



Air pollution and health over the life course

Francqui Chair UCLouvain, Ecole de Santé Publique

Tim Nawrot, PhD.

Centre for Environmental Sciences, Hasselt University

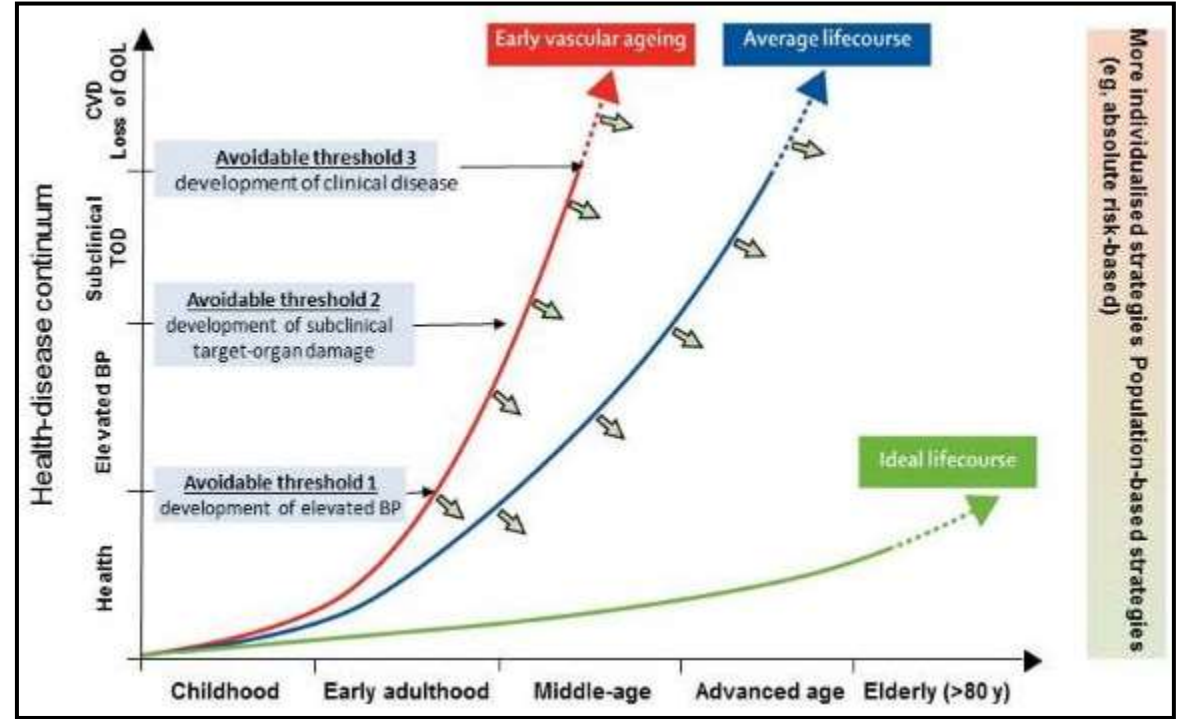
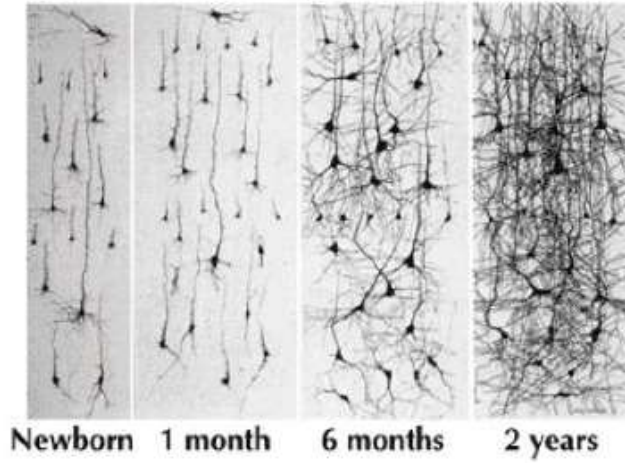
Environment & Health Unit, Leuven University

Why is the early life important?

EARLY LIFE as a key target period for solid, cost-effective preventive actions and policies related to multiple adverse environmental exposures

- ✓ Vulnerable periods of rapid organ development
- ✓ Chronic diseases have part of their origin in early life
- ✓ Lifetime influence
- ✓ Effective prevention

Brain Development Over Time



Ozone

Particulate
matter

Nitric dioxide

Smog

Black carbon



Monet (1840-1926)



"Need smoke be "black" to constitute an offence?"

is at least need for some expansion of the public health services and a general coördination of its several branches.

THE PISTOLS ACT.

THE first case that has come before a magistrate under the Pistols Act, 1903, was heard by Mr. Curtis Bennett recently as the result of a young man accidentally shooting a tobacconist who was serving him. It was found by the police that the pistol used upon this occasion had been lent to the person carrying it by the owner, a youth under 18 years of age, and that he had bought it from a man trading in the Edgware-road, who had committed two offences under the new Act—in selling without observing the formalities prescribed by the new Act and also in selling at all to a youth under 18 years of age. The seller of the pistol pleaded complete ignorance of the Act which only came into force on August 11th, very shortly before the sale in question took place. He was accordingly bound over to come up for judgment when called upon under the first summons and under the second was fined 5s. with 2s. costs. The youth who bought the pistol was also summoned and bound over and the person who was carrying it without a licence and whose careless handling of it had injured the tobacconist was fined. These two, also, were ignorant of the provisions of the law.

the pistol by criminals may be said in general to vary in inverse proportion to their sanity. It is to those reckless of the penalty attaching to murder that it has generally proved attractive. It may be suggested that the police should take steps throughout the country in order that no one dealing in cheap pistols should be able to plead ignorance of the law. It is not a plea that will excuse him but it may be taken into account by the bench which tries him. The official printers, who in London are Messrs. Eyre and Spottiswoode, East Harding-street, E.C., sell the Act at $\frac{1}{2}d.$ a copy, so that even the hooligan of less than 18 years of age may easily possess a copy should he desire to do so.

NEED SMOKE BE "BLACK" TO CONSTITUTE AN OFFENCE?

IN the report of the medical officer of health of the City of London for the nine weeks ending on Sept. 12th, 1903, we are glad to note that the authorities are keeping an active watch over those who have no regard for the purity of the air and its freedom from filthy smoke. A list of offenders is given and the medical officer has recommended that notices should be served upon the owners or occupiers of the premises named to abate the nuisance and to do what is necessary for pre-

New York Times, 1930

5 Dec 1930

Belgium's Poison Fog Cases Likened to the 'Black Death'

Special Cable to THE NEW YORK TIMES.
LONDON, Dec. 5.—The suggestion that the Belgian fog deaths may be due to some form of plague was advanced tonight by Professor J. B. S. Haldane, prominent Cambridge scientist.

"It seems like something in the nature of the Black Death to me," he told The Daily Mail tonight. "I don't think it can be caused by war gas, because the deaths occurred in different villages. They have been having floods in that district lately and that may be responsible."

The Black Death was the name given in the Middle Ages to the bubonic plague, which was responsible for the deaths of millions of people in the 14th century.

Spanish flu?

Courtesy of B. Nemery, KU Leuven

6 Dec 1930

FOG BROUGHT DEATH ONLY TO OLD AND ILL

Toll of 70 in Belgian Towns
Laid to Natural Causes as
Menace Passes Away.

PEASANTS STILL IN TERROR

Many Credit Malignant Force
—Authorities the World Over
Speculate on Phenomenon.

Microbes from the Sahara?

8 Dec 1930

BELGIAN FOG DEATHS LAID TO POISONOUS GAS

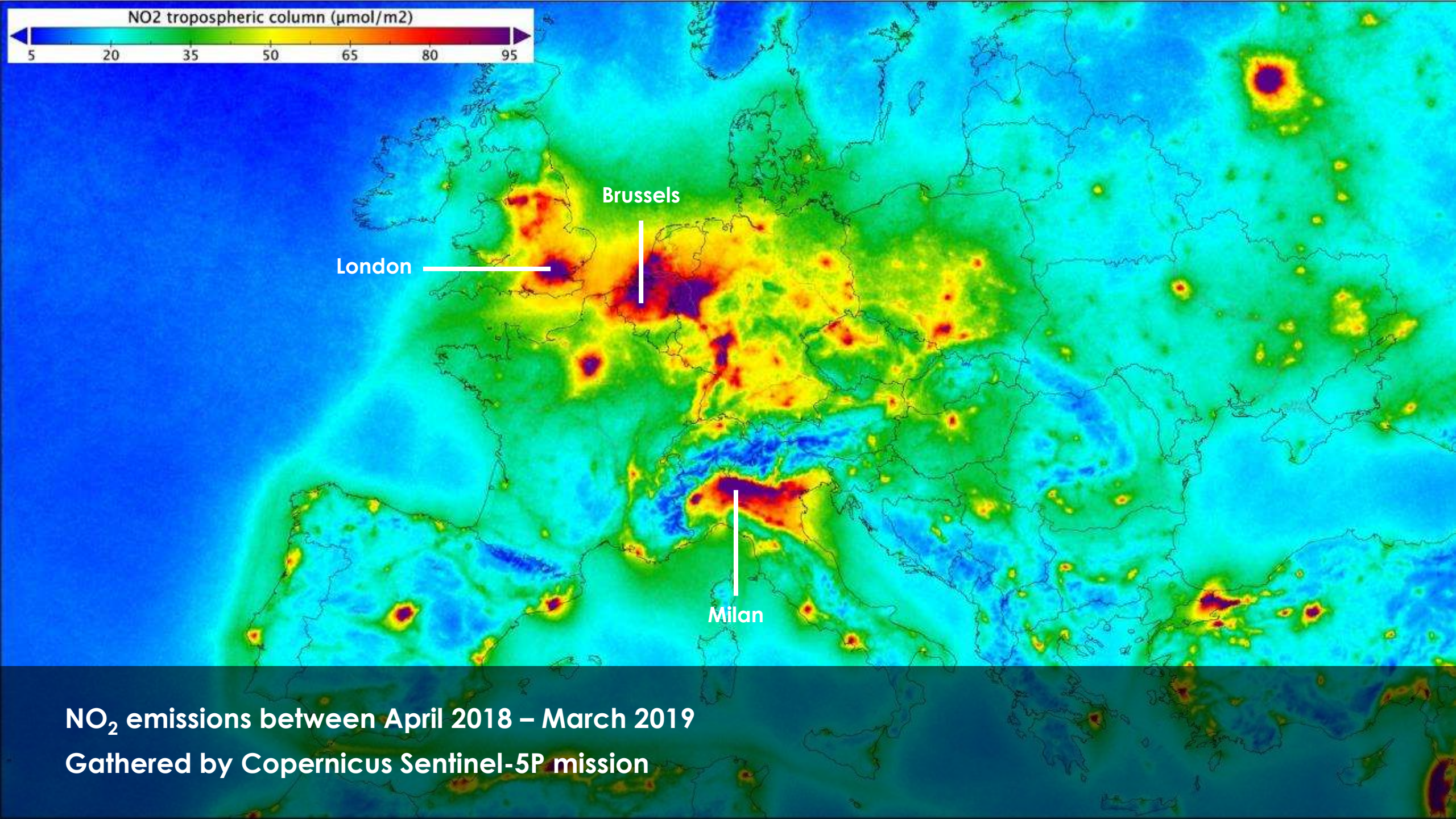
Doctor Who Performs Autopsy
Unable to Identify It—
Brussels Inquiry Today.

Special Cable to THE NEW YORK TIMES.
BRUSSELS, Dec. 8.—The deaths caused by the fog in the Meuse Valley were ascribed to a poisonous gas by Professor Firket, who performed an autopsy upon several victims today in Liège. He said, however, that he had been unable to determine exactly what gas had wrought the havoc.

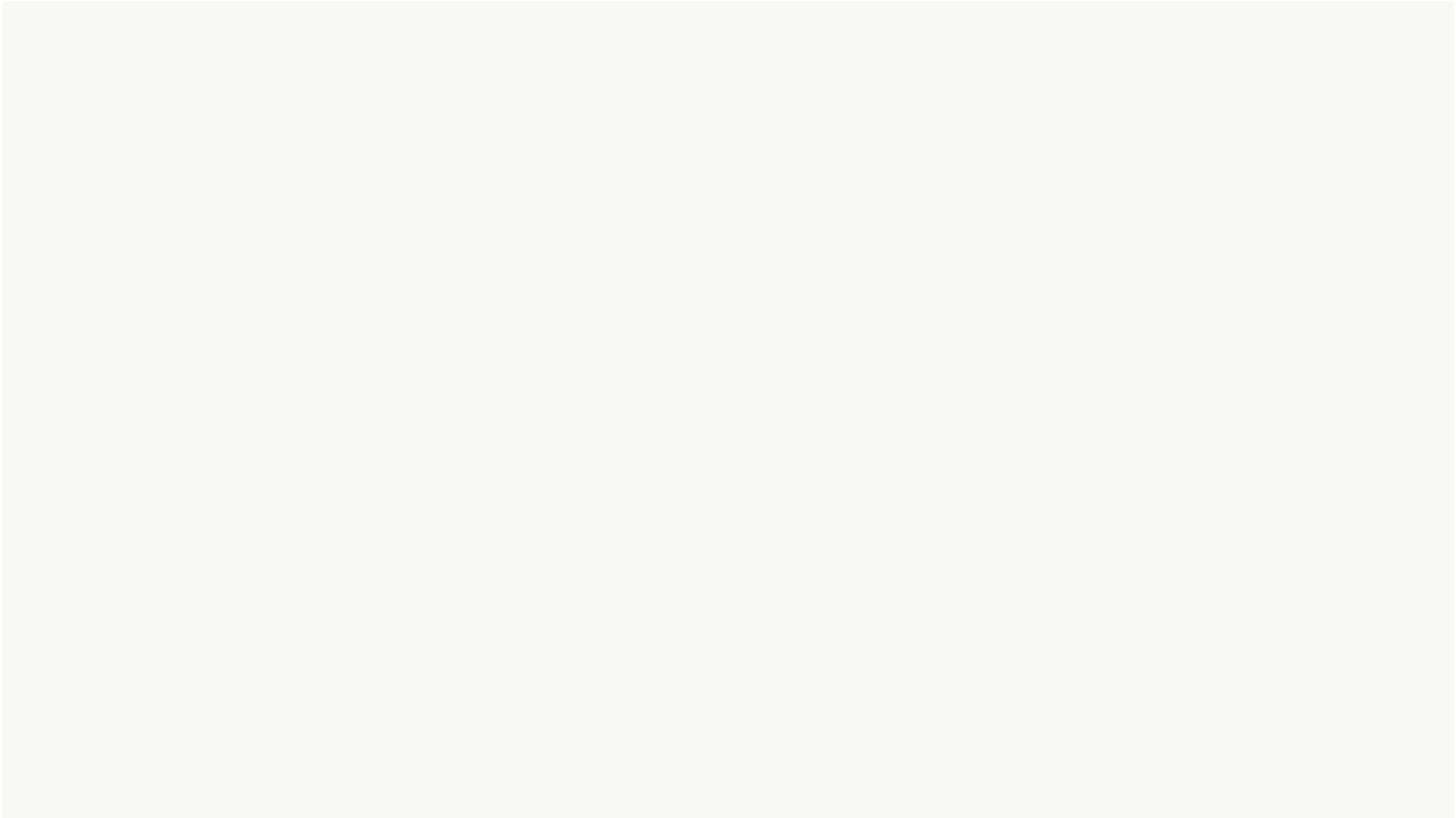
"It is neither any known form of war gas, nor a gas such as might be derived from an ammonia explosion," he said. "We rather incline to the theory that it had its origin in some industrial accident which

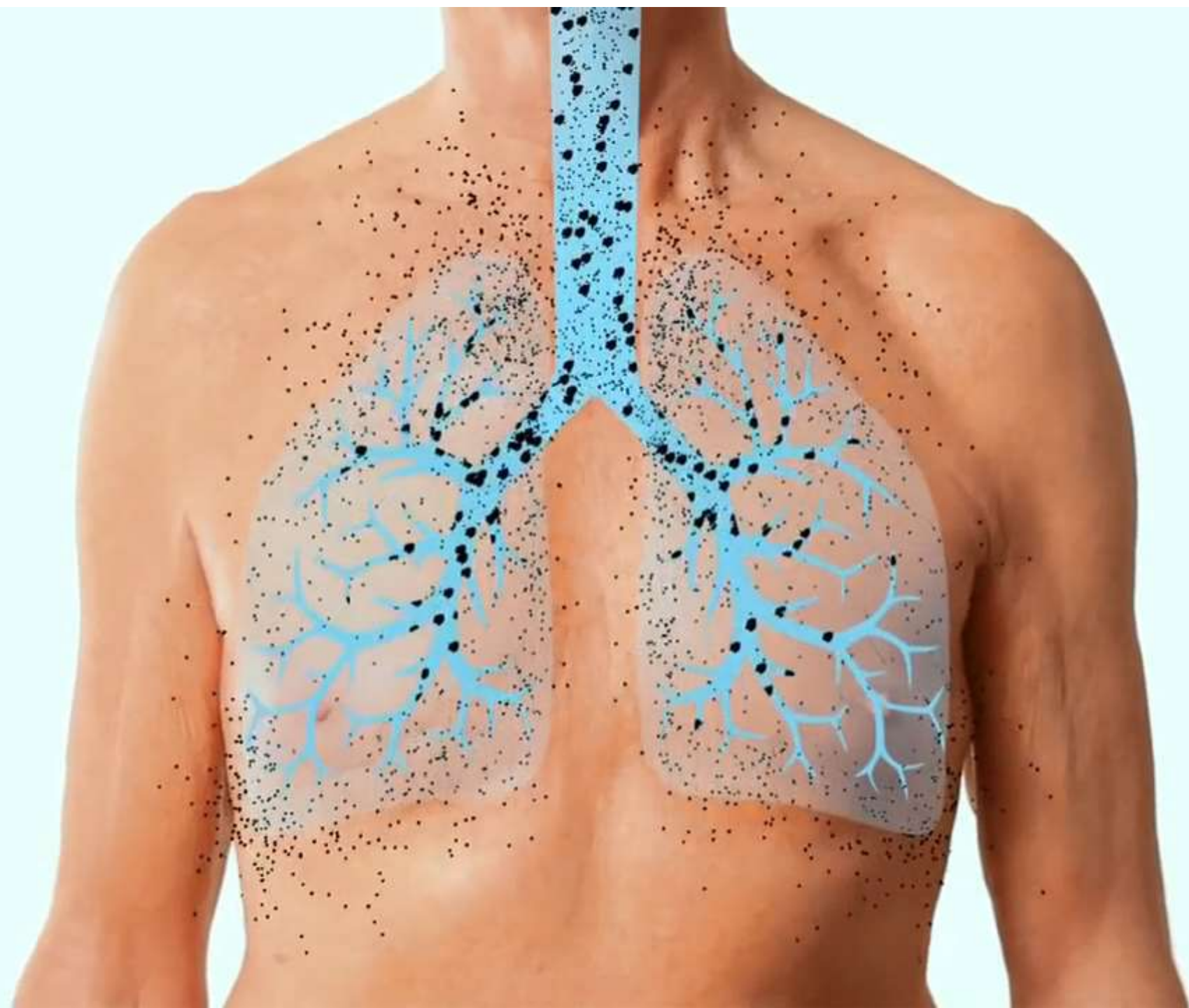
Chemical warfare?

could be carried by the fog. At the same time, no progress has been made by the authorities in discovering information concerning any such accident, and for the moment the mystery remains unsolved.



NO₂ emissions between April 2018 – March 2019
Gathered by Copernicus Sentinel-5P mission





Children's Urinary Environmental Carbon Load

A Novel Marker Reflecting Residential Ambient Air Pollution Exposure?

