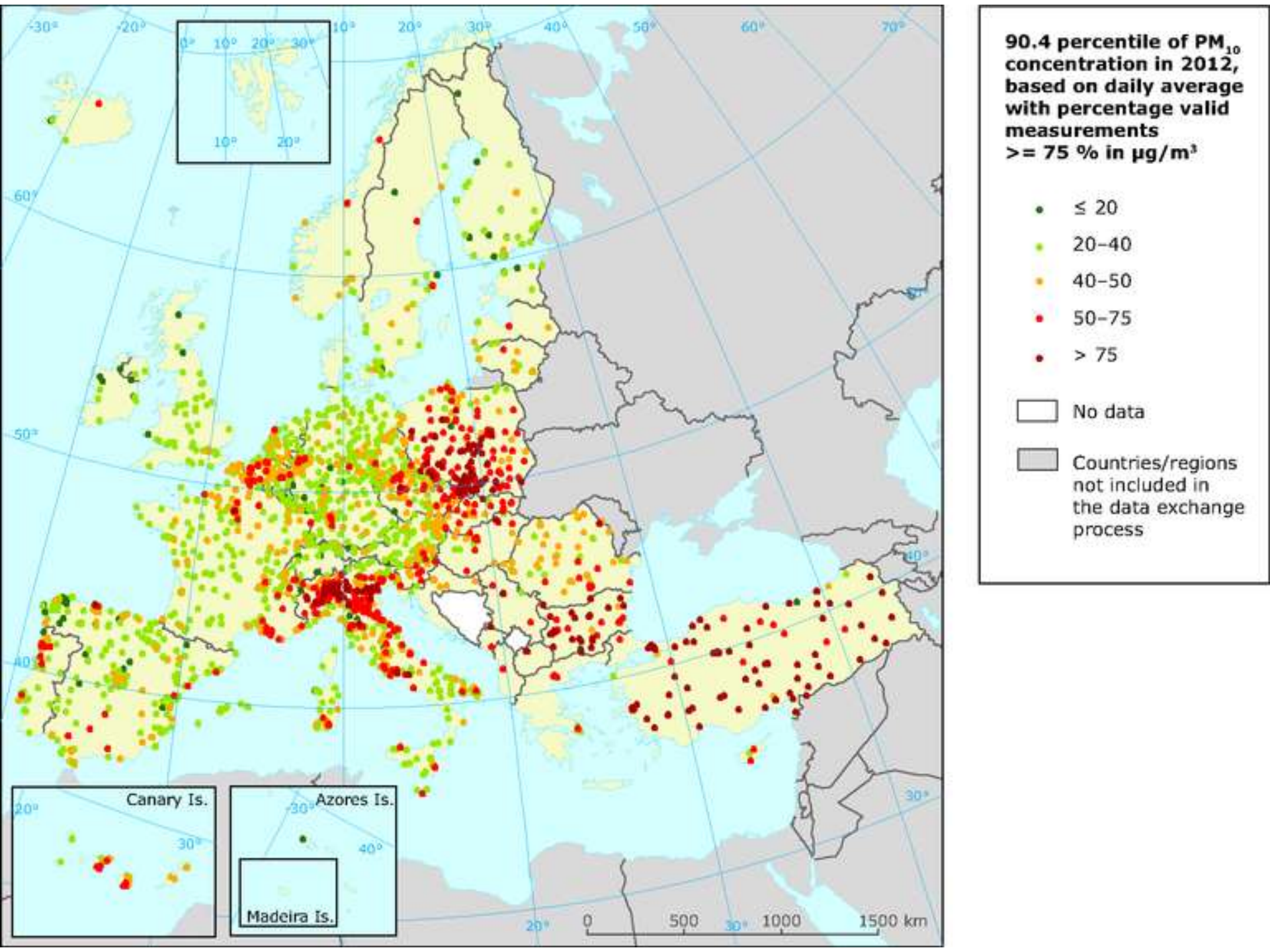


Environmental respiratory health and disease



Particle Category	Diameter (µm)	Size comparisons (if the PM was 100,000 times bigger):
Coarse: PM_{10}	2.5 – 10.0	 football (220 mm)
Fine: $PM_{2.5}$	< 2.5	 golf ball (40 mm)
Ultrafine PM (nanoparticles)	< 0.1	 large grain of sugar (1-2 mm)