Nelly D. Saenen^{1*}, Hannelore Bové^{2,3*}, Christian Steuwe³, Maarten B. J. Roeffaers³, Eline B. Provost¹, Wouter Lefebvre⁴, Charlotte Vanpoucke⁵, Marcel Ameloot², and Tim S. Nawrot^{1,6}

Am J Respir Crit Care Med Vol 196, Iss 7, pp 873–881, Oct 1, 2017

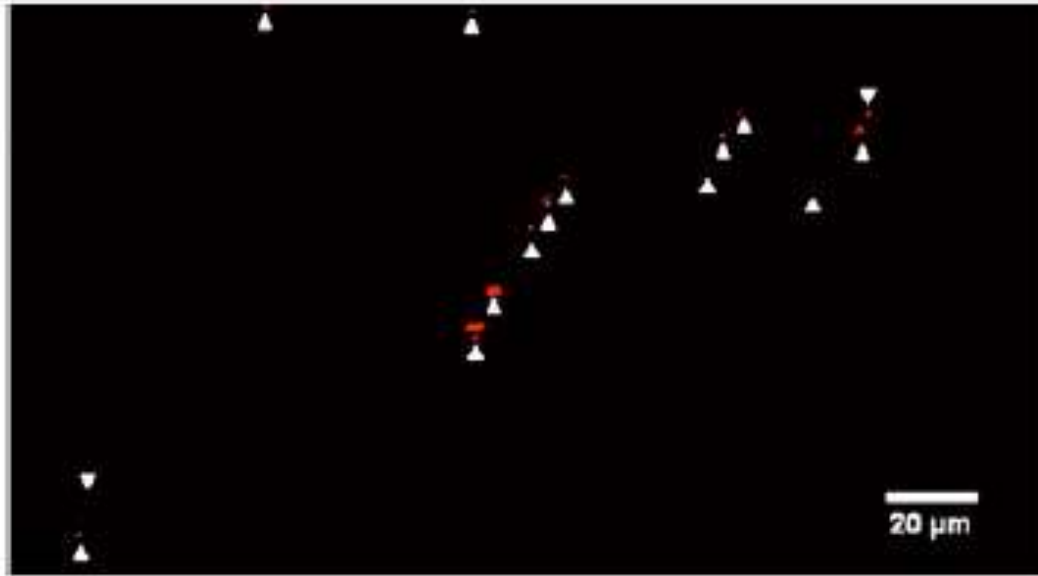
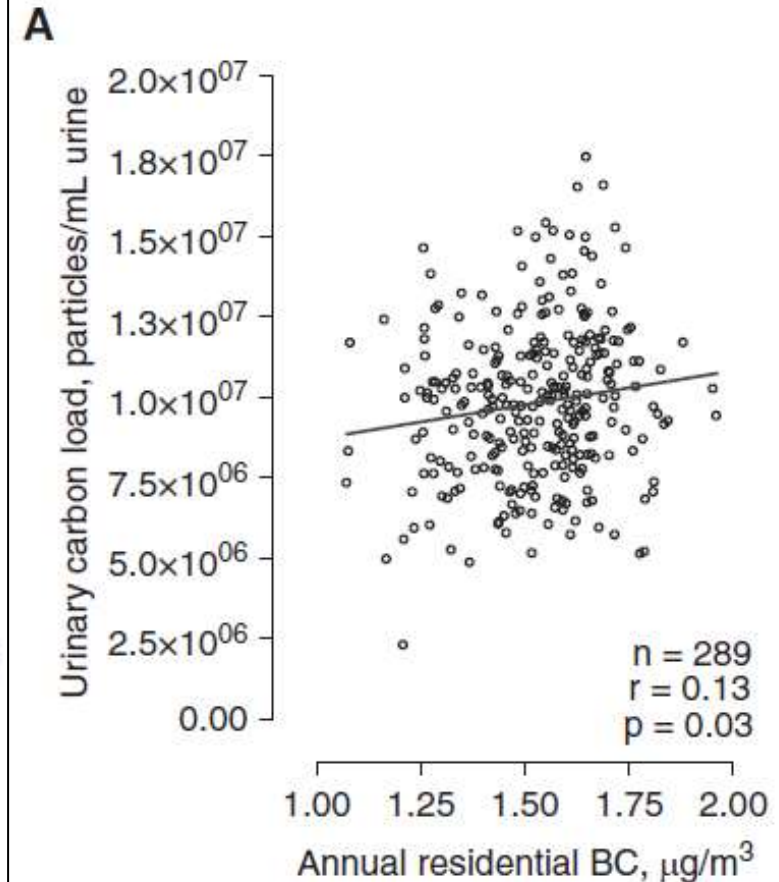
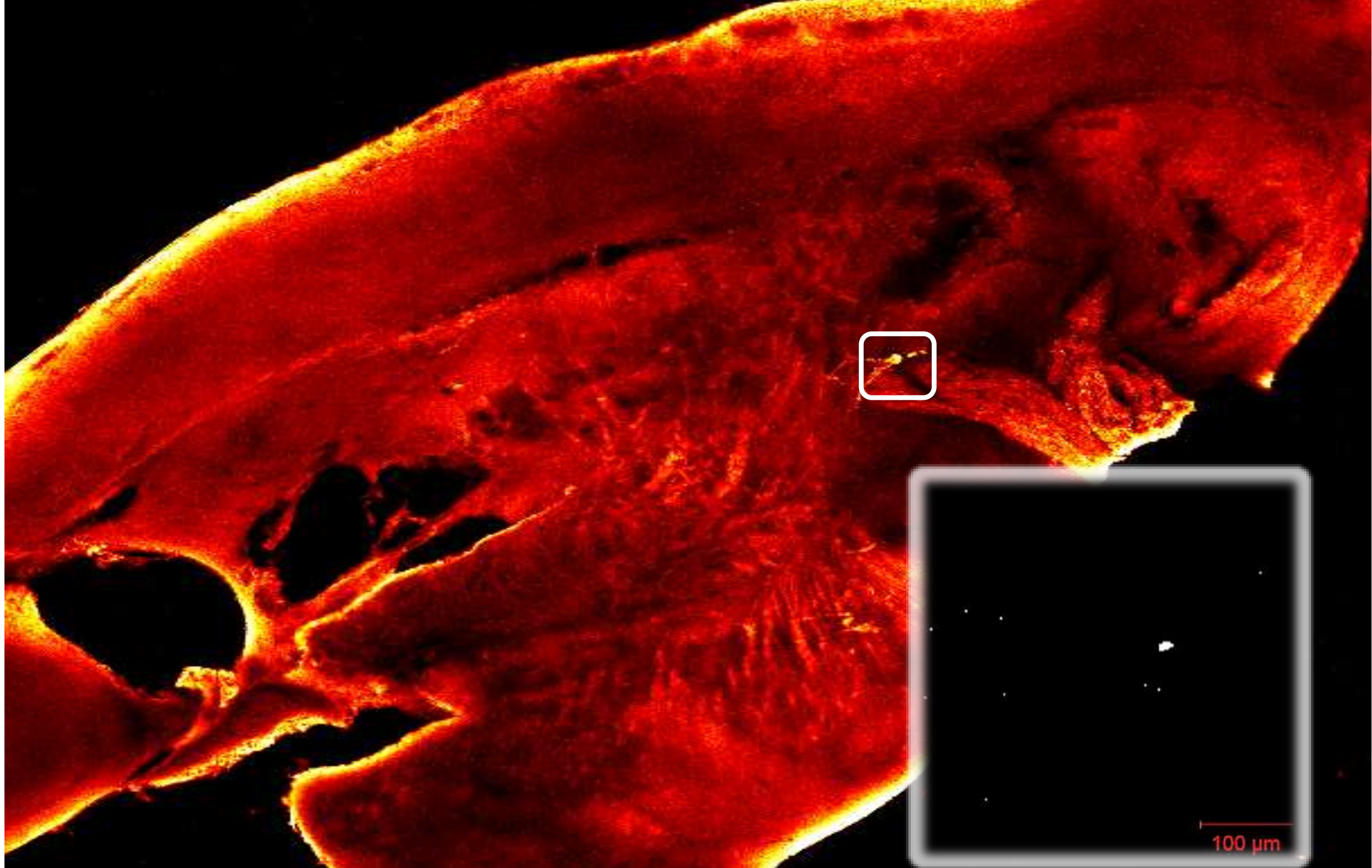
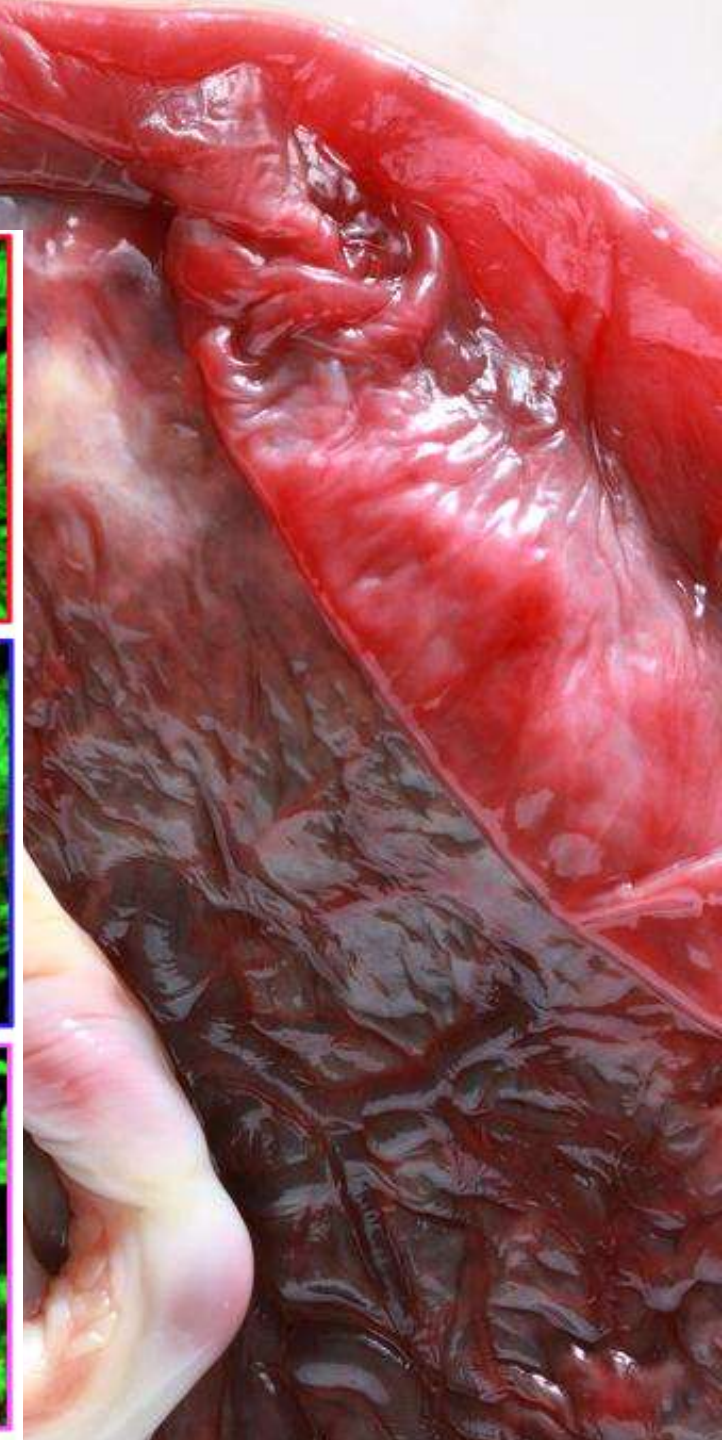
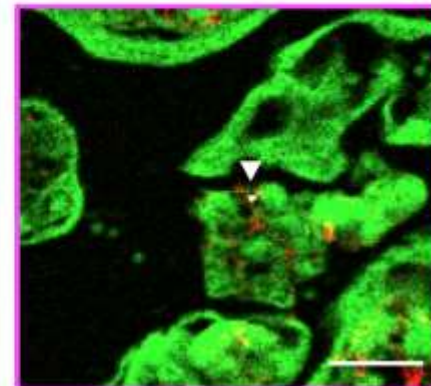
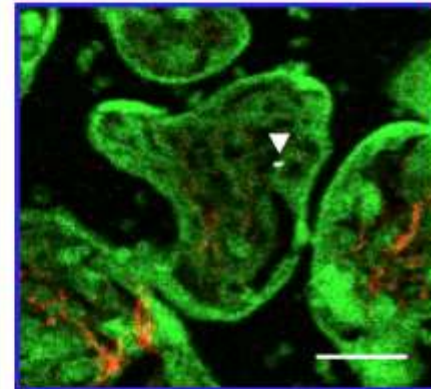
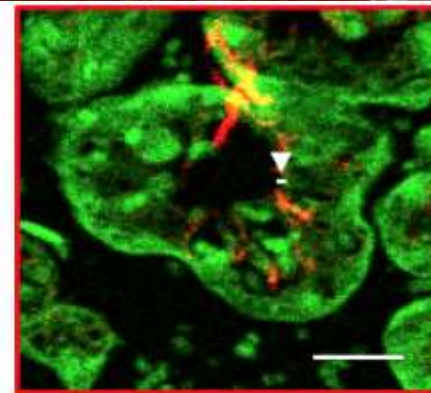
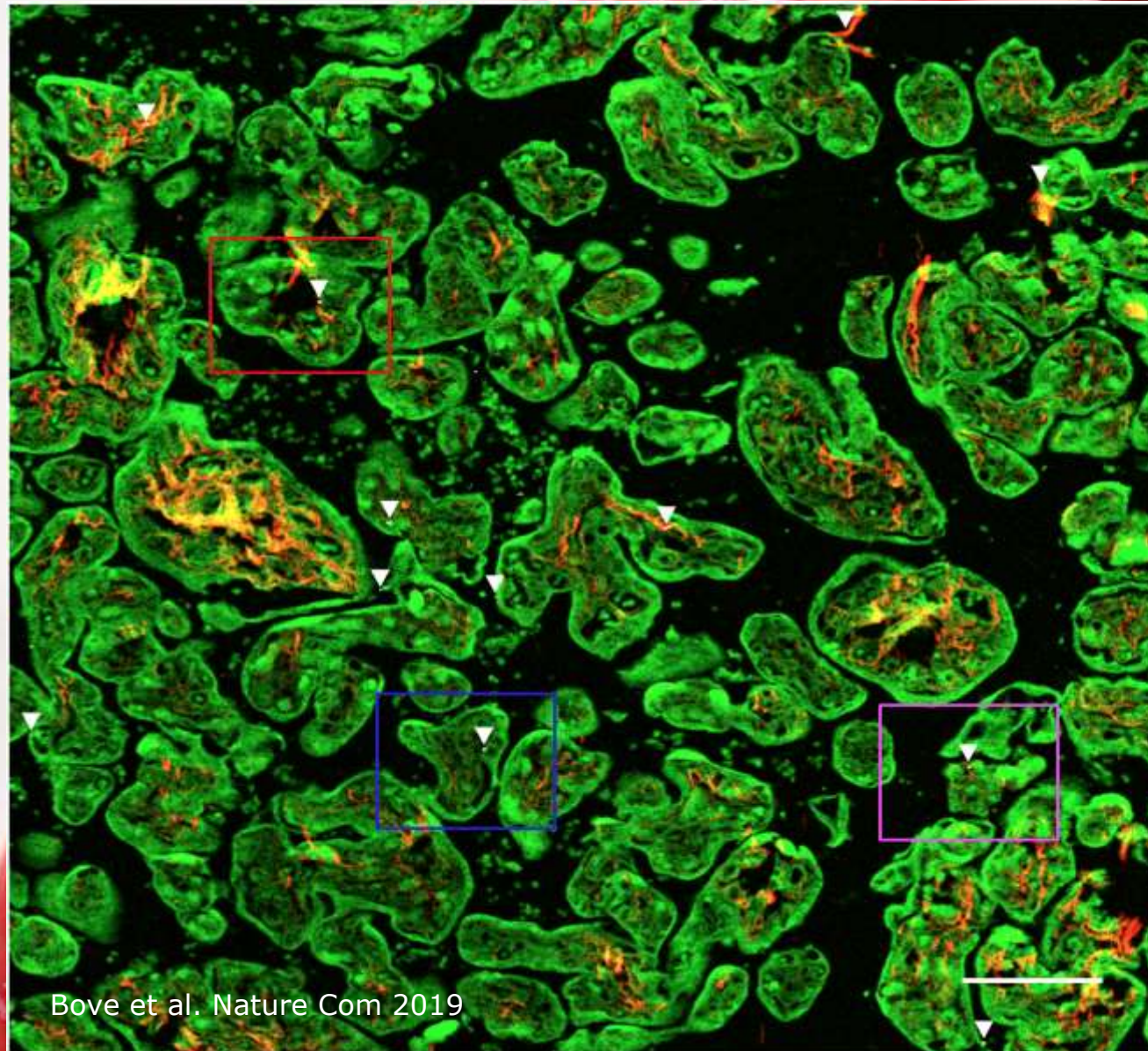


Figure 2. Black carbon particles in urine. Black carbon particles and aggregates (*arrowheads*) visualized by femtosecond pulsed laser excitation at 810 nm and observation at 400–410 nm.

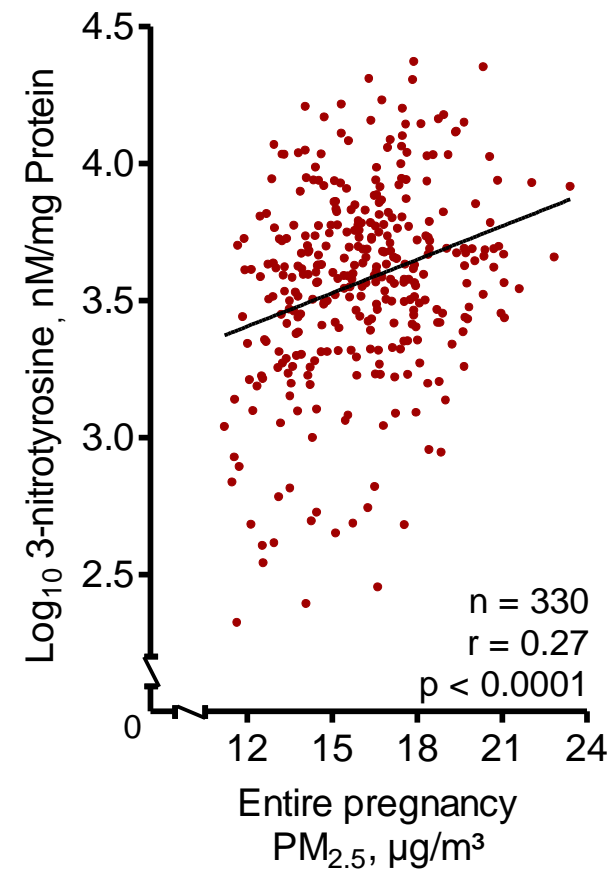




Fetal exposure to black carbon



Placental nitrosative stress and air pollution



PM _{2.5}	IQR	% change ^a	95% CI	P-value
Trimester 1	8.8	29.0	4.9, 58.6	0.02
Trimester 2	7.4	39.3	12.3, 72.7	0.003
Trimester 3	9.4	13.2	-9.4, 41.3	0.27

^a Percentage change in 3-Nitrotyrosine for an interquartile range increment in PM_{2.5} exposure, adjusted for gestational age, maternal age, maternal education, pregestational body mass index, smoking status, newborn's sex, newborn's ethnicity, and seasonality.