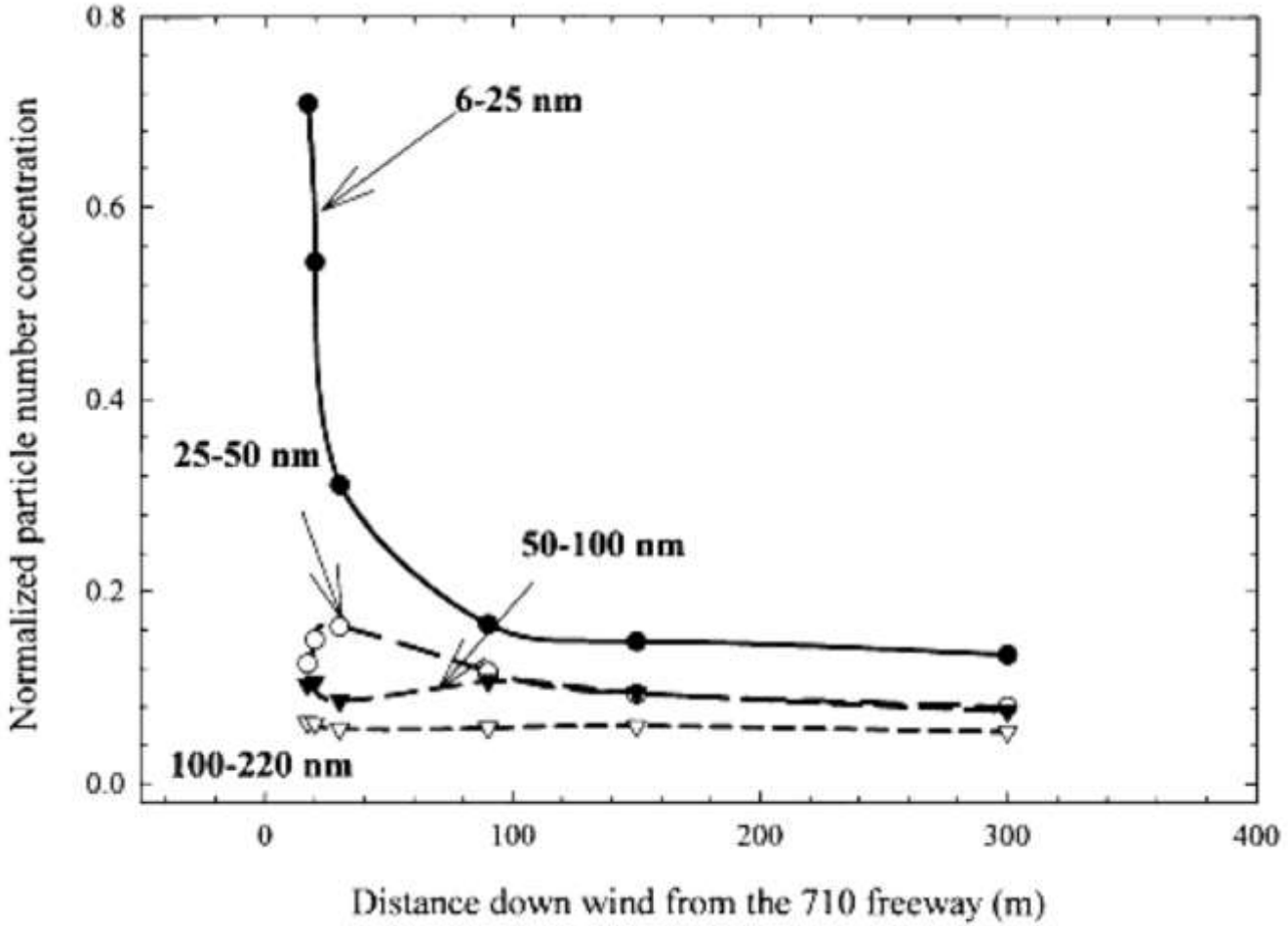



90.4 percentile of PM10 concentration in 2012, based on daily average with percentage valid measurements >= 75 % in µg/m³
≤ 20
20–40
40–50
50–75
> 75
No data
Countries/regions not included in the data exchange process
Canary Is.
Azores Is.
Madeira Is.
0
500
1000
1500 km

PM concentration gradient when approaching motorways

Near-highway pollutants in motor vehicle exhaust: A review of epidemiologic evidence of cardiac and pulmonary health risks

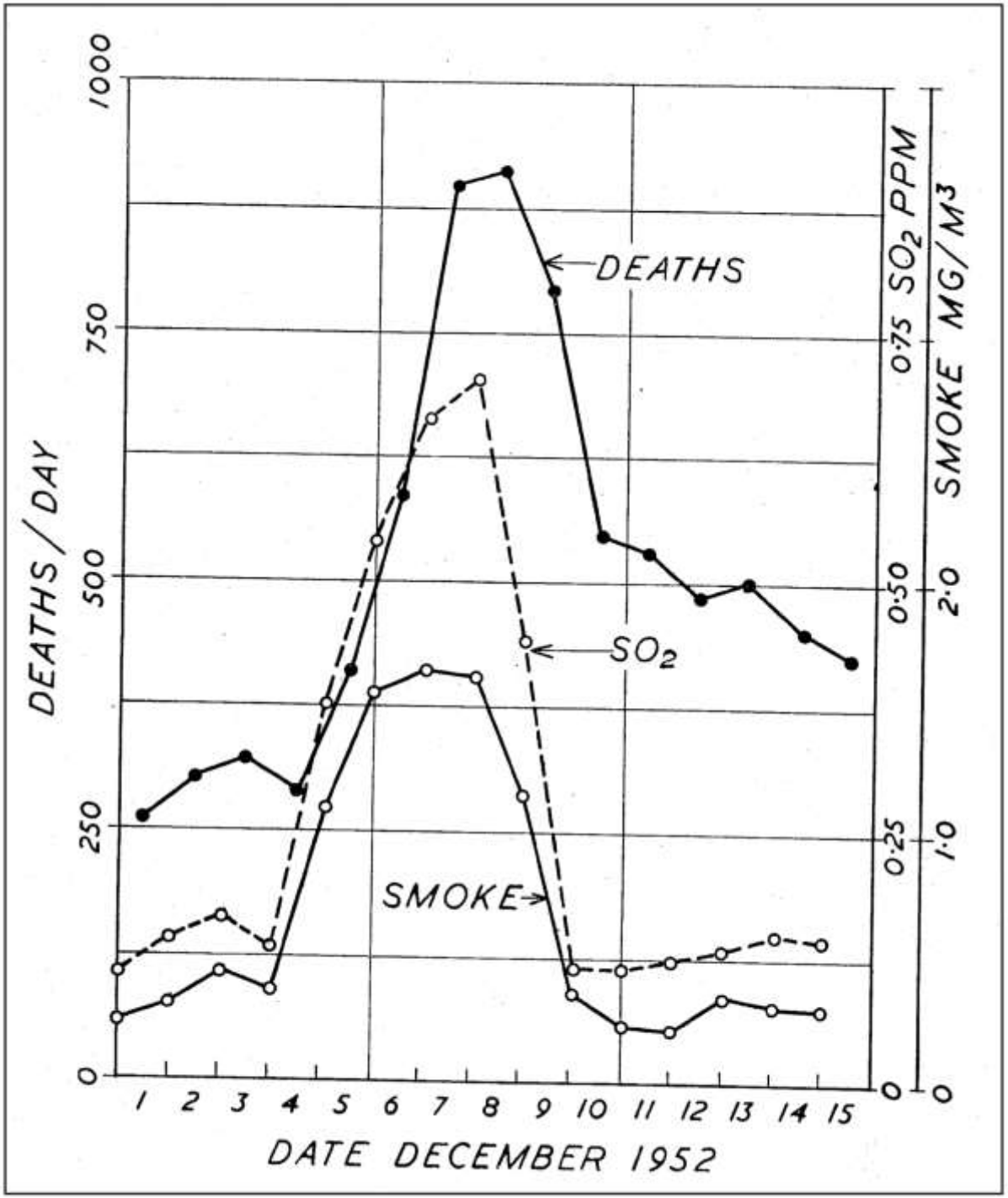
Doug Brugge*[1], John L Durant[2] and Christine Rioux[3]