Air pollution and health over the life course

↓ birth weight

↓ neurodevelopment

↑ allergies

↑ asthma

↑ respiratory
infections

↑ bronchitis

↑ asthma

↑ COPD

↓ cognition

↑ inflammation

↑ cardiovascular
morbidity

↑ lung cancer

↑ mortality

↑ cardiovascular
mortality



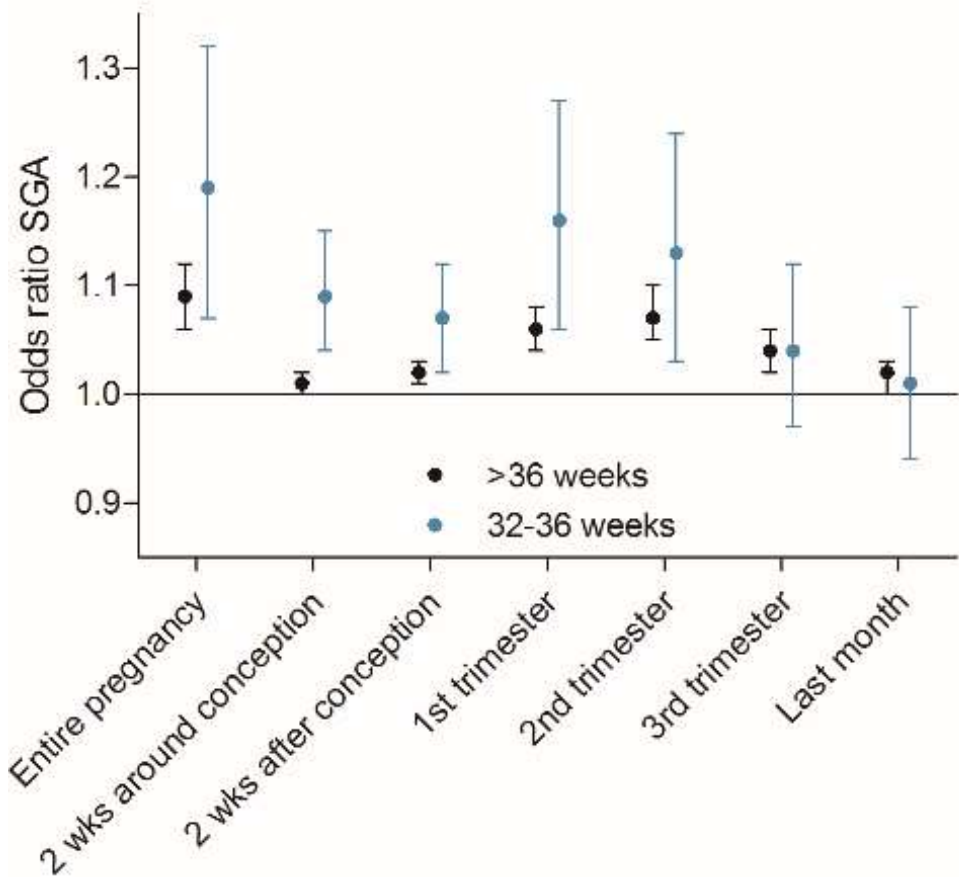
newborn

adult

elderly

Fetal growth and maternal exposure to particulate air pollution – *More marked effects at lower exposure and modification by gestational duration*

Ellen Winckelmans^{a,1}, Bianca Cox^{a,1}, Evelyne Martens^b, Frans Fierens^c, Benoit Nemery^d, Tim S. Nawrot^{a,d,*}



The study population consisted of 525,635 singleton live births in Flanders (Belgium) between 1999 and 2009. (SPE register)

Adjusted for year of birth, season of conception, parity, maternal age, marital status, maternal and paternal education, national origin of the mother.

Air pollution and health over the life course

↓ birth weight

↓ neurodevelopment

↑ allergies

↑ asthma

↑ respiratory
infections

↑ bronchitis

↑ asthma

↑ COPD

↓ cognition

↑ inflammation

↑ cardiovascular
morbidity

↑ lung cancer

↑ mortality

↑ cardiovascular
mortality



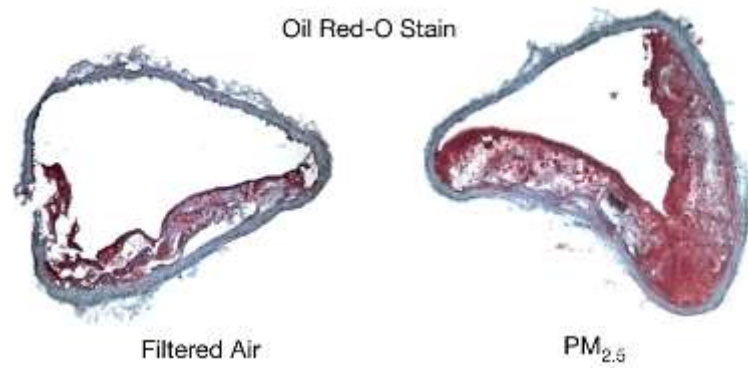
newborn

adult

elderly

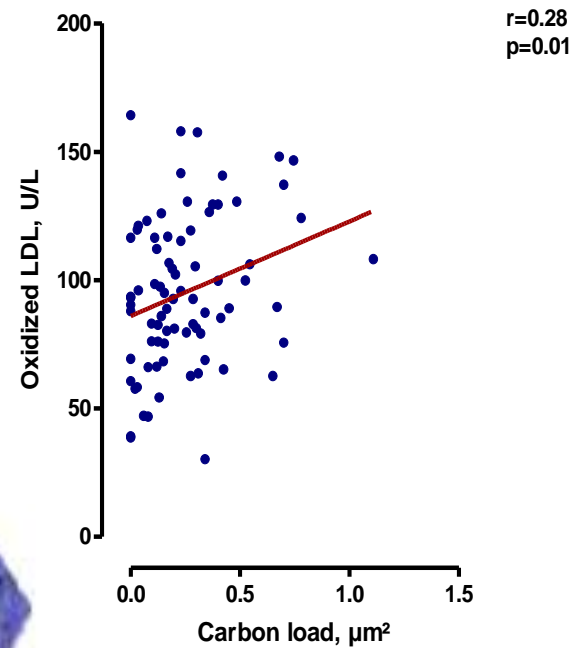


Atherosclerosis en PM

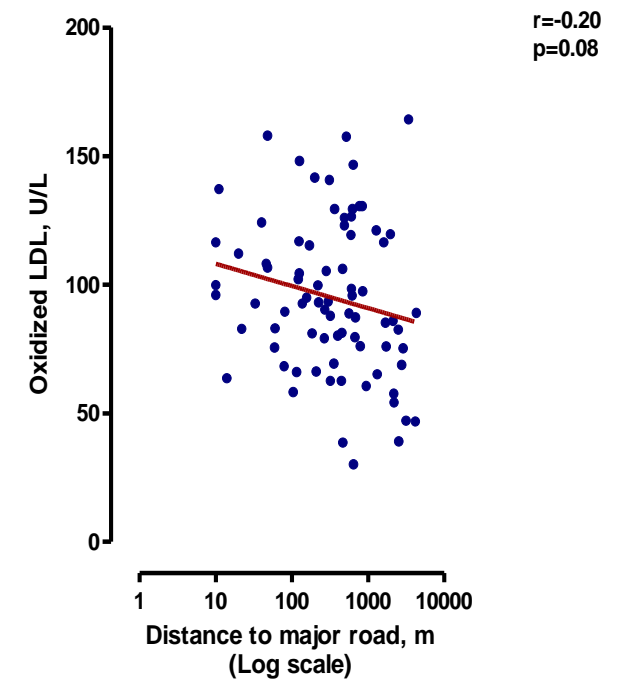


Long-term Air Pollution Exposure and Acceleration of Atherosclerosis and Vascular Inflammation in an Animal Model

Sun Q. *et al.* JAMA 2005.



Jacobs L. *et al.* Plos One 2011

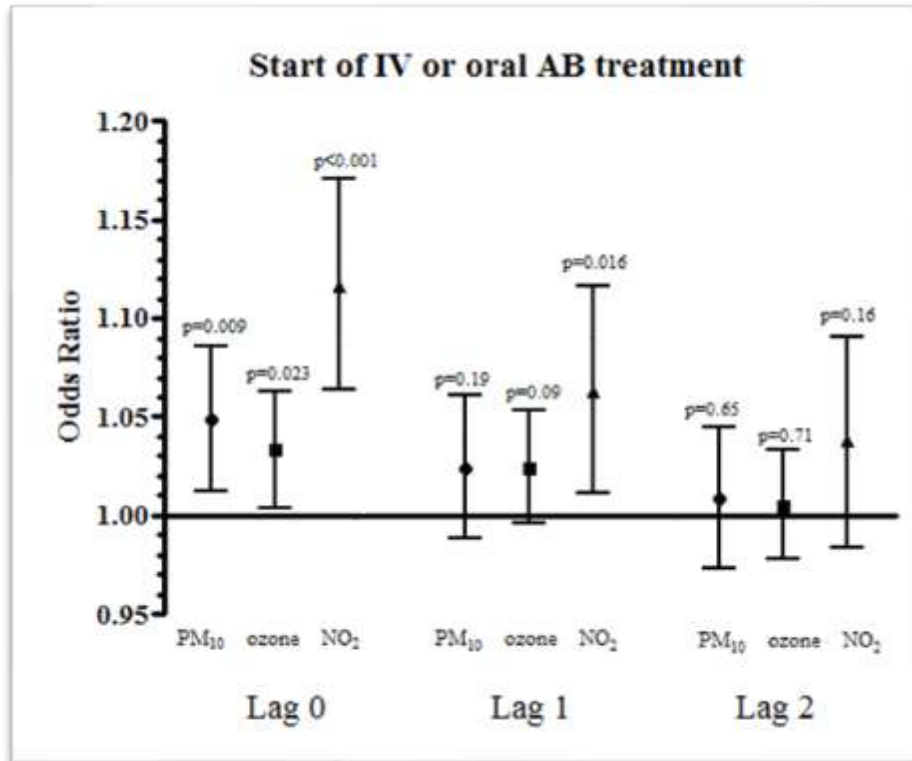


The concept of population vulnerability



Cystic fibrosis

- 215 CF patients
- A pulmonary exacerbation = **use of intravenous / oral antibiotics at home or in hospital.** [Bilton D et al. *Journal of Cystic Fibrosis* 2011]



Demography	
- Age	21 years ± 13
- Gender	49% male/ 51% female
- Total antibiotic treatments	2204 (1107 IV + 1097 oral)
- CF genotype	
◦ DF508 homozygous	55%
◦ DF508 heterozygous	35%
◦ Other	10%
- Pseudomonas status	
◦ Chronic infection	30%
◦ Intermittent infection	14%
◦ Free of infection	13%
◦ Never infected	43%

lung transplant patients

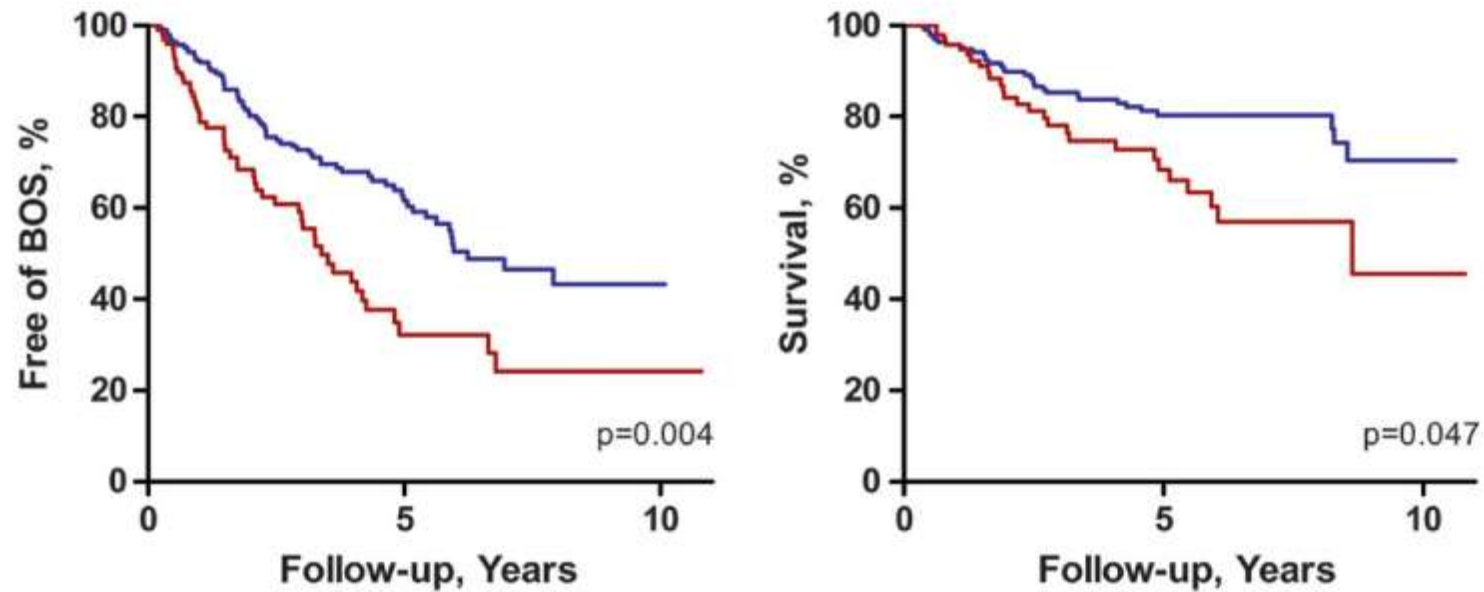
Aim: Association between proximity of the home to major roads and incidence of chronic rejection and mortality in a cohort of lung transplants.



Methods

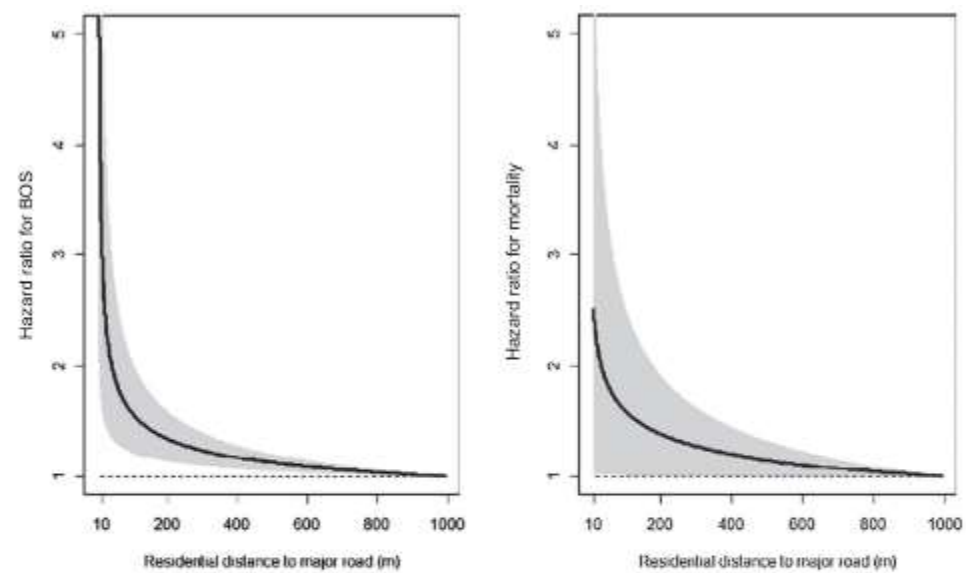
- Follow-up (median 2.7 y) of 288 lung transplant patients.
- Geocoding.
- Cox regression

Incidence of BOS and % survival in association with residential distance to a major road (1)



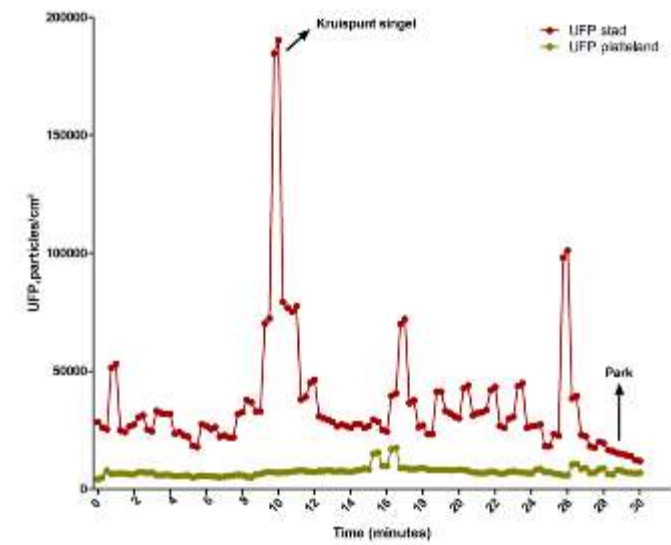
Red line represents those living within 171 m (lowest tertile) of a major road

Incidence of BOS and % survival in association with residential distance to a major road (1)



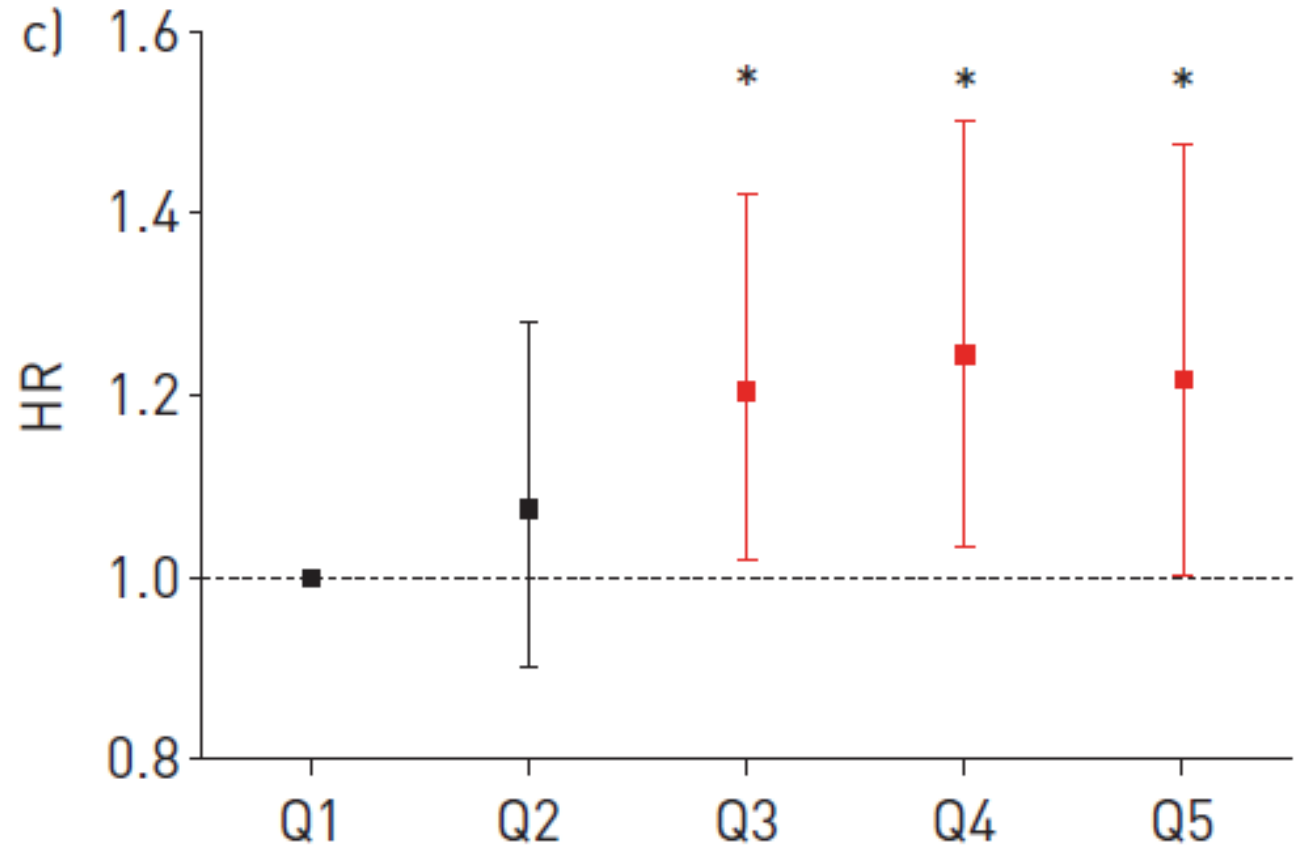
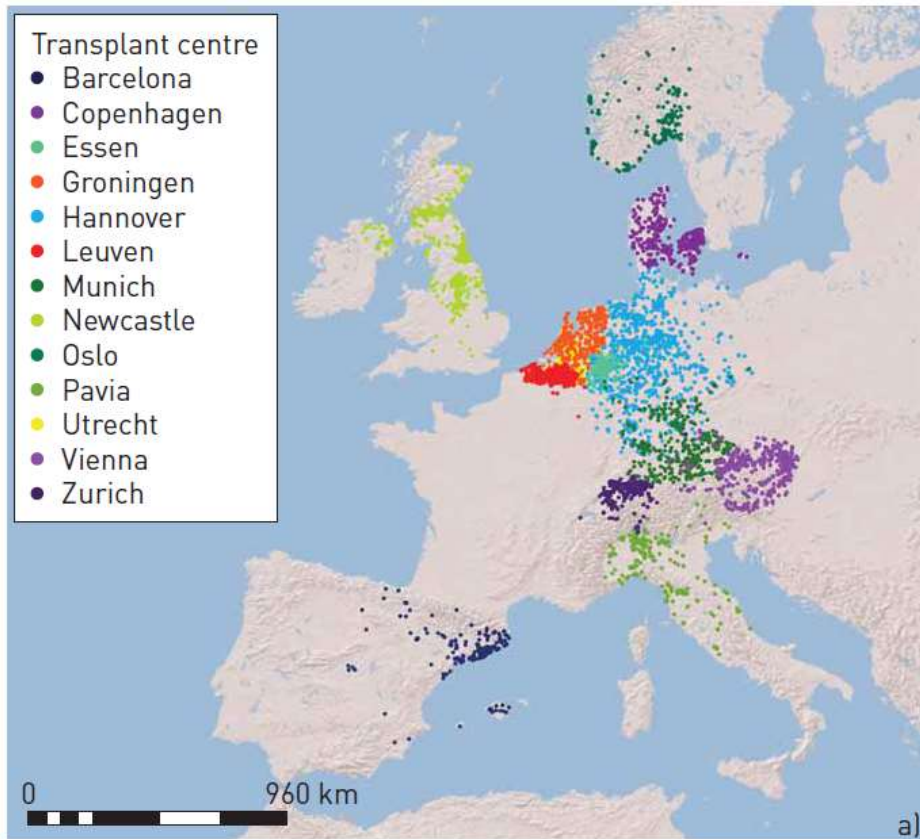
Distance to major road, m	Hazard ratio (95% CI) for BOS	Attributable fraction
1000	1.00	-
800	1.04 (1.02-1.06)	3.8%
600	1.09 (1.04-1.14)	8.2%
400	1.17 (1.04-1.28)	14.7%
200	1.34 (1.14-1.58)	25.4%
150	1.43 (1.17-1.74)	30.0%
100	1.57 (1.22-2.02)	36.3%
50	1.88 (1.32-2.66)	46.7%