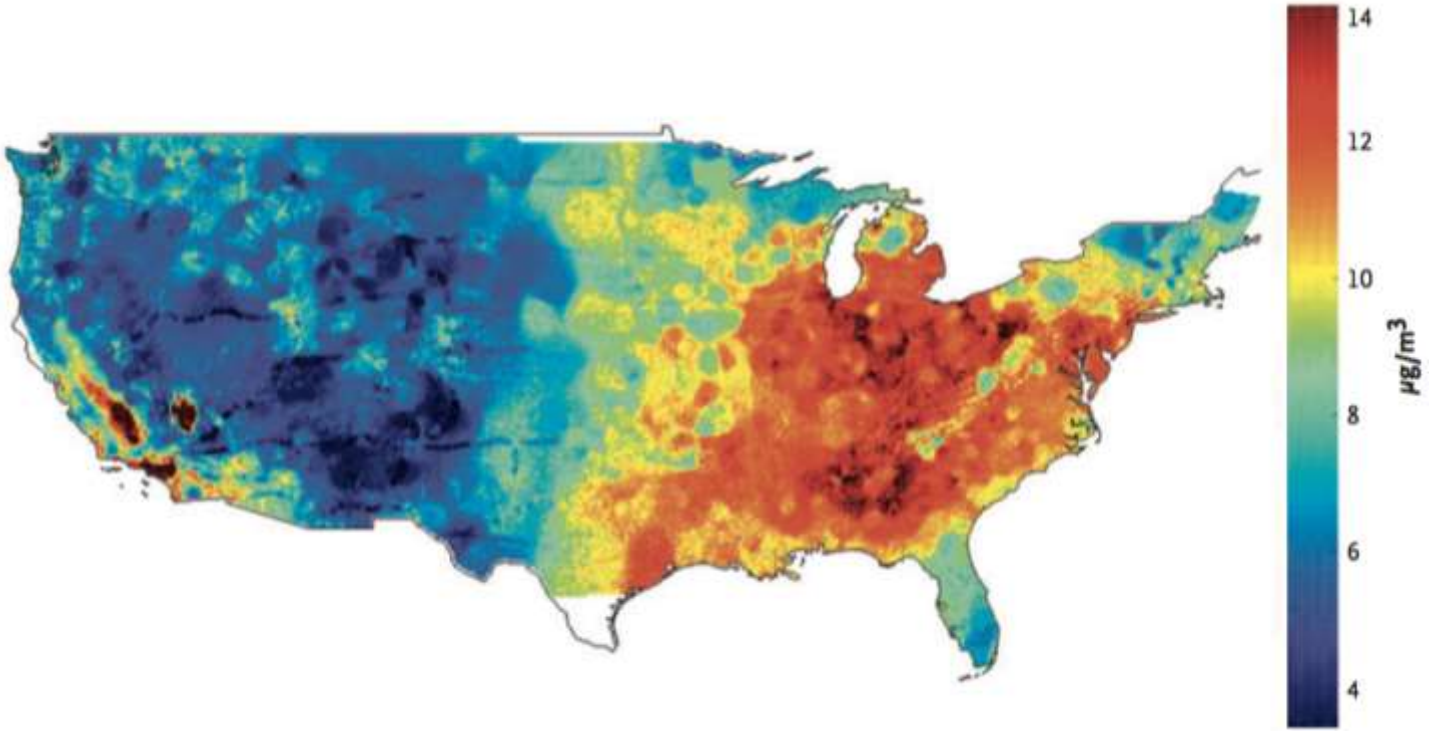
Environmental Health 2007, **6**:23

London great smog - 1952


6


DEATHS / DAY
1000
750
500
250
0
DEATHS
SO2
SMOKE
0·75 SO2 PPM
0·50
0·25
0
SMOKE MG/M3
2·0
1·0
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
DATE DECEMBER 1952