Distance to major road, m	Hazard ratio (95% CI) for mortality	Attributable fraction
1000	1.00	-
800	1.05 (1.00-1.09)	4.8%
600	1.11 (1.00-1.23)	9.8%
400	1.20 (1.00-1.45)	16.9%
200	1.39 (1.01-1.90)	27.8%
150	1.47 (1.01-2.14)	31.9%
100	1.60 (1.02-2.52)	37.2%
50	1.83 (1.02-3.30)	45.4%

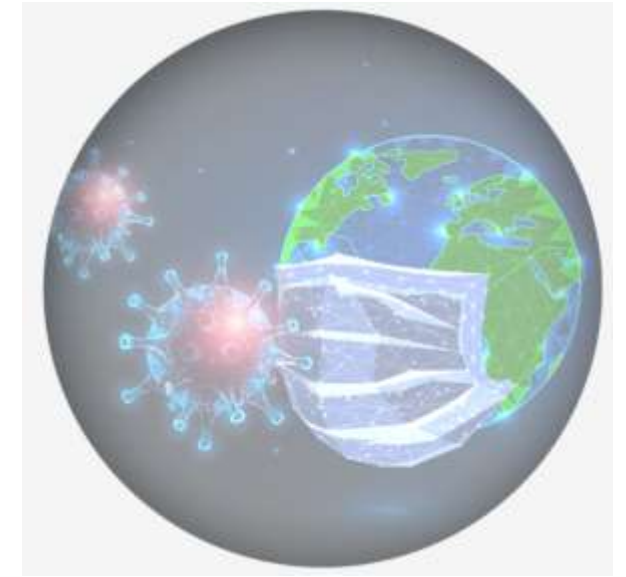
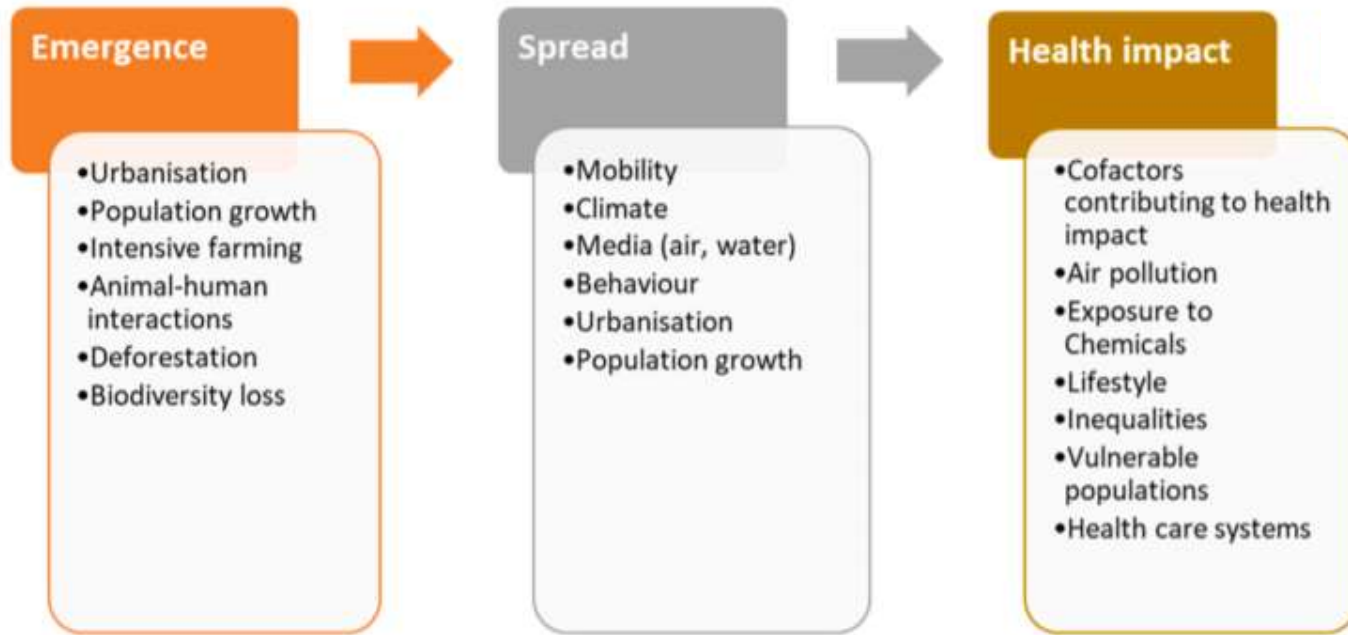


Adjustements applied for sex, age, type of transpalntation (single or double lung), infections, acute rejections, SES, time trend.

An association of particulate air pollution and traffic exposure with mortality after lung transplantation in Europe



COVID-19 and environmental factors



Current evidence is weak but hypothesis is relevant

- Air pollution has been shown to **reduce respiratory resistance** against bacterial and viral infections other than SARS-CoV-2.
- Evidence is emerging that people **living in high pollution areas might be more frequently infected** by SARS-CoV-2, and more likely to develop COVID-19 once outbreaks occur.
- Almost all studies used **aggregate data**
- **Outbreaks** as well as **air pollution** are related to **population density** and other spatial variables.

It has been very difficult until now to disentangle any independent effects of air pollution from effects of other causes of the disease outbreaks.

Pre-admission air pollution exposure prolongs the duration of ventilation in intensive care patients



entilation

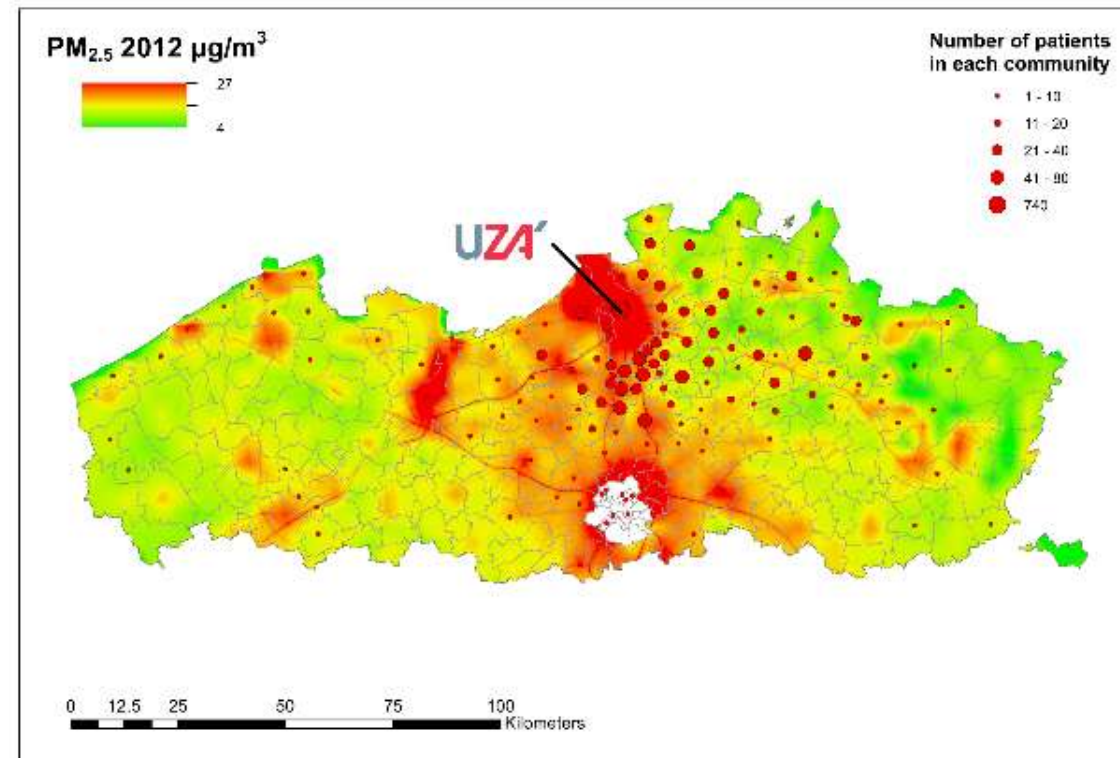


Purpose: Air pollutant exposure constitutes a serious risk factor for the emergence or aggravation of (existing) pulmonary disease. The impact of pre-intensive care ambient air pollutant exposure on the duration of artificial ventilation was, however, not yet established.

Pre-admission air pollution exposure prolongs the duration of ventilation in intensive care patients



- 2,003 patients admitted to the ICU, who were ventilated
- Daily air pollutant exposure ($PM_{2.5}$, PM_{10} , NO_2 and BC) up to 10 days prior to hospital admission
- The association between duration of artificial ventilation and air pollution exposure during the last 10 days before ICU admission was assessed.





Pre-admission air pollution exposure prolongs the duration of ventilation in intensive care patients

Results: Controlling for pre-specified confounders, an IQR increment in BC ($1.2 \mu\text{g}/\text{m}^3$) up to 10 days before admission was associated with an estimated cumulative increase of 12.4% in ventilation duration (95% CI 4.7–20.7). Significant associations were also observed for $\text{PM}_{2.5}$, PM_{10} and NO_2 , with cumulative estimates ranging from 7.8 to 8.0%.

Conclusion: Short-term ambient air pollution exposure prior to ICU admission represents an unrecognized environmental risk factor for the duration of artificial ventilation in the ICU.

Air pollution and health over the life course

↓ birth weight

↓ neurodevelopment

↑ allergies

↑ asthma

↑ respiratory
infections

↑ bronchitis

↑ asthma

↑ COPD

↓ cognition

↑ inflammation

↑ cardiovascular
morbidity

↑ lung cancer

↑ mortality

↑ cardiovascular
mortality

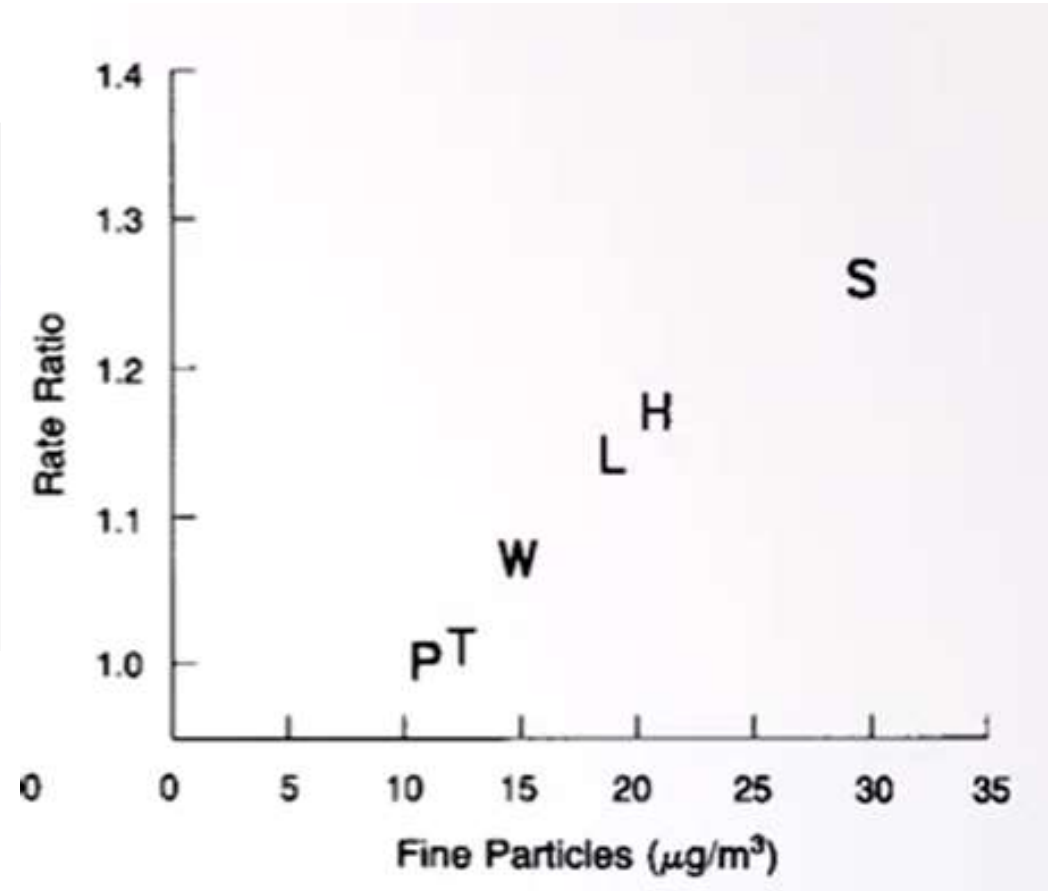
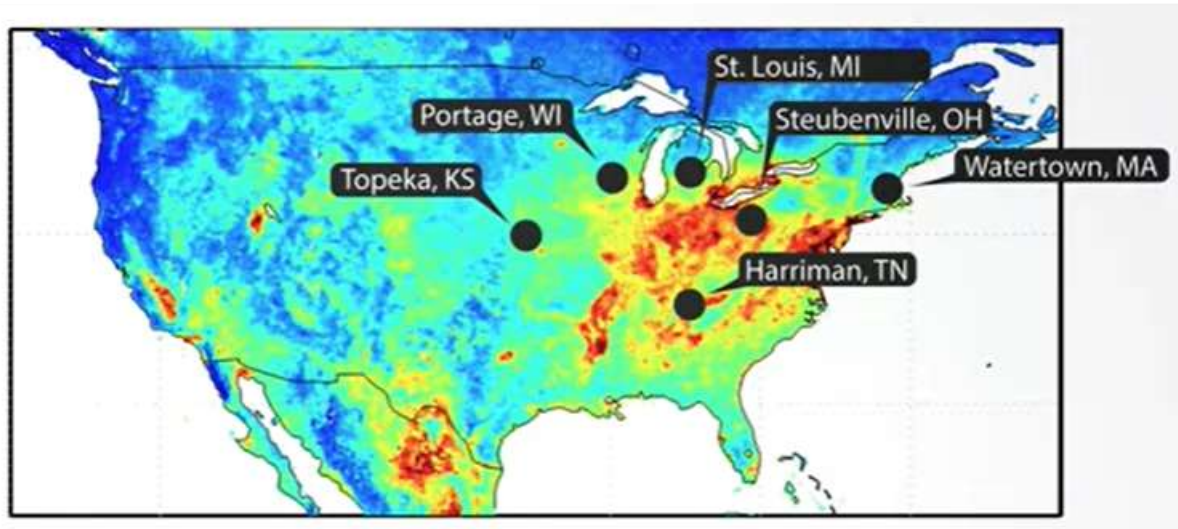