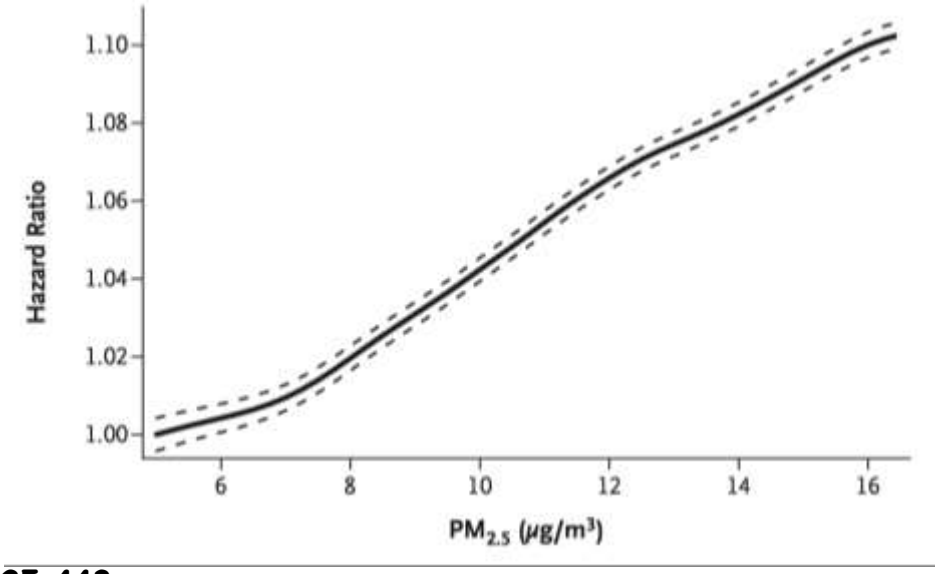
PM 2.5 average concentration



Di et al. NEJM 2019

Correlations with all-cause mortality

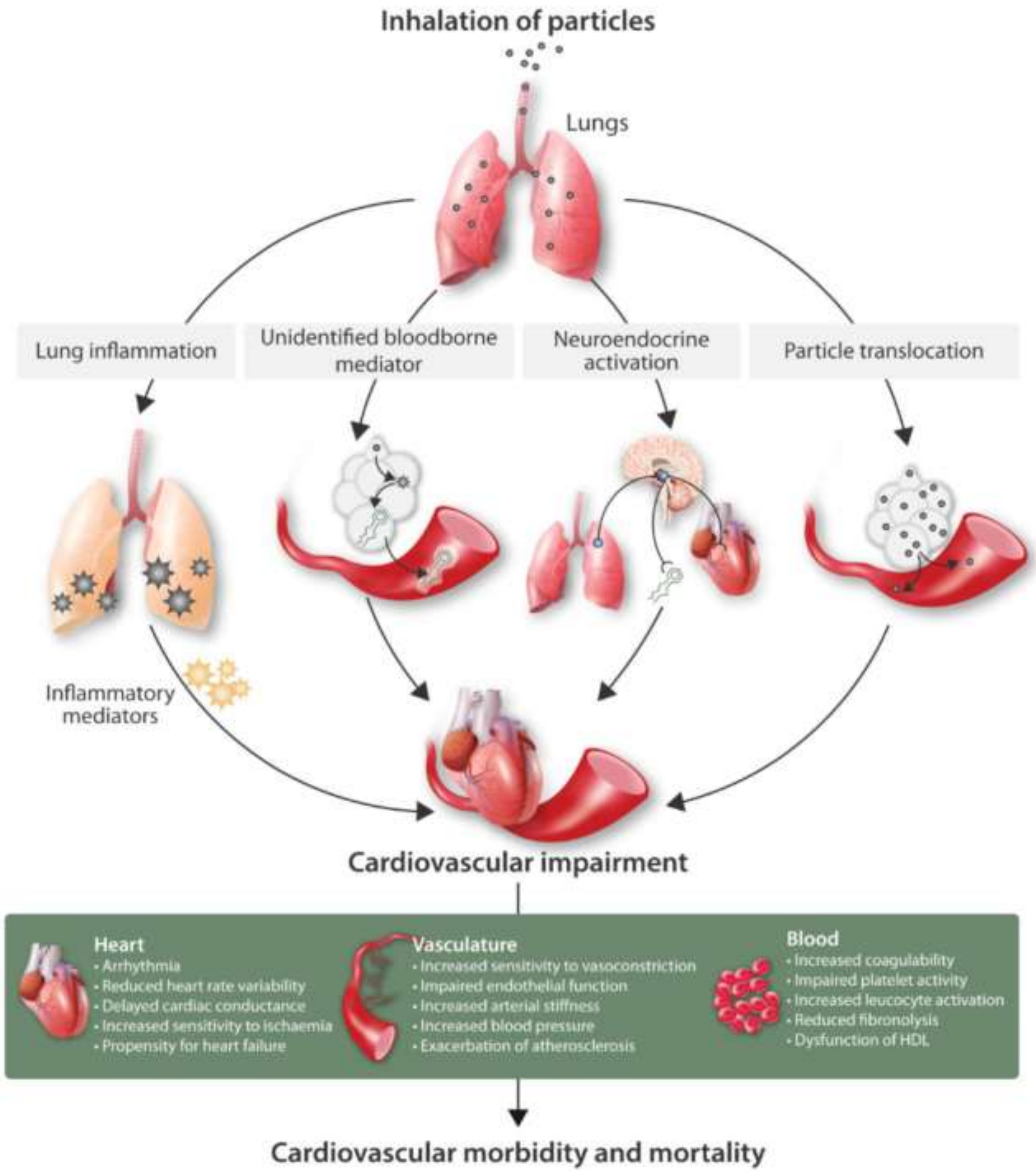
Exposure to PM 2.5



n = 60,925,443
460,310,521 person-year