newborn

adult

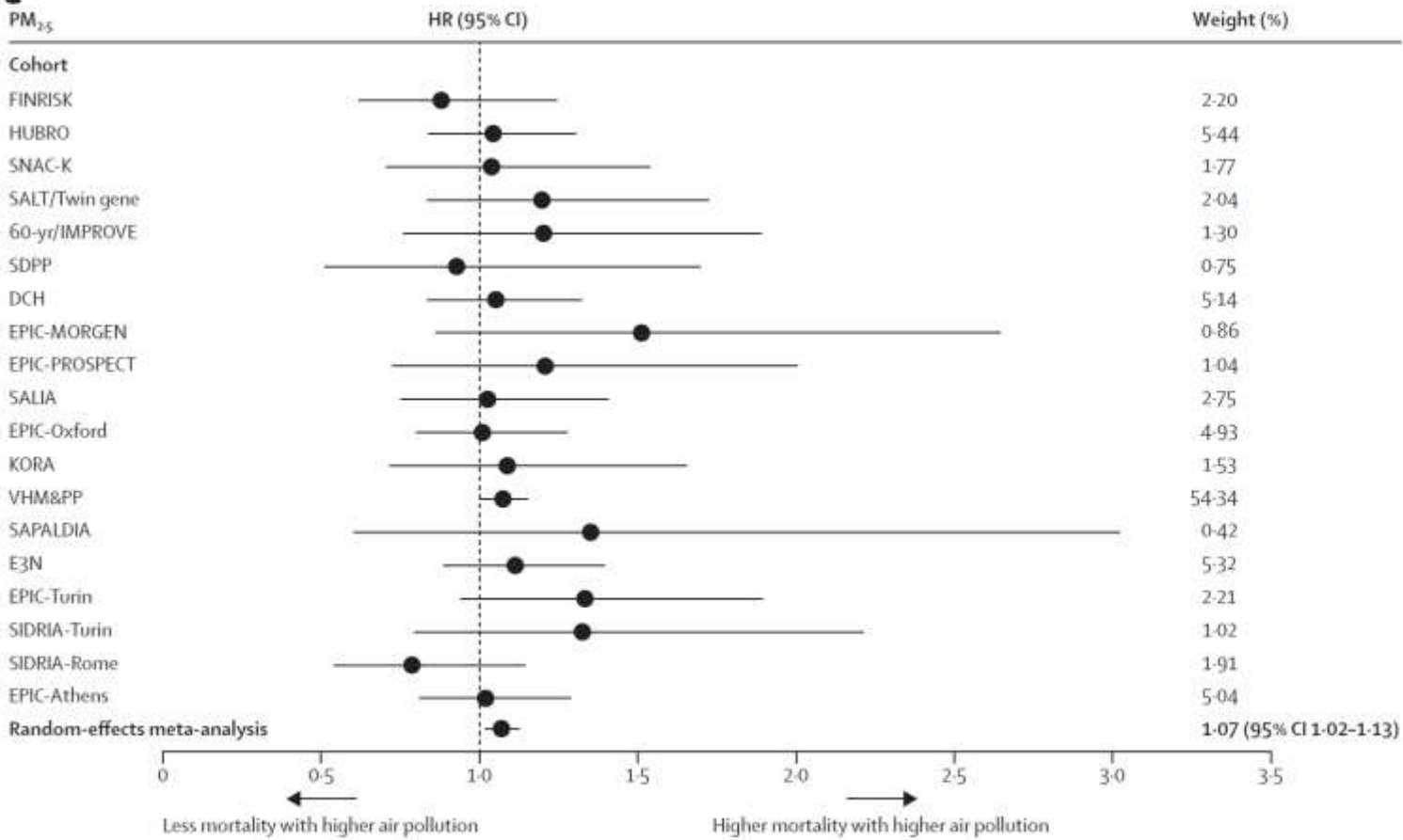
elderly

Landmark study: US six city study



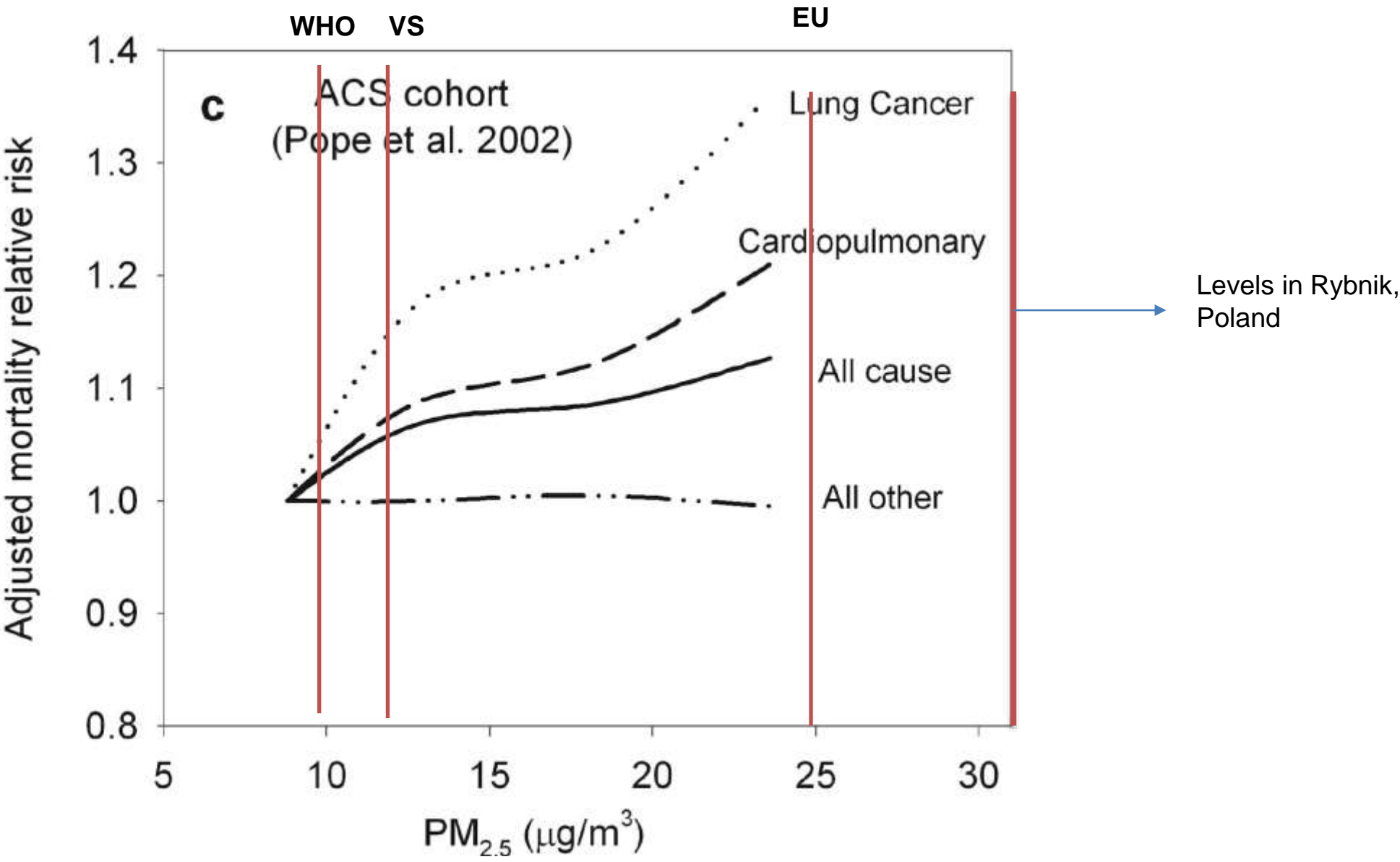
Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project

- Data from 22 European cohorts
- Including 367 251 participants



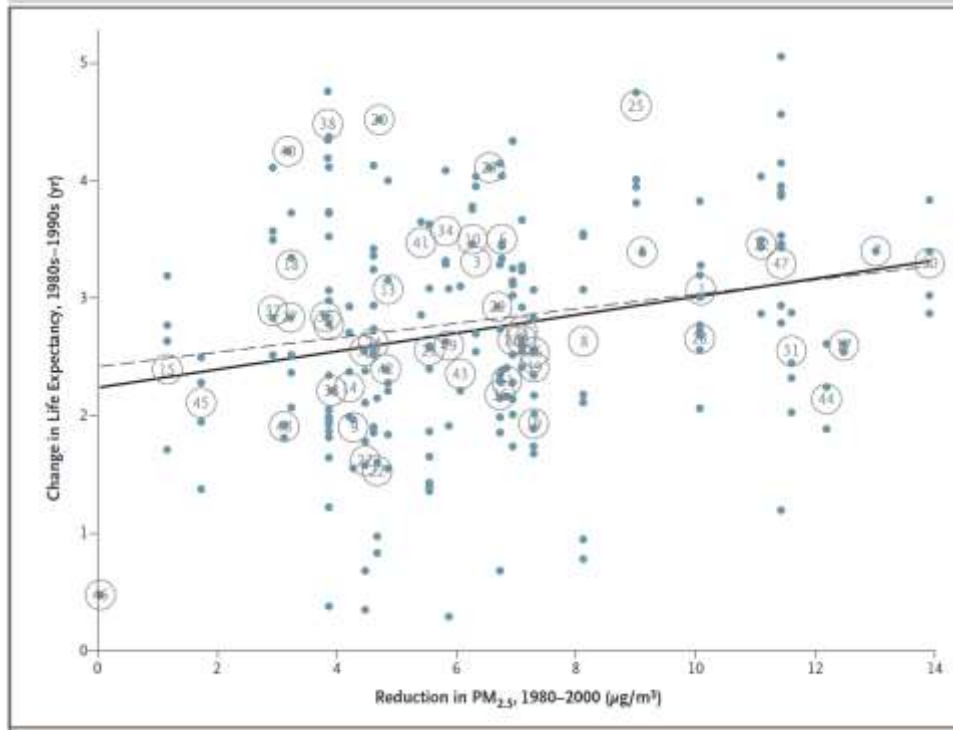
Interpretation Long-term exposure to fine particulate air pollution was associated with natural-cause mortality, even within concentration ranges well below the present European annual mean limit value.

Dose response association and thresholds / guidelines



Fine-Particulate Air Pollution and Life Expectancy in the United States

C. Arden Pope III, Ph.D., Majid Ezzati, Ph.D., and Douglas W. Dockery, Sc.D.

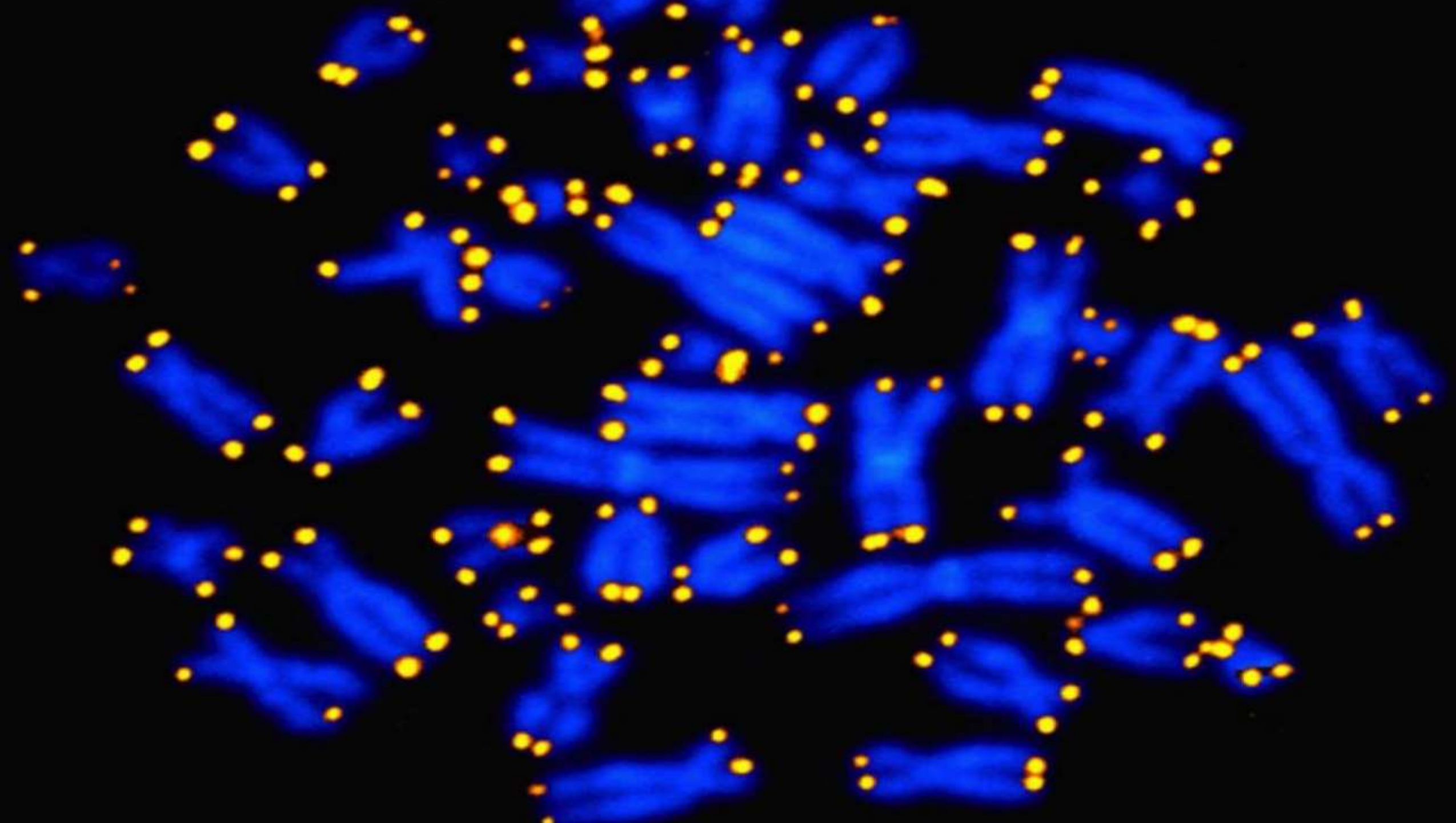


RESULTS

A decrease of 10 μg per cubic meter in the concentration of fine particulate matter was associated with an estimated increase in mean ($\pm\text{SE}$) life expectancy of 0.61 ± 0.20 year ($P=0.004$). The estimated effect of reduced exposure to pollution on life expectancy was not highly sensitive to adjustment for changes in socioeconomic, demographic, or proxy variables for the prevalence of smoking or to the restriction of observations to relatively large counties. Reductions in air pollution accounted for as much as 15% of the overall increase in life expectancy in the study areas.

CONCLUSIONS

A reduction in exposure to ambient fine-particulate air pollution contributed to significant and measurable improvements in life expectancy in the United States.



The Nobelprize in Medicine (2009)

“For the discovery of how chromosomes are protected by telomeres and the enzyme telomerase”

**Elizabeth
Blackburn**



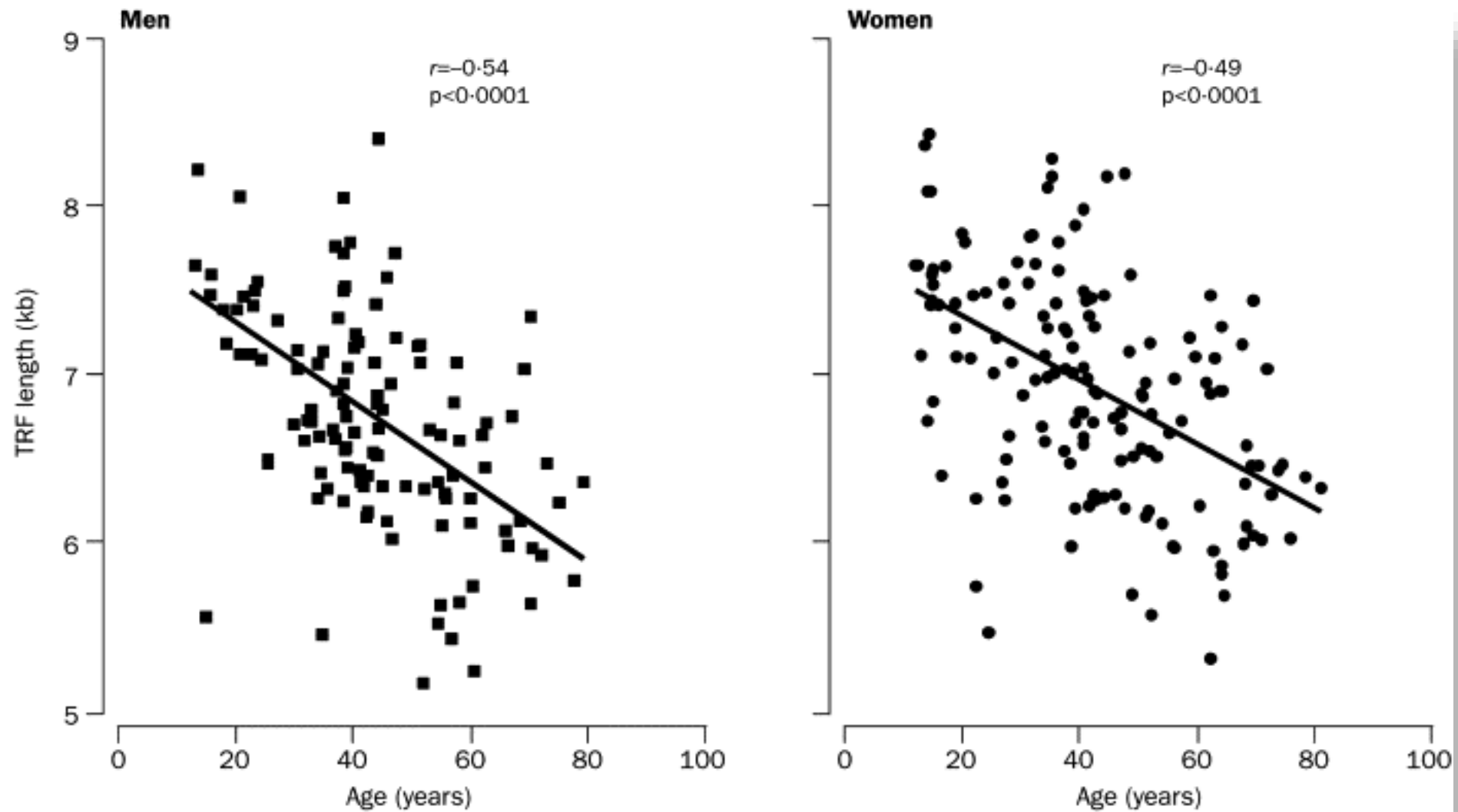
**Jack
Szostak**



**Carol
Greider**



Telomere length and ageing



The Hallmarks of Aging

Carlos López-Otín,¹ Maria A. Blasco,² Linda Partridge,^{3,4} Manuel Serrano,^{5,*} and Guido Kroemer^{6,7,8,9,10}



Defining the molecular core axis of ageing

ARTICLE

doi:10.1038/nature09787

Telomere dysfunction induces metabolic and mitochondrial compromise

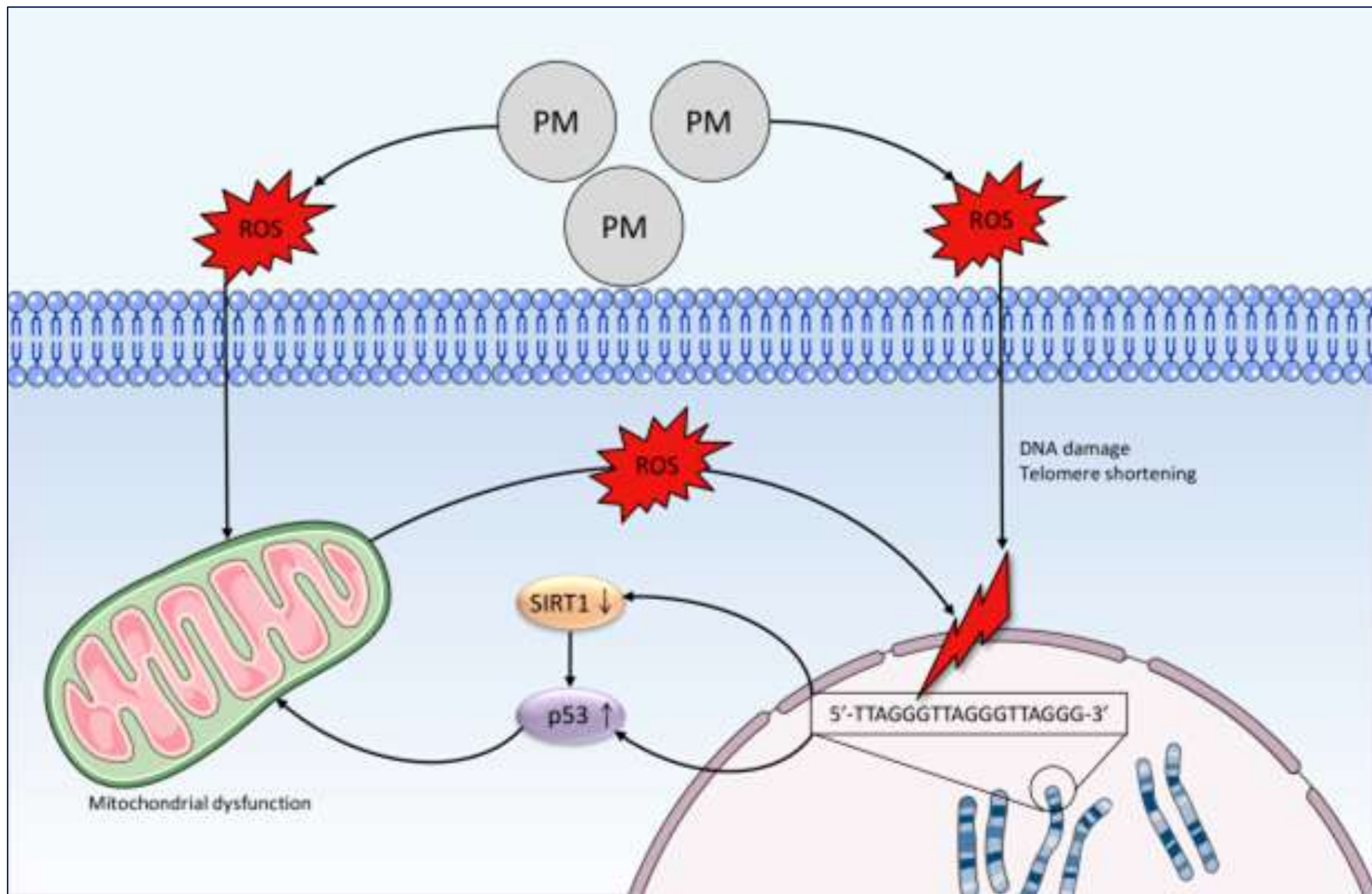
Ergün Sahin^{1,2}, Simona Colla^{1,2*}, Marc Liesa^{3*}, Javid Moslehi^{2,4}, Florian L. Müller^{1,2}, Mira Guo⁵, Marcus Cooper⁶, Darrell Kotton³, Attila J. Fabian⁷, Carl Walkey⁸, Richard S. Maser^{1,2}, Giovanni Tonon^{1,2}, Friedrich Foerster^{1,2}, Robert Xiong¹, Y. Alan Wang¹, Sachet A. Shukla¹, Mariela Jaskelioff^{1,2}, Eric S. Martin^{1,2}, Timothy P. Heffernan¹, Alexei Protopopov¹, Elena Ivanova¹, John E. Mahoney¹, Maria Kost-Alimova¹, Samuel R. Perry¹, Roderick Bronson⁹, Ronglih Liao⁴, Richard Mulligan⁷, Orian S. Shirihai³, Lynda Chin^{1,2} & Ronald A. DePinho^{1,2,4,7}

INSIGHT REVIEW

NATURE | Vol 464 | 25 March 2010 | doi:10.1038/nature08982

Linking functional decline of telomeres, mitochondria and stem cells during ageing

Ergün Sahin¹ & Ronald A. DePinho¹



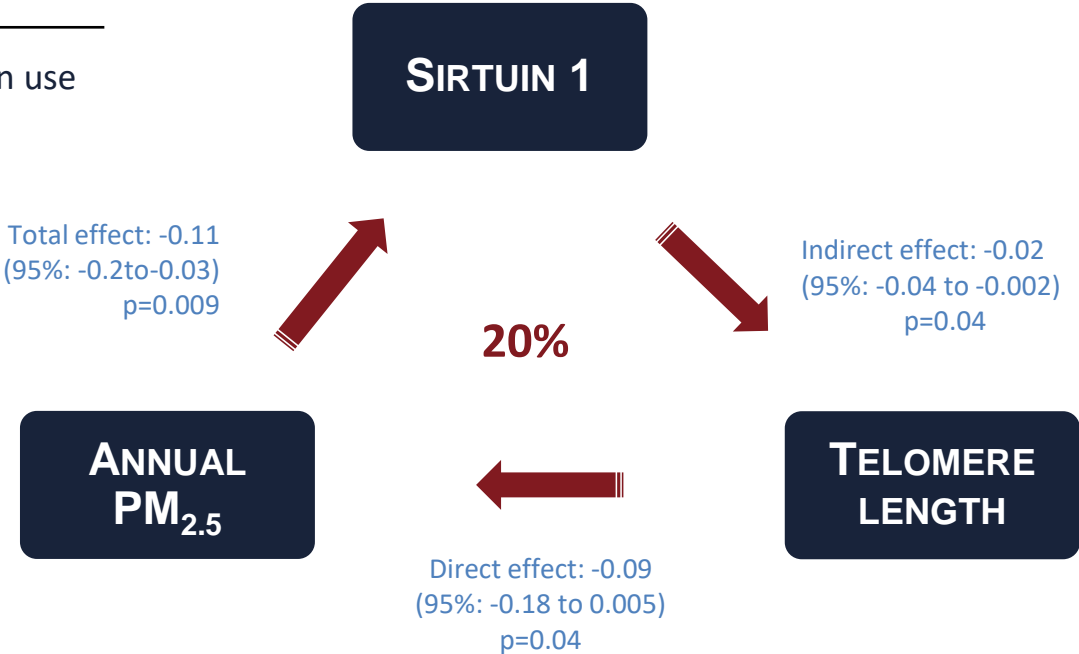
Air pollution and molecular core axis of ageing

Estimates given for 5 µg/m³ ↑ in PM_{2.5}

	% change	95% CI	p-value
Telomere length	-16.1%	-26.0 to -7.4	0.0005
MtDNA content	-25.7%	-35.2 to -16.2	<0.0001
SITR1	-17.4%	-30.0 to -5.1	0.006

Adjusted for gender, age, body mass index, socio-economic status and statin use

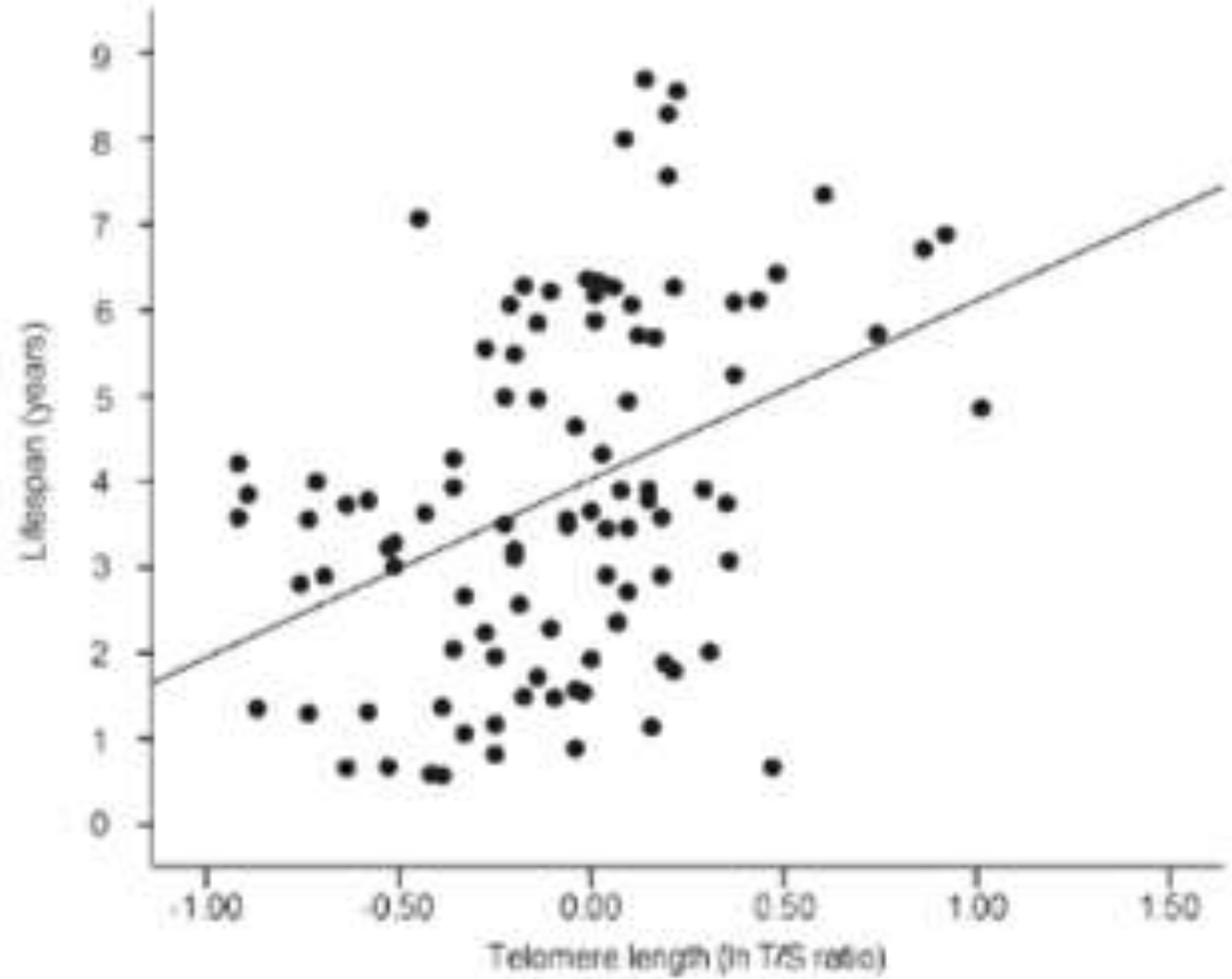
- 182 elderly, average age (SD): 71 (4.6) years
- PM_{2.5} range 15-23 µg/m³







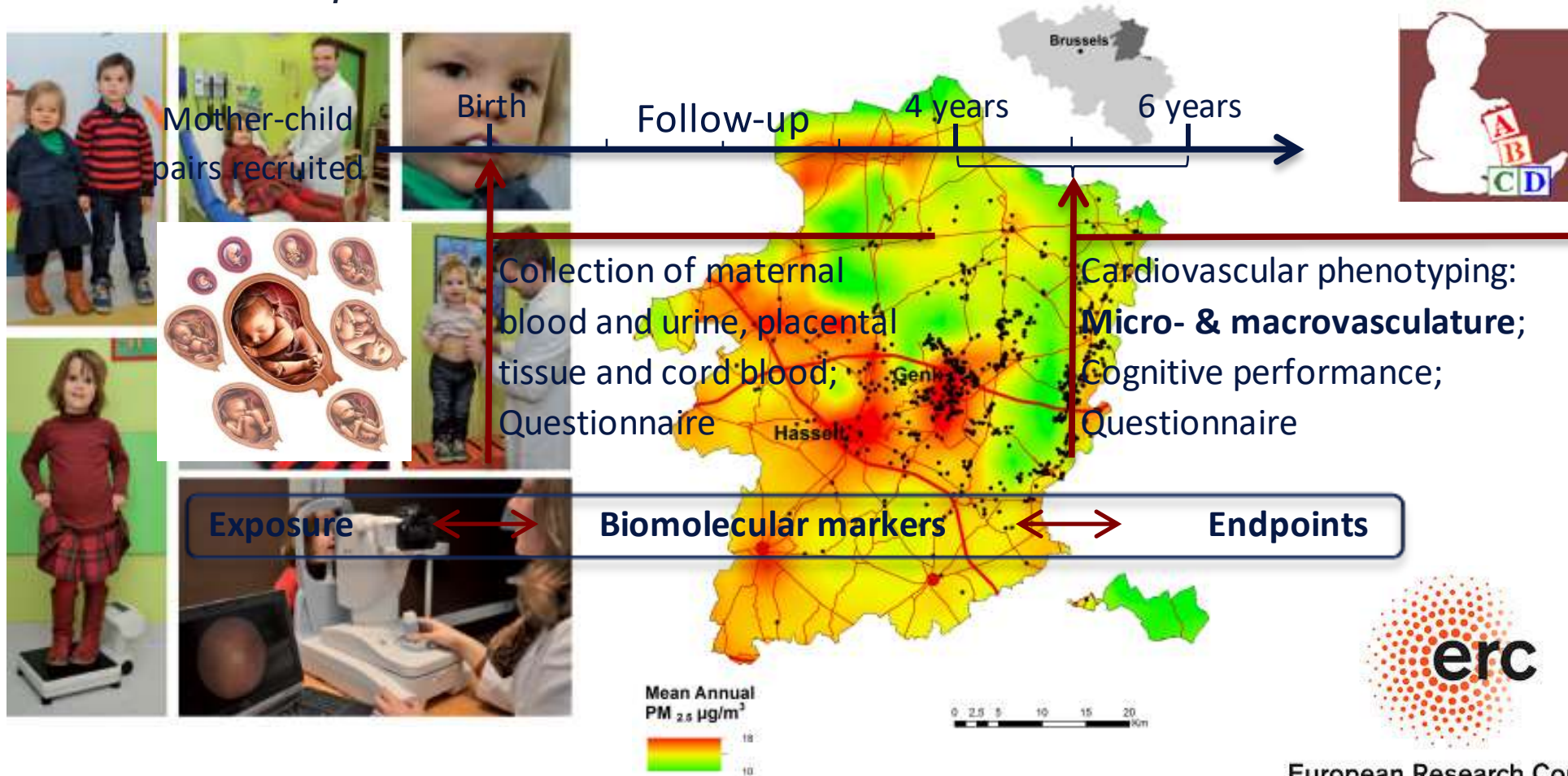
Telomere length early in life and life expectancy



ENVIRonAGE birth cohort

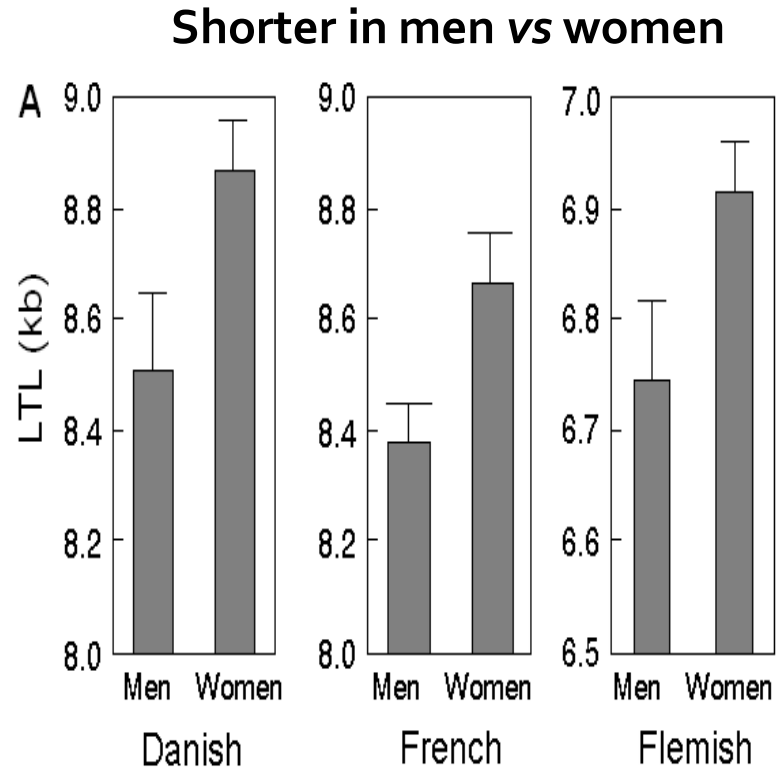
ENVIRonAGE ENVIRonmental influence ON early AGEing:

environmental pollution – nutrition – lifestyle – and their interactions with genes



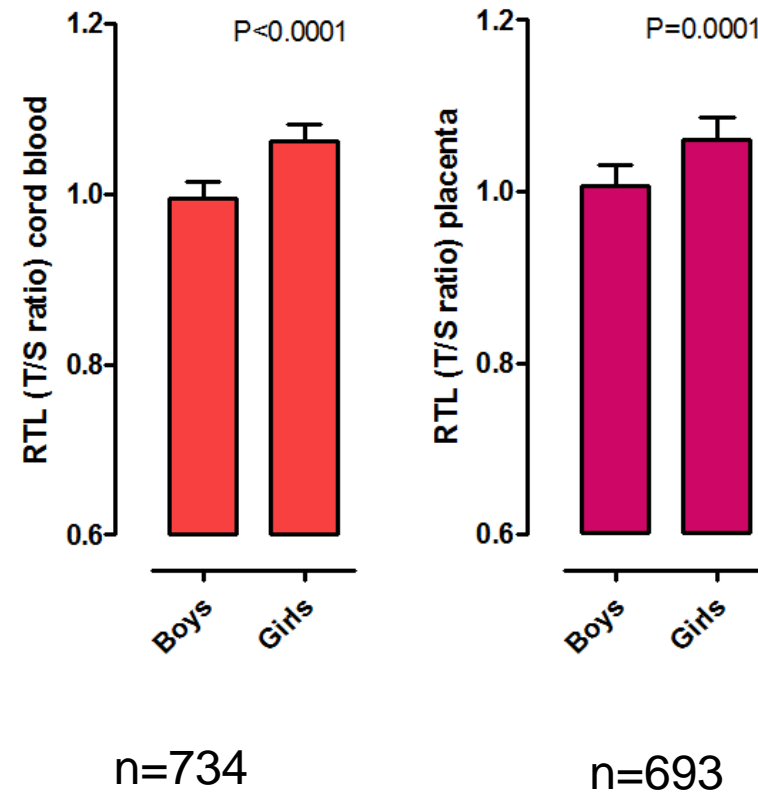
Sex differences of telomere length at birth

ADULTS (several cohorts)



*Hypertension, 2000, 2001; Lancet, 2004;
Circulation, 2008; AJE, 2007; Aging Cell, 2008*

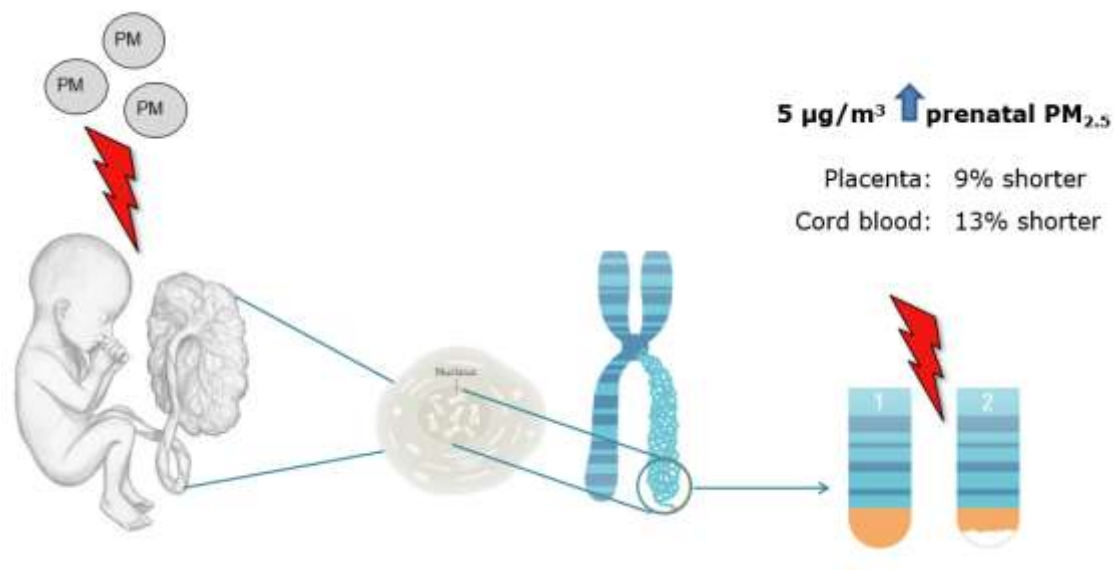
NEWBORNS (ENVIRONAGE)



Martens et al. JAMA Pediatrics 2017

Prenatal Air Pollution and Newborns' Predisposition to Accelerated Biological Aging

Dries S. Martens, MSc; Bianca Cox, PhD; Bram G. Janssen, PhD; Diana B. P. Clemente, MSc; Antonio Gasparini, PhD; Charlotte Vanpoucke, MSc; Wouter Lefebvre, PhD; Harry A. Roels, PhD; Michelle Plusquin, PhD; Tim S. Nawrot, PhD



Models were adjusted for date of delivery, gestational age, maternal body mass index, maternal age, paternal age, newborn sex, newborn ethnicity, season of delivery, parity, maternal smoking status, maternal educational level, pregnancy complications, and ambient temperature.