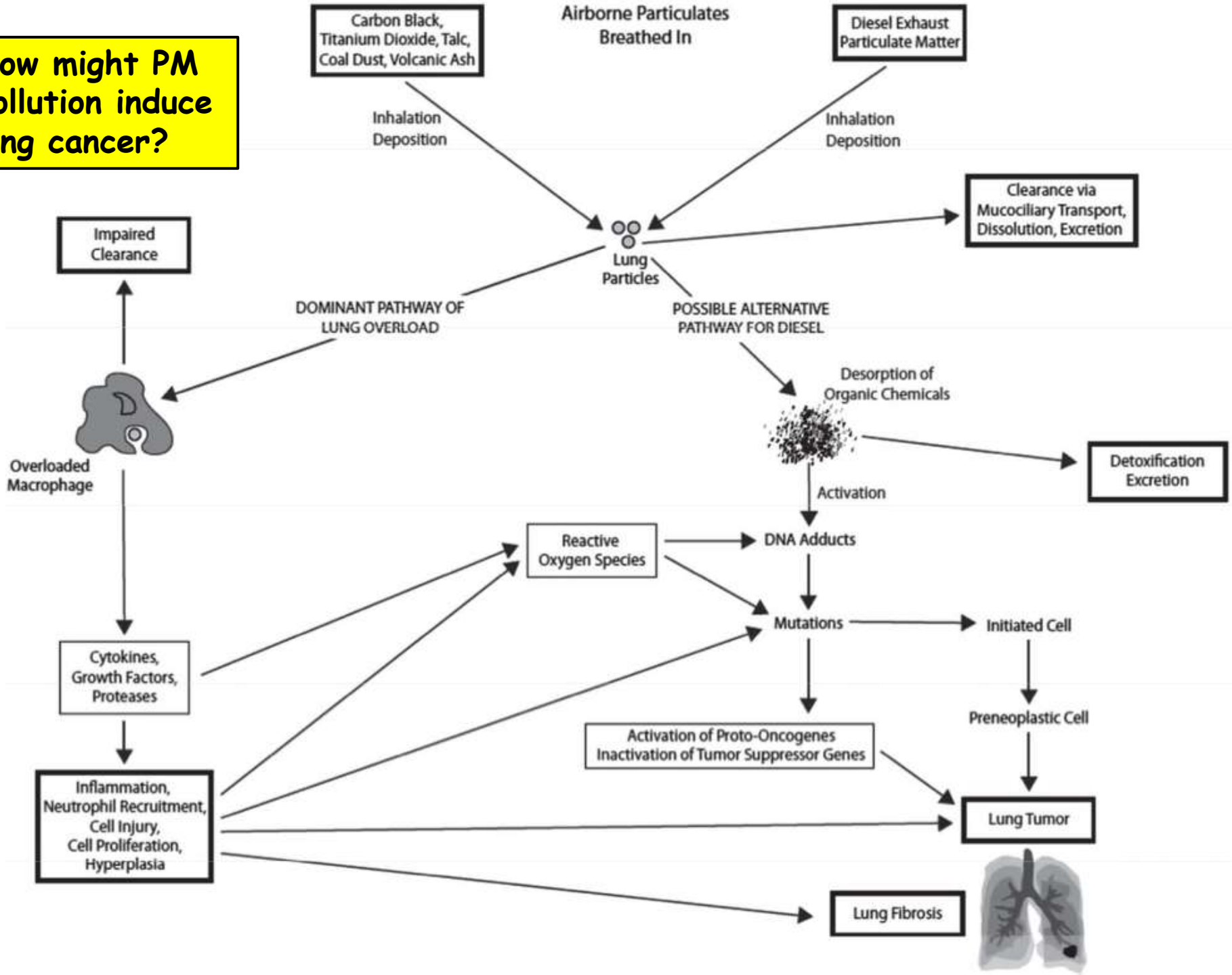
Di et al. NEJM 2019

Mechanisms of cardiovascular morbidity

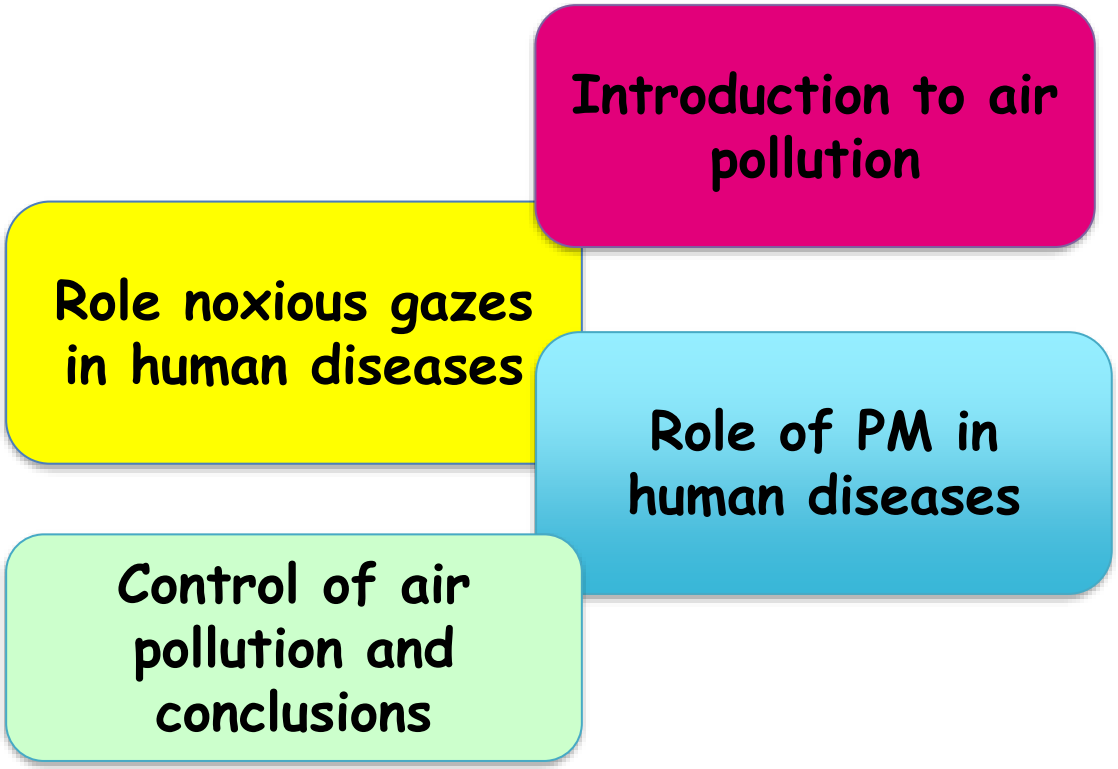


Miller & Newby, Cardiovasc Res, 2019

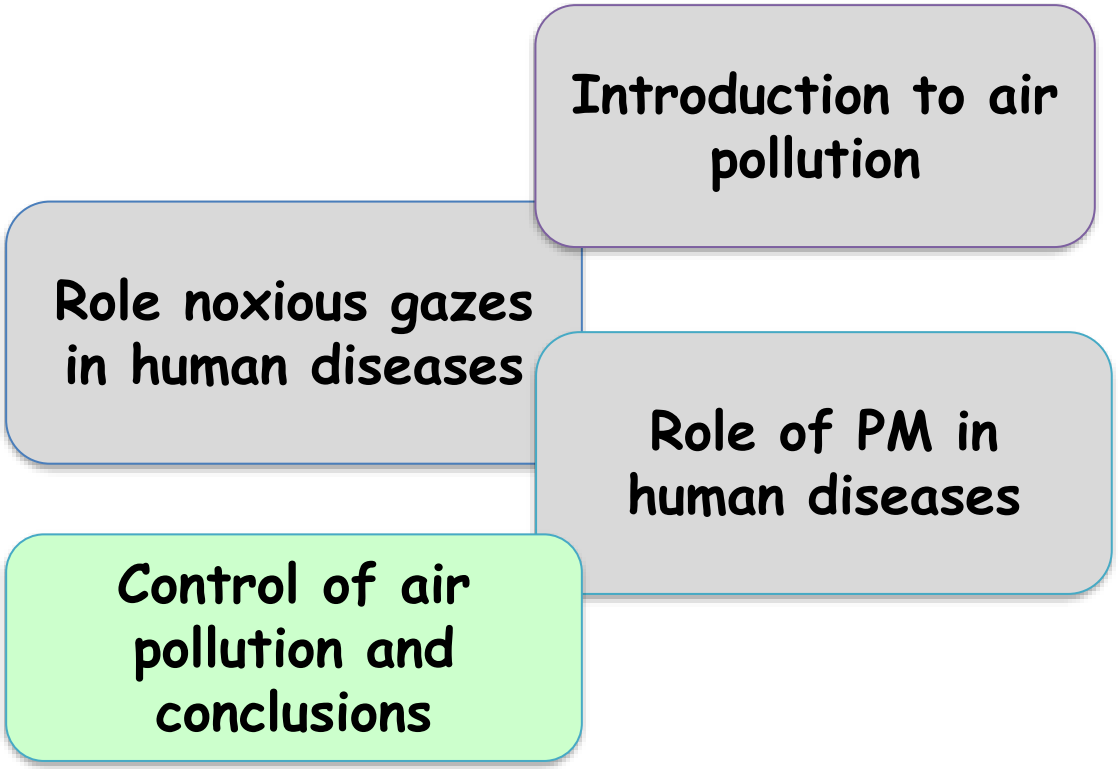
How might PM pollution induce lung cancer?