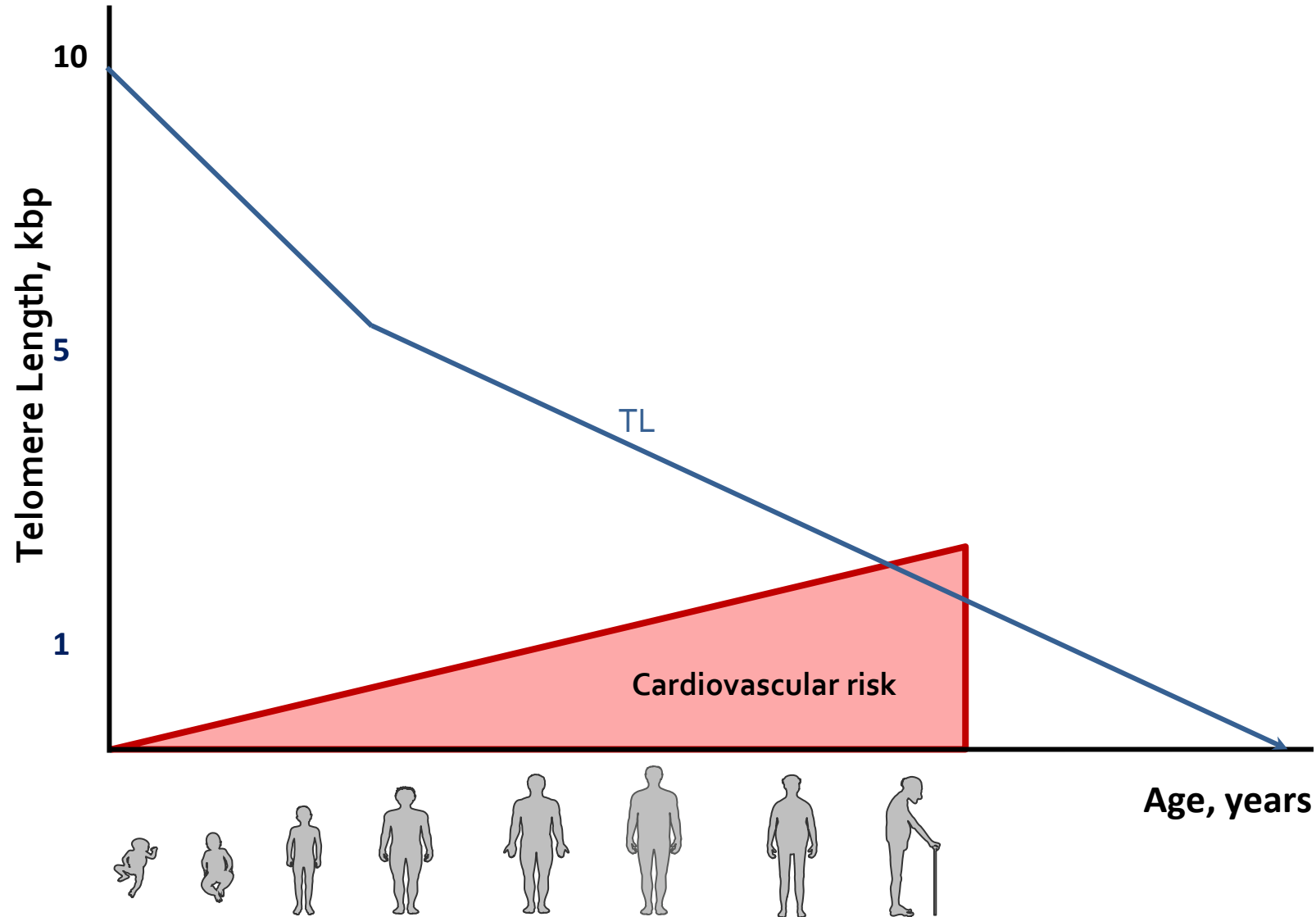
Key Points

Question Is telomere length at birth (a marker of biological aging) influenced by exposure to particulate matter air pollution during in utero life?

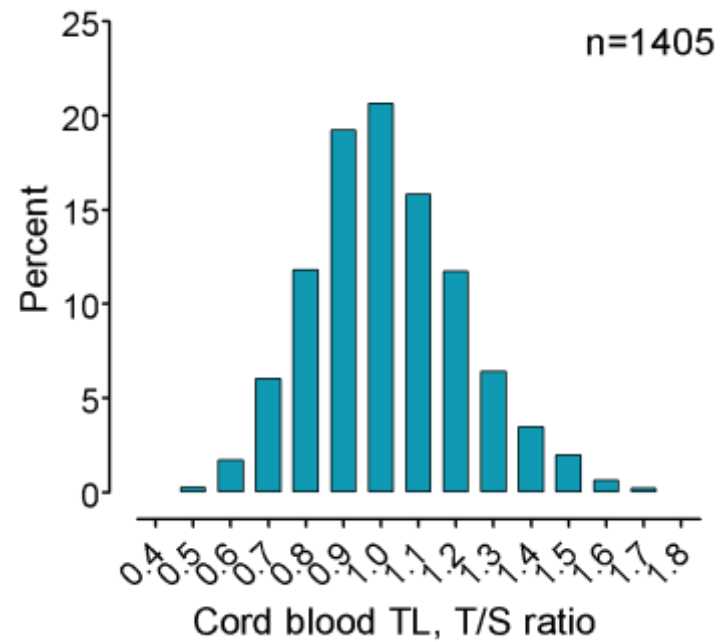
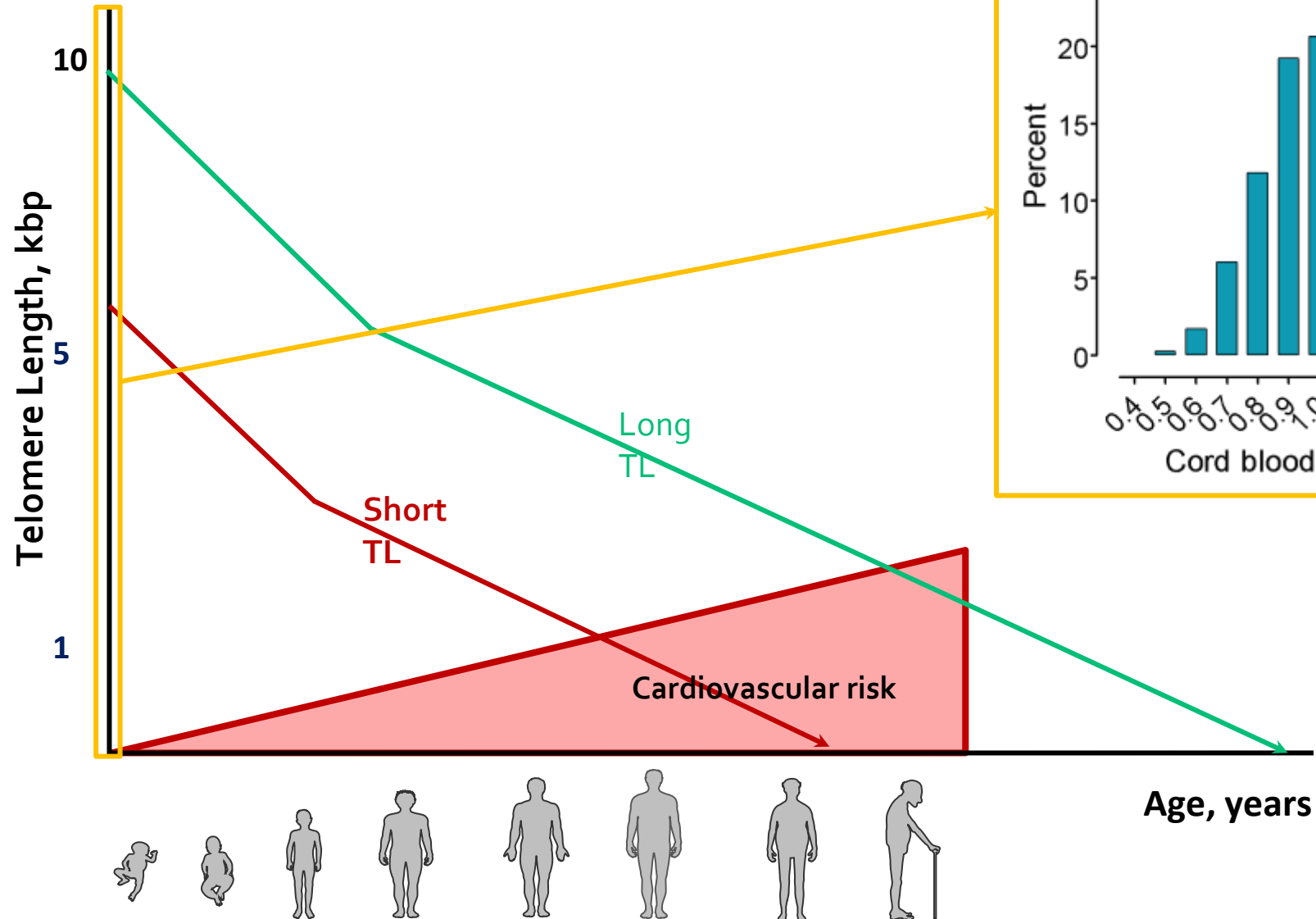
Findings In this birth cohort study of 641 mother-newborn pairs, mothers with higher residential exposure to PM_{2.5} (particulate matter with an aerodynamic diameter ≤2.5 µm air pollution) gave birth to newborns with significantly lower telomere length that could not be explained by other factors including socioeconomic class. For a 5-µg/m³ increase in residential PM_{2.5} exposure during pregnancy, cord blood telomeres were 9% shorter and placental telomeres 13% shorter.

Meaning Improved air quality may promote molecular longevity from birth onward.

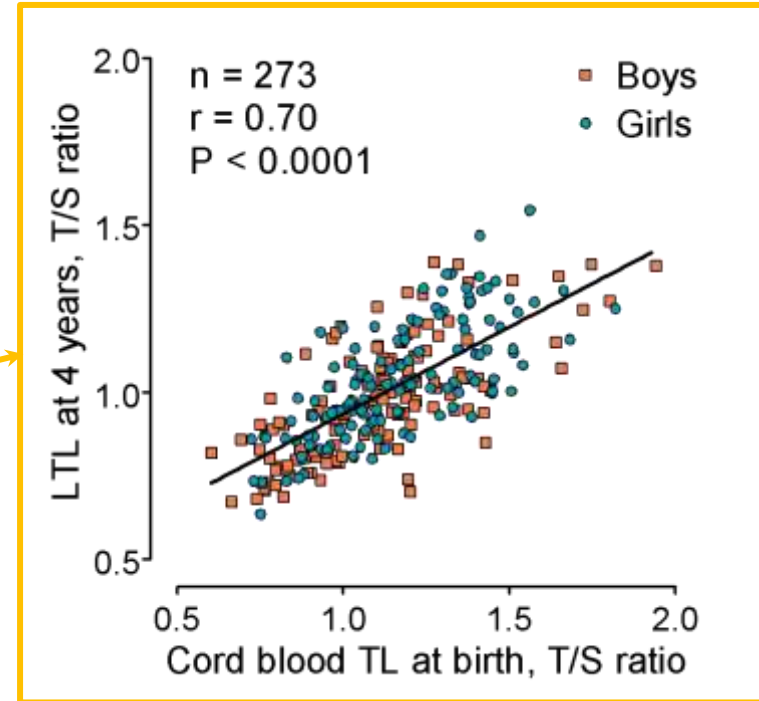
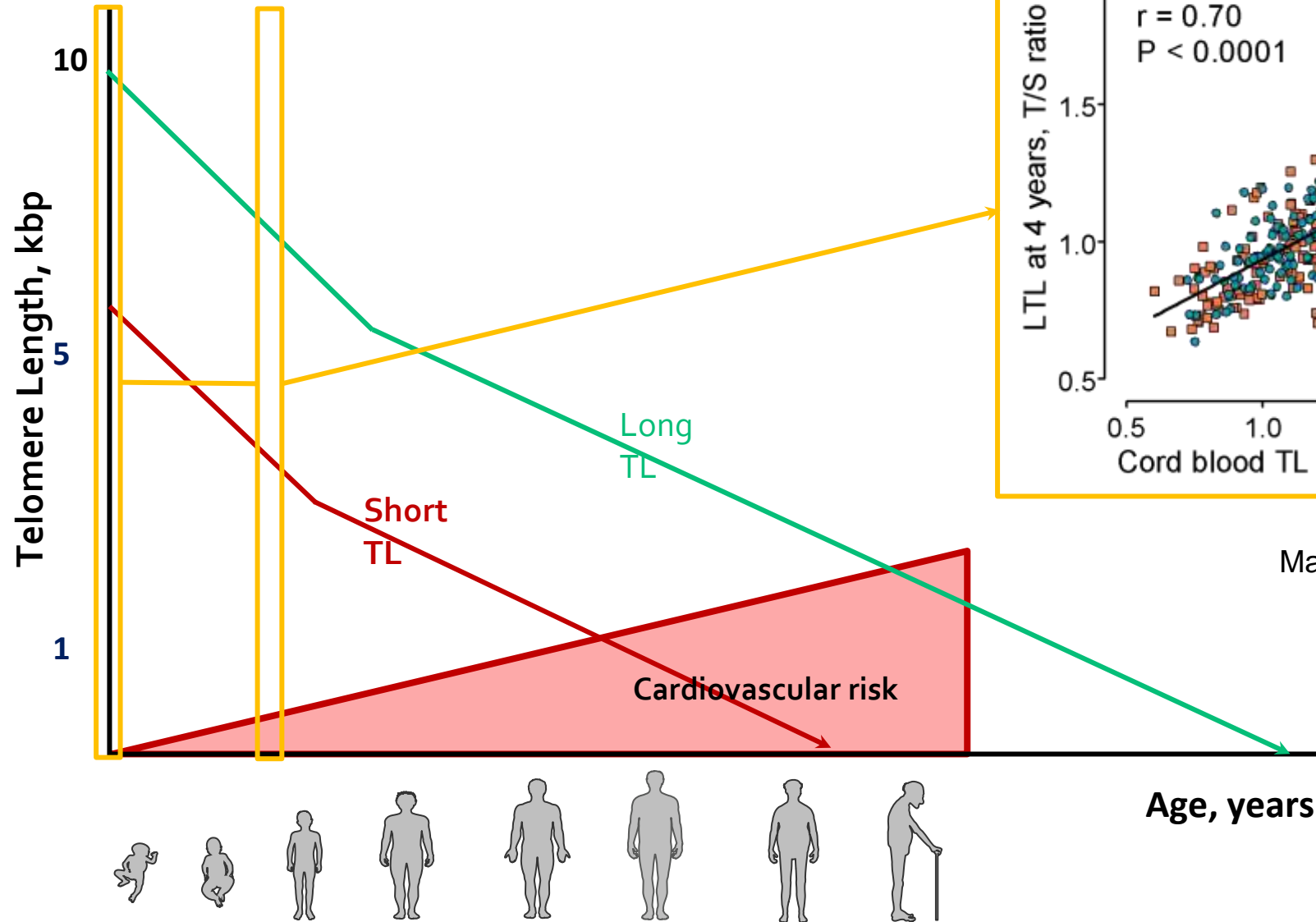
Telomere length at birth



Telomere length at birth



Telomere length at birth



Martens *et al.* eBiomedicine *in press*



Pre-pregnancy BMI

+1 unit; ↓0.5% cord TL
↓0.6% placenta TL
(Martens *et al.*, *BMC Med.* 2016)

Pre-pregnancy BMI

+1 unit; ↓0.2% TL
(Clemente *et al.*, *Sci Rep.* 2019)

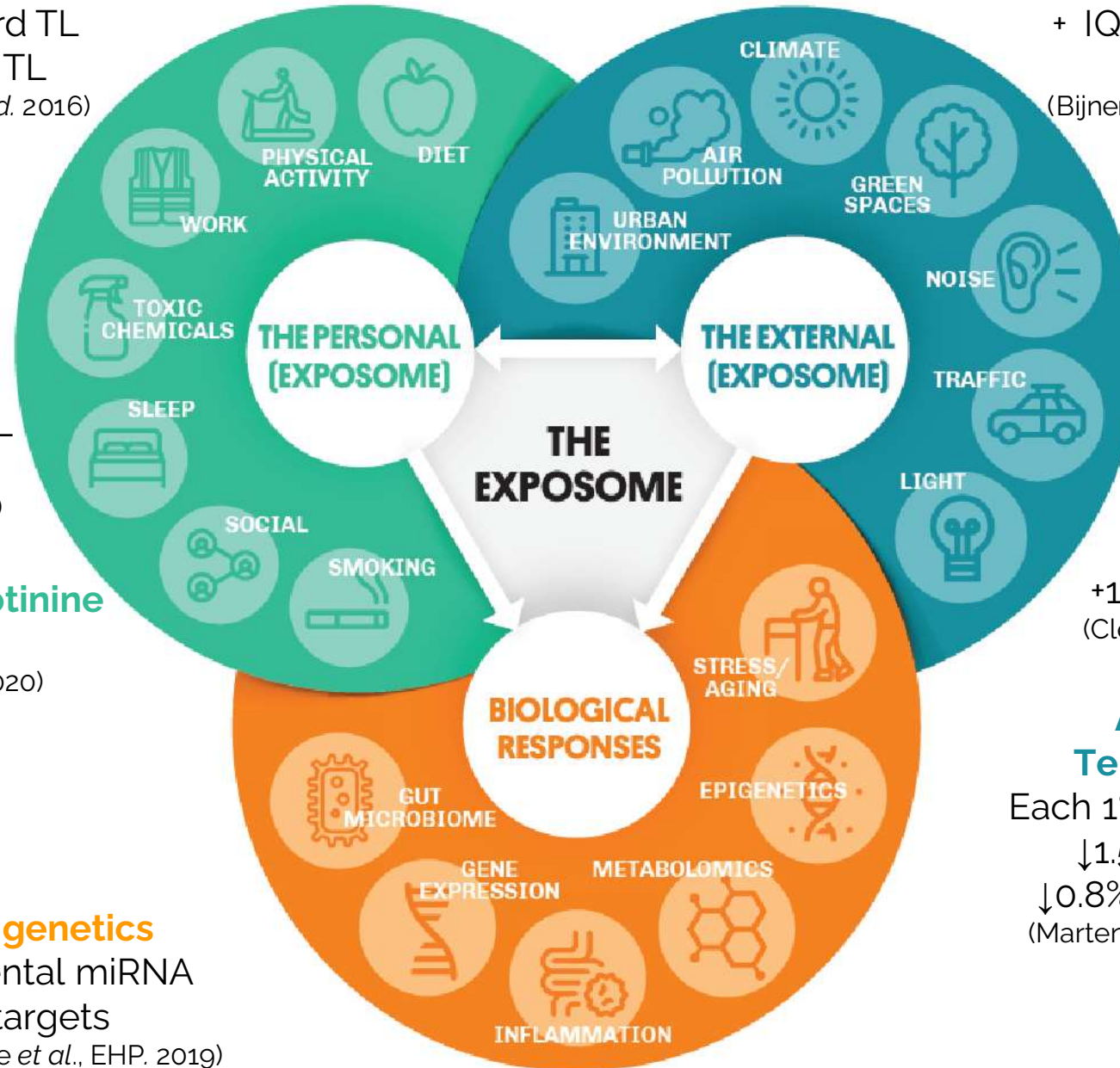
Maternal education

Low vs High ↓3.3% cord TL
↓3.4% placenta TL
(Martens *et al.*, *JAMA Open.* 2020)

Maternal pregnancy cotinine

↓3.9% child TL
(Osorio *et al.*, *Sci Tot Env.* 2020)

Epigenetics
placental miRNA
targets
(Clemente *et al.*, *EHP.* 2019)



Residential green space

+ IQR, ↑ 3.6% placenta TL
(Bijmens *et al.*, *Environ Int.* 2015)

Distance to major road

2-fold ↑, ↑ 5.3% placenta TL
(Bijmens *et al.*, *Environ Int.* 2015)

Prenatal PM_{2.5}

+ 5 µg/m³; ↓8.8% cord TL
↓13.2% placenta TL
(Martens *et al.*, *JAMA Ped.* 2017)

Prenatal NO₂

+1SD, ↓1.5% child TL
(Clemente *et al.*, *EHP.* 2019)

Ambient Temperature

Each 1°C above 20°C;
↓1.5% cord TL
↓0.8% placenta TL
(Martens *et al.*, *EHP.* 2019)