Environmental respiratory health and disease



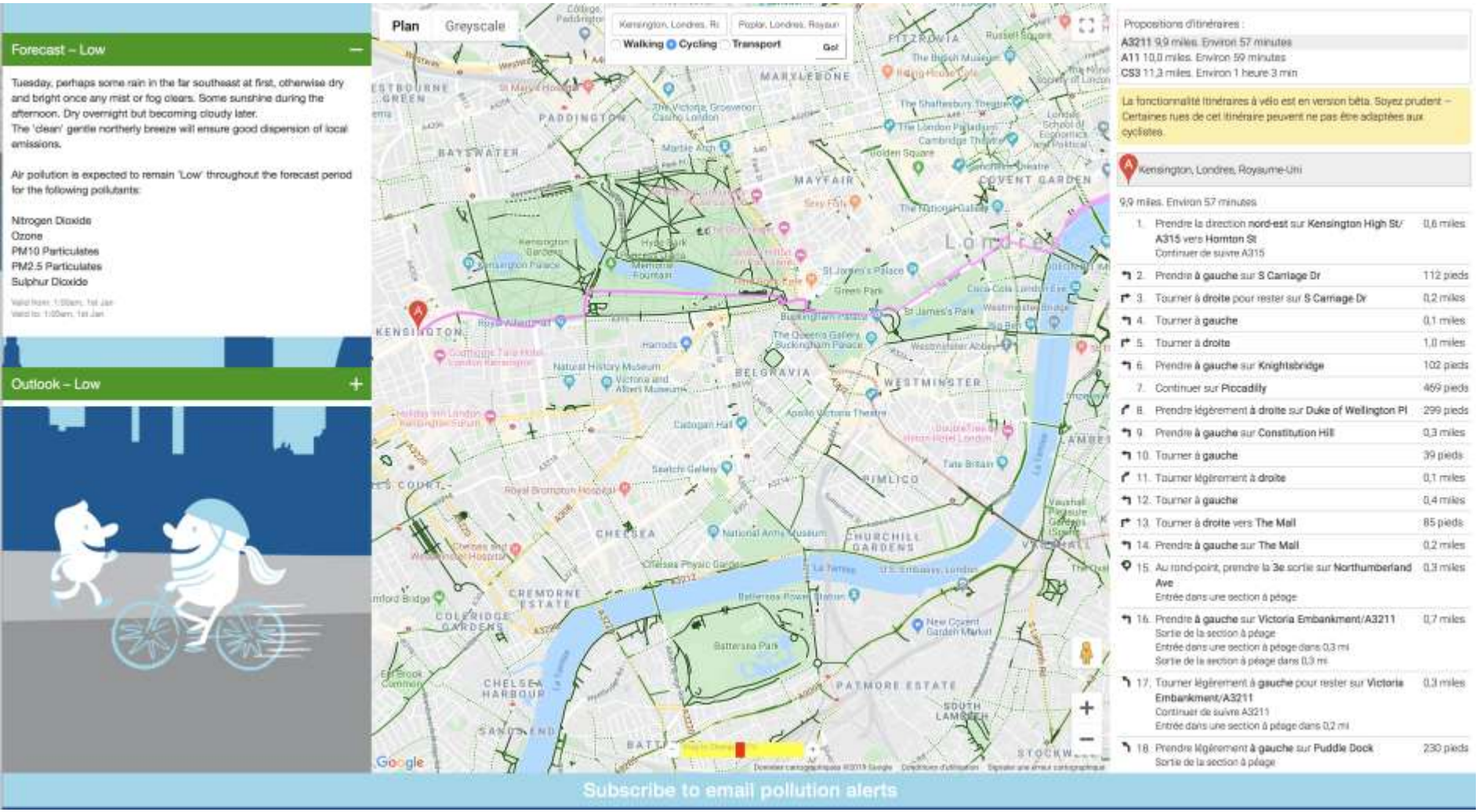
Environmental respiratory health and disease



Can we avoid air pollution?

Public information experiment : CityAir app (London)

Allows to select low pollution routes



And it works !

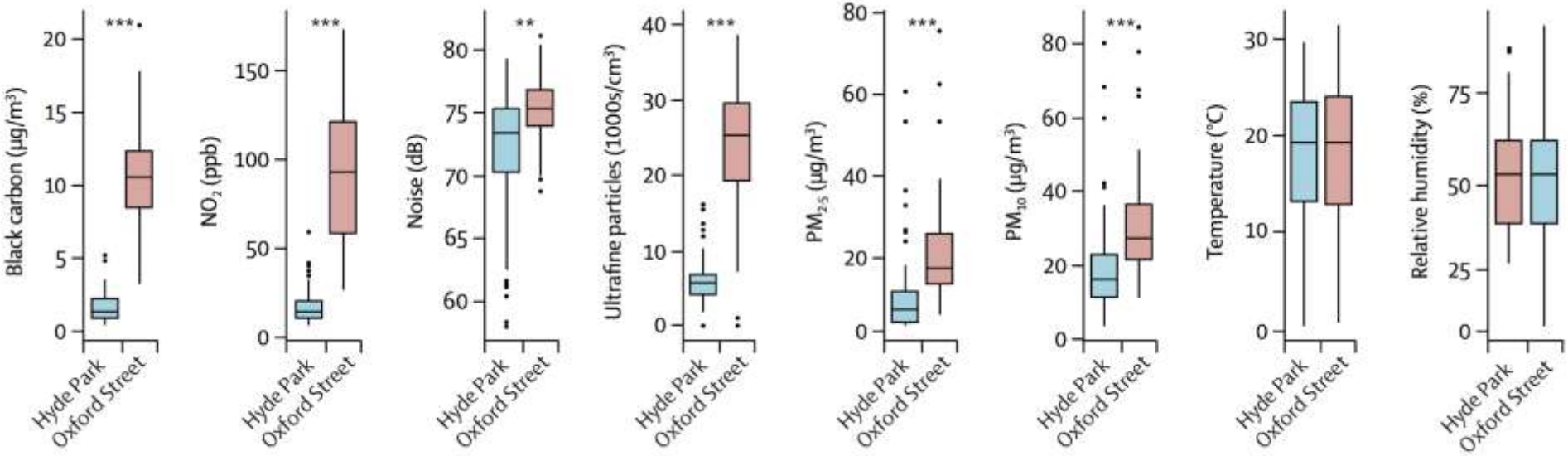
Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomised, crossover study

Rudy Sinharay, Jicheng Gong*, Benjamin Barratt, Pamela Ohman-Strickland, Sabine Ernst, Frank J Kelly, Junfeng (Jim) Zhang, Peter Collins, Paul Cullinan, Kian Fan Chung*

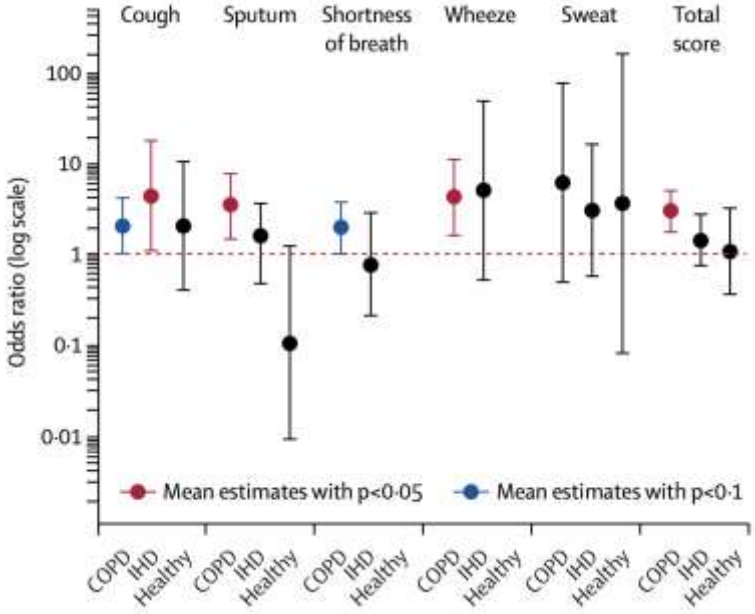
- **40 Healthy volunteers, 40 COPD, 40 Ischaemic heart disease**
- **2 hours walking**
- **Oxford street *versus* Hyde park**
- **Measurements of black carbon, NO_2 , $PM_{2.5}$, PM_{10}**

Lancet 2018; 391: 339–49

Pollutant levels

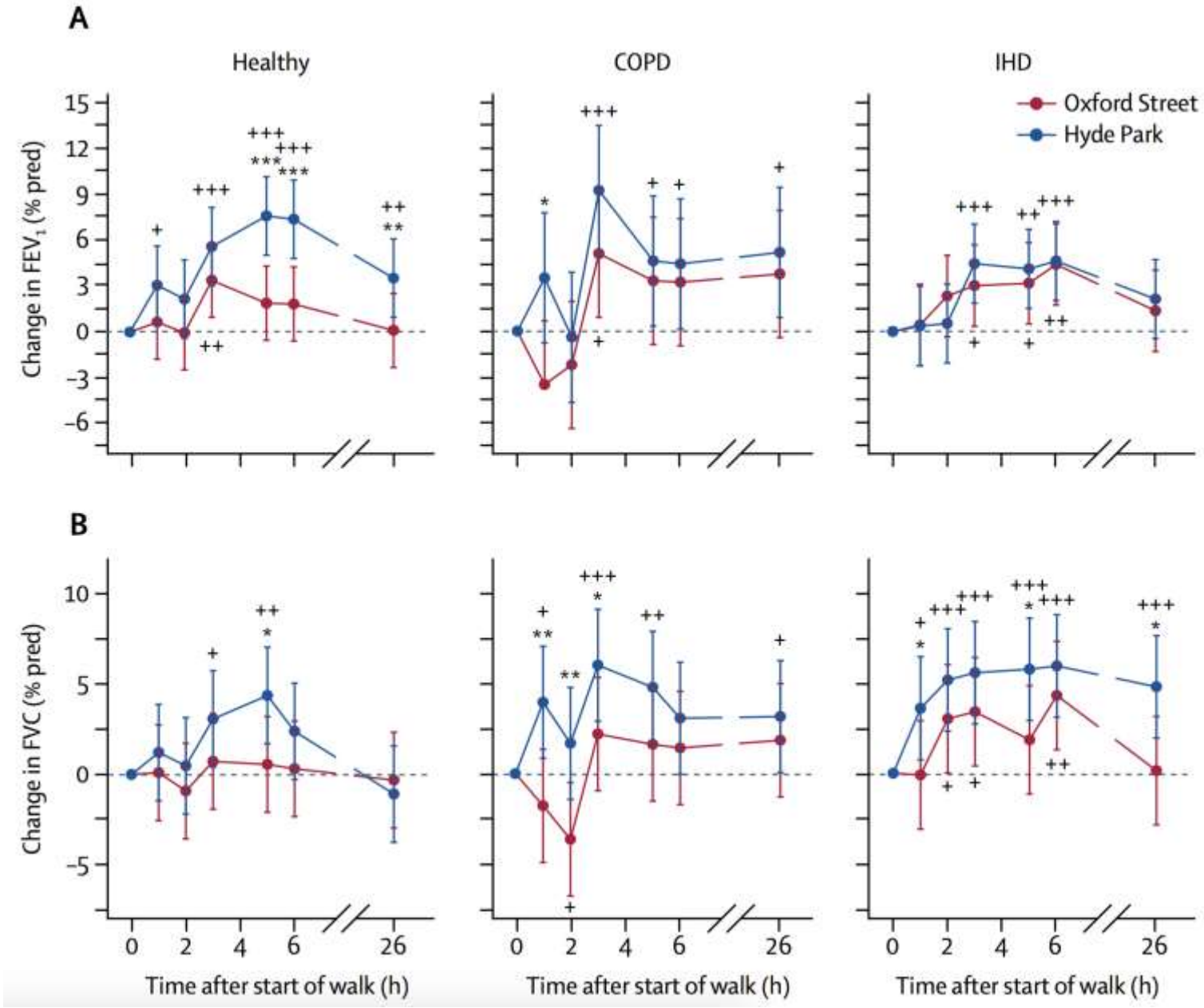


Odds ratio of getting worse symptoms in Oxford street



Lancet 2018; 391: 339–49

Lung function



Lancet 2018; 391: 339–49

Low Emission Zone .brussels

IN PRACTICE - MY VEHICLE - ENFORCEMENT ALTERNATIVES - INCENTIVES - DOCUMENTATION - SIMULATOR NEWS

DIESEL	2018	2019	2020	2021	2022	2023	2024	2025
EURO 6, 6b, 6d, temp / VI	Access	Access	Access	Access	Access	Access	Access	Access
EURO 5, 5a, 5b / V ou EEV	Access	Access	Access	Access	Access	Access	Access	No access*
EURO 4 / IV	Access	Access	Access	Access	No access*	No access*	No access*	No access*
EURO 3 / III	Access	Access	No access*	No access*	No access*	No access*	No access*	No access*
EURO 2 / II	Access	No access*	No access*	No access*	No access*	No access*	No access*	No access*
EURO 1 / I	No access*	No access*	No access*	No access*	No access*	No access*	No access*	No access*
No EURO standard	No access*	No access*	No access*	No access*	No access*	No access*	No access*	No access*

* A maximum of 8 days' per year and per vehicle is available by purchasing a paid-for day pass.

PETROL/LPG/CNG	2018	2019	2020	2021	2022	2023	2024	2025
EURO 6, 6b, 6d, temp / VI	Access	Access	Access	Access	Access	Access	Access	Access
EURO 5, 5a, 5b / V ou EEV	Access	Access	Access	Access	Access	Access	Access	Access
EURO 4 / IV	Access	Access	Access	Access	Access	Access	Access	Access
EURO 3 / III	Access	Access	Access	Access	Access	Access	Access	Access
EURO 2 / II	Access	Access	Access	Access	Access	Access	Access	No access*
EURO 1 / I	Access	No access*	No access*	No access*	No access*	No access*	No access*	No access*
No EURO stantard	Access	No access*	No access*	No access*	No access*	No access*	No access*	No access*

Patients should be advised to

- Recognize the risk of short term exposure to air pollution
- Use air pollution monitors (internet – or small devices)
- Be aware that indoor pollution is lower during peaks (O_3 and PM)
- Avoid outdoor exercises during peaks
- Know that long term risks exist
- Revise house location if exposure is important
- Change their lifestyle to be encline to active transport

What will be the solution(s) ?

Acknowledgments

LBTD team

Pr. Didier Cataldo
Pr. Agnès Noel
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Christine Fink
Alison Gillard
Fabienne Perin
Damien Polys
Alicia Demanche
Laura Gerardelli
Perrine Donay
Marie-Laure Delhez
Cassandre Yip

Pr. Thomas Marichal
Coraline Radermacker

BELGIAN
RESPIRATORY
SOCIETY

Backup slides

PM_{10} composition

	$\mu g/m^3$		$\mu g/m^3$
PM_{10} mass	22.61±1.26	**Ammonium**	0.16±0.03
Organic Carbon (OC)	4.19±0.20	**Barium**	0.08±0.003
Sulfate	4.00±0.34	**Zinc**	0.08±0.01
Elemental Carbon (EC)	3.26±0.17	**Copper**	0.04±0.03
Chloride	2.52±0.41	**Titanium**	0.02±0.004
Nitrate	1.92±0.13	**Manganese**	0.02±0.002
Iron	0.85±0.04	**Lead**	0.02±0.002
Calcium	0.43±0.03	**Vanadium**	0.01±0.002
Silicon	0.35±0.02	**Chromium**	0.01±0.001
Aluminium	0.17±0.02	**Nickel**	0.01±0.001

Chan, AJP Lung 2019

Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE)

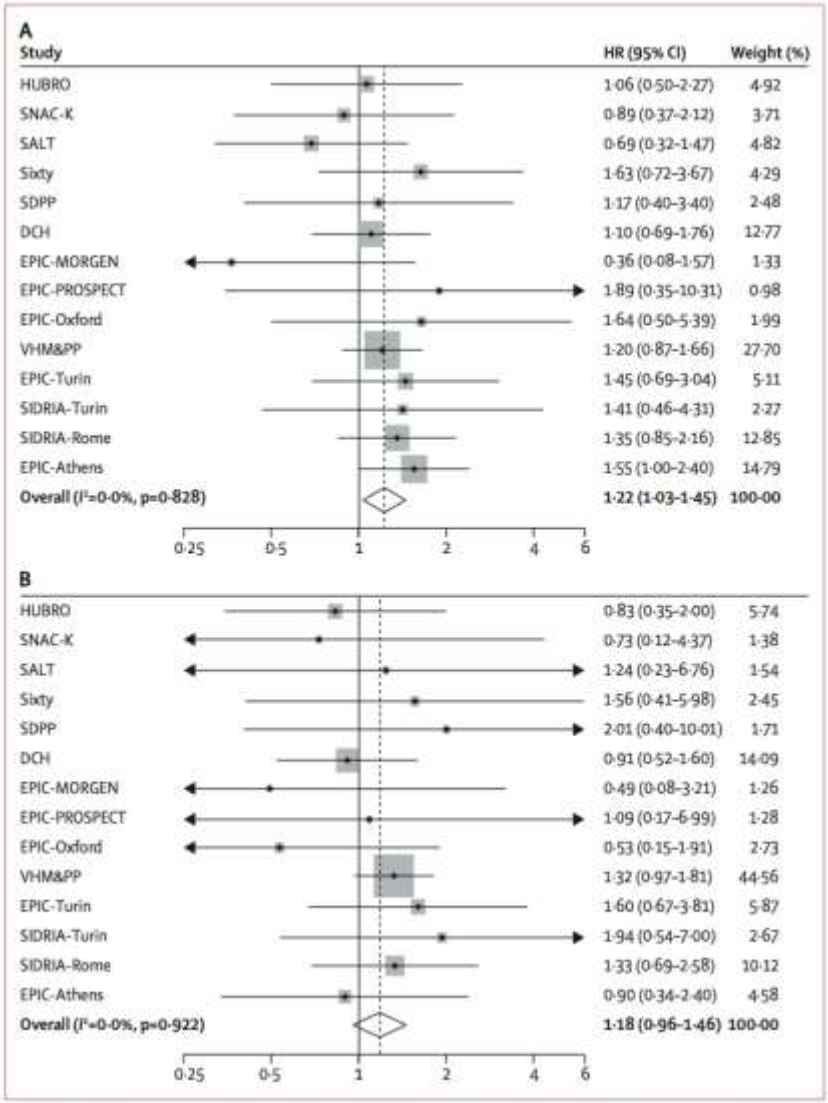

Figure 3: Risk for lung cancer according to concentration of particulate matter in each cohort study

In the ACS cohort study, lung cancer incidence increased by 8% per 10 µg/m^3 increase in $PM_{2.5}$ levels, measured as between-city difference
In a Danish cohort study, lung cancer incidence increased by 3.7% per 10 µg/m^3 increase in NOx, used as a marker of exposure to traffic-related pollutants. Most importantly, particles – in particular those from diesel engines – are loaded with carcinogens.

The Californian Environmental Protection Agency as well as the International Agency for Research on Cancer list diesel exhaust as an established carcinogen. ERS white book

International Agency for Research on Cancer

World Health Organization

PRESS RELEASE
N° 213

12 June 2012

IARC: DIESEL ENGINE EXHAUST CARCINOGENIC

Lyon, France, June 12, 2012 -- After a week-long meeting of international experts, the International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO), today classified diesel engine exhaust as **carcinogenic to humans (Group 1)**, based on sufficient evidence that exposure is associated with an increased risk for lung cancer.

Group 1: *The agent is carcinogenic to humans*.
This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.