Telomere length depends on



Where you live

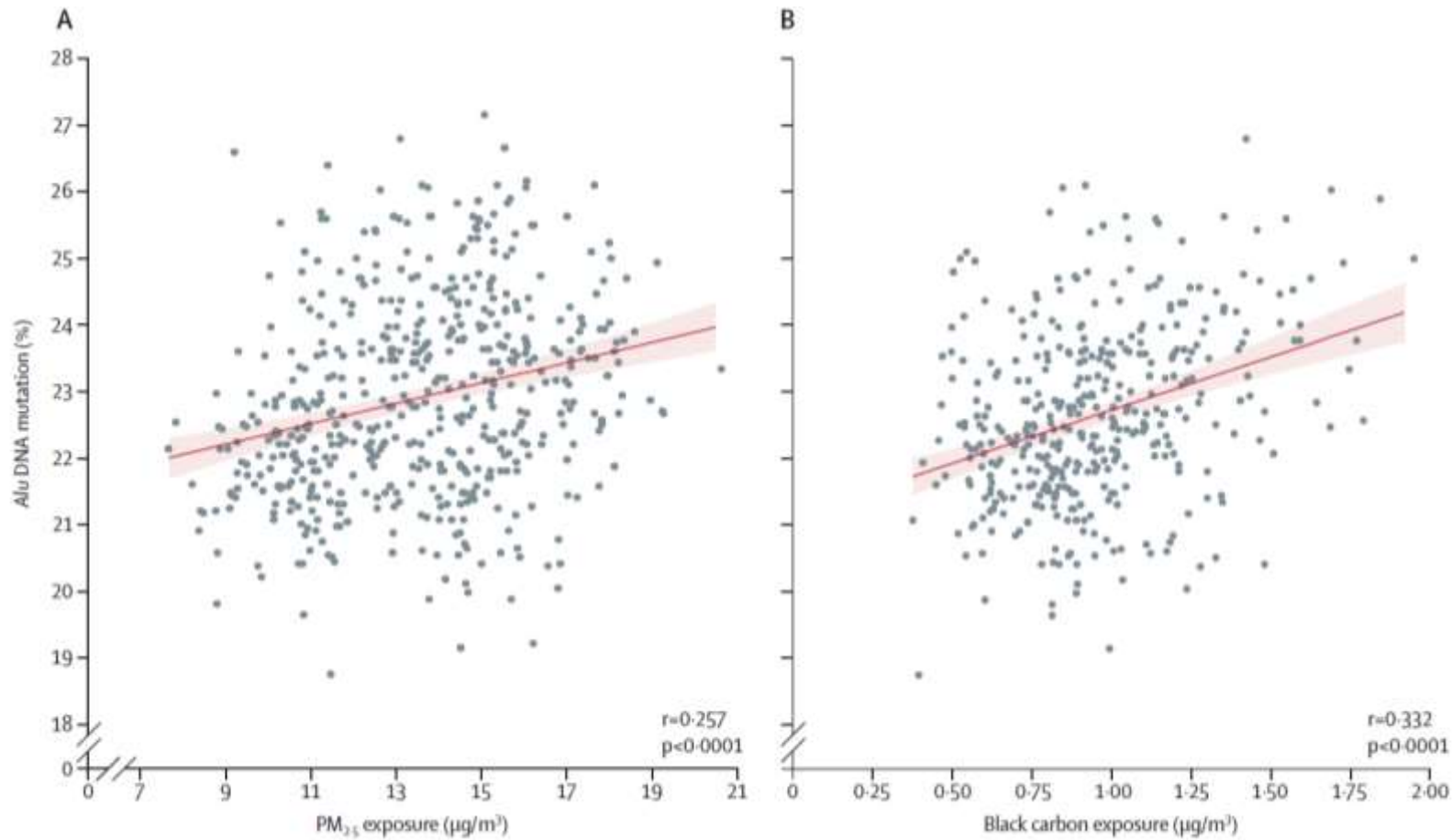


How you live

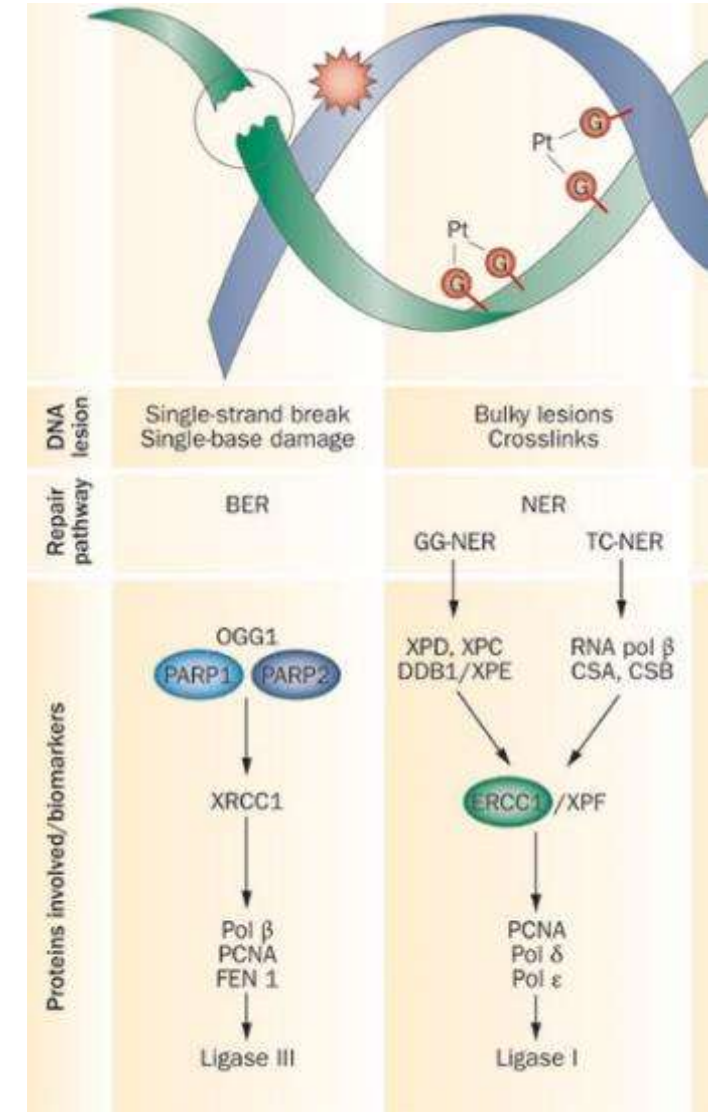


Who you are

What about DNA repair and damage during *in utero* life?

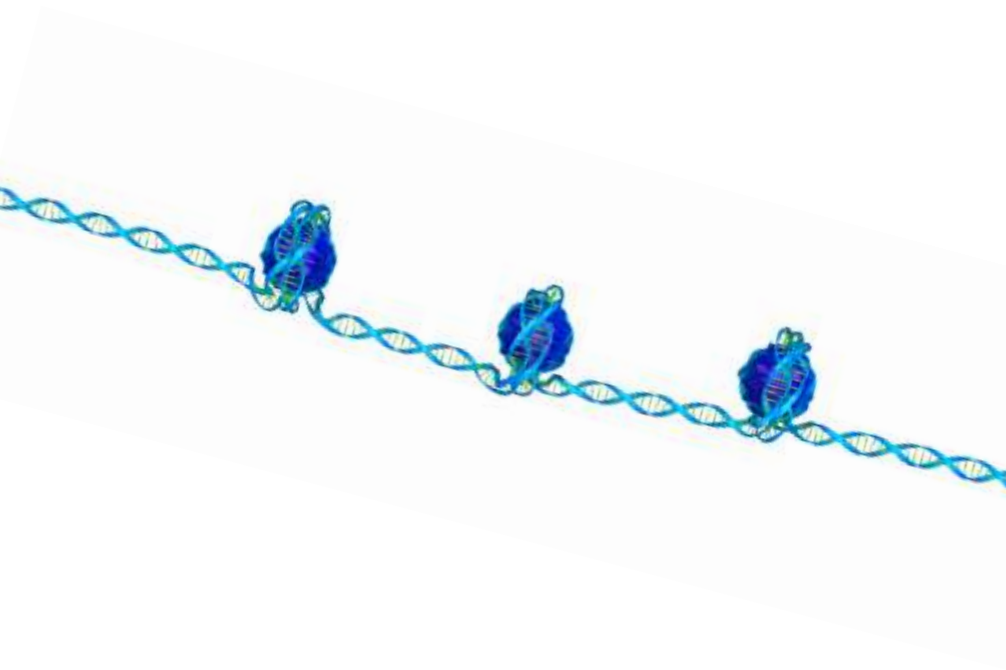


Current PM_{2.5} EU limit 25 µg/m³

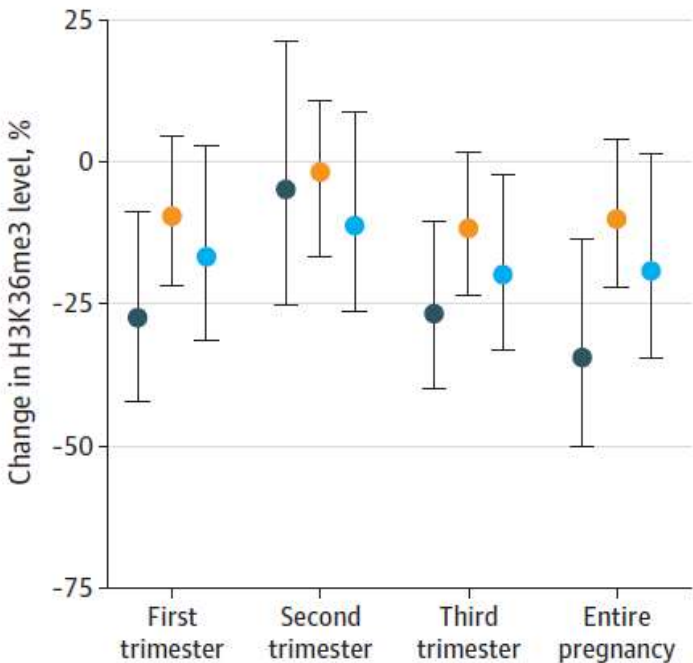


Association of Prenatal Exposure to Ambient Air Pollution With Circulating Histone Levels in Maternal Cord Blood

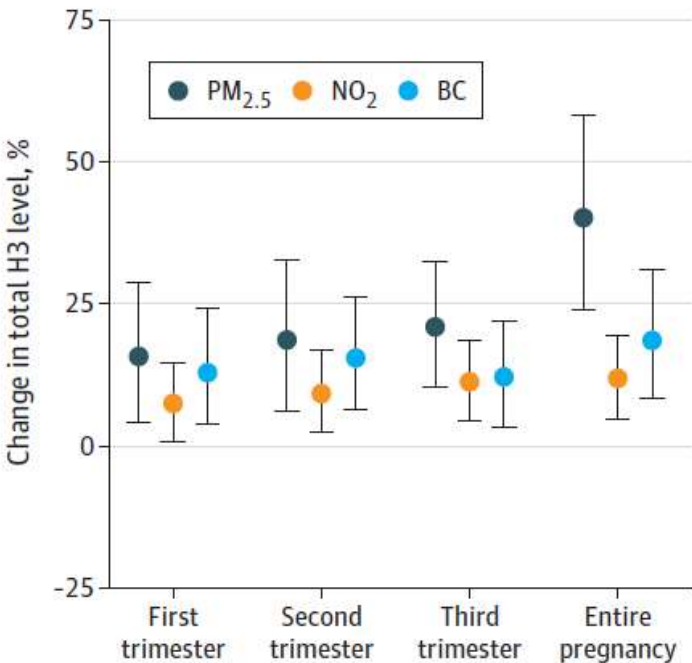
Karen Vrijens, PhD; Ann-Julie Trippas, MSc; Wouter Lefebvre, PhD; Charlotte Vanpoucke, PhD; Joris Penders, MD; Bram G. Janssen, PhD; Tim S. Nawrot, PhD



B H3K36me3 levels



C Total H3 level

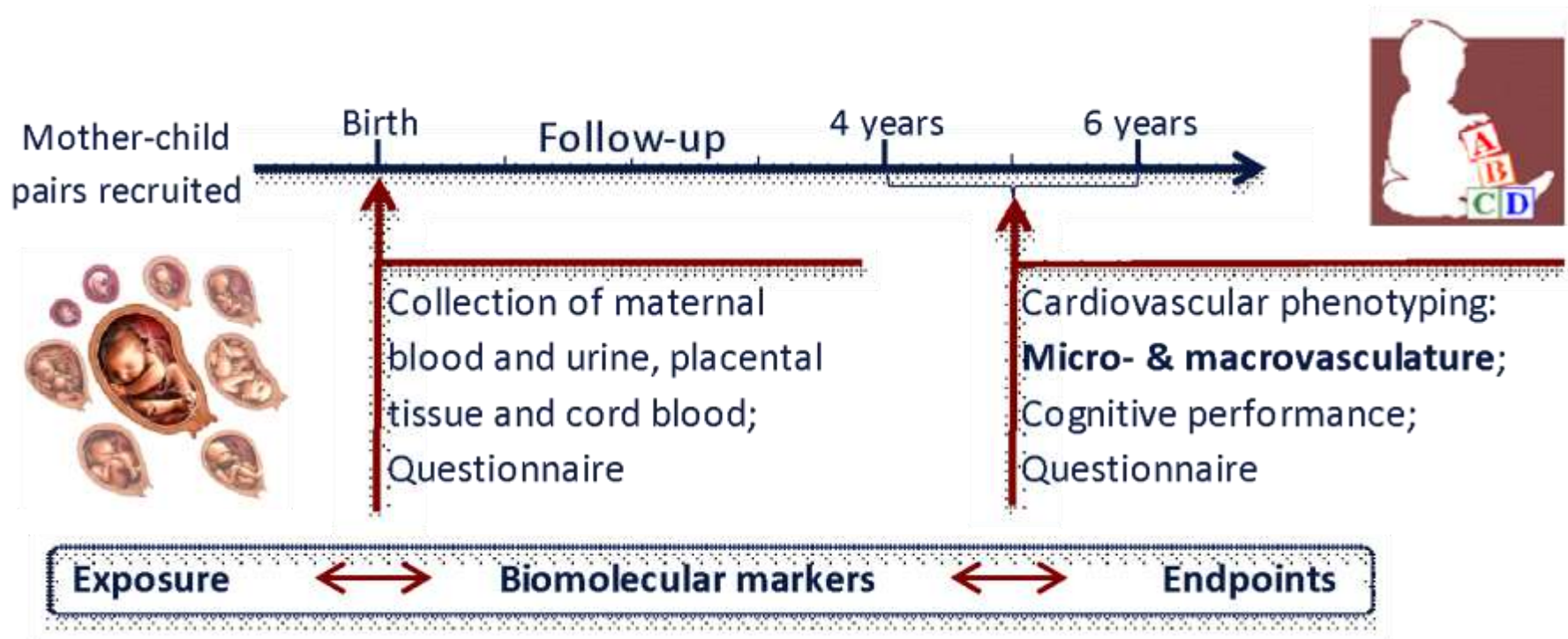


CONCLUSIONS AND RELEVANCE Associations of ambient air pollution with cord plasma histone H3 modifications during early life might indicate that circulating histones are a risk factor in the development of air pollution-associated disease later in life. Additional study is required to correctly estimate the long-term consequences of our findings.

ENVIRonAGE birth cohort

ENVIRonAGE ENVIRonmental influence ON early AGEing:

environmental pollution – nutrition – lifestyle – and their interactions with genes



Why do we study the microcirculation?

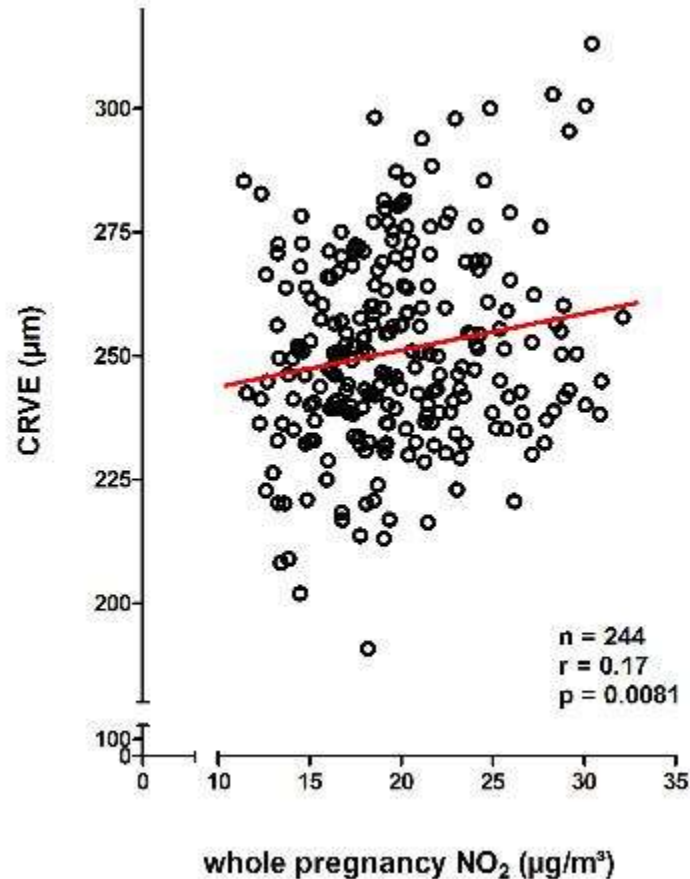


- The primary function of the microcirculation is to supply **oxygen** and **nutrients** to all organs.
- It also has an important role in regulating coronary blood flow and blood pressure
- It is related to cognitive function

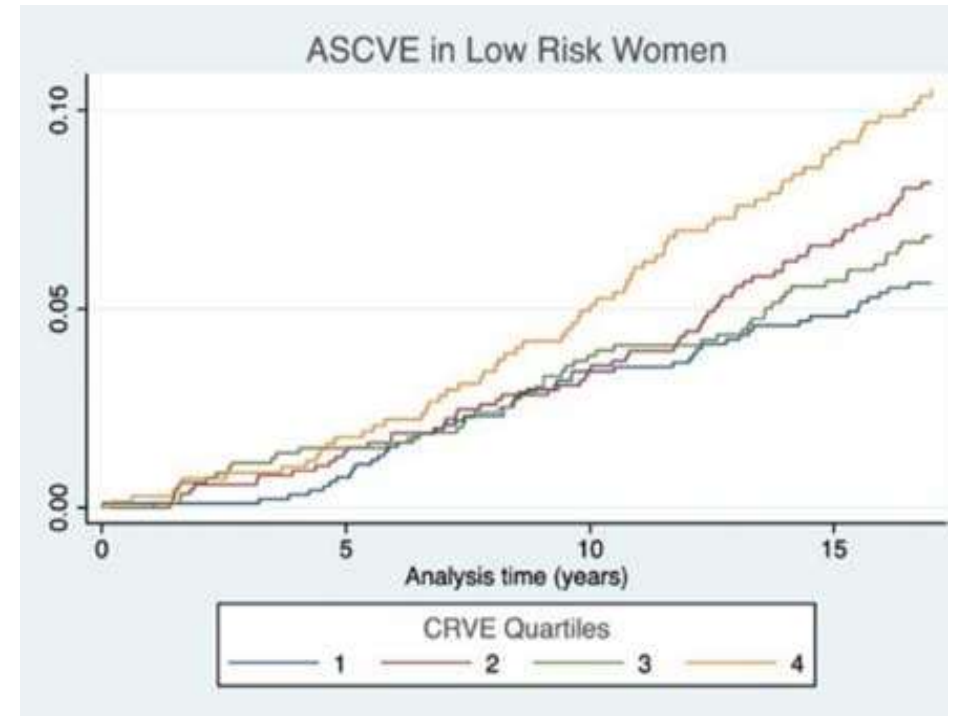


Prenatal air pollution and microvascular function @ age of 4

Central retinal venular equivalent (CRVE)
= average width of 6 largest veins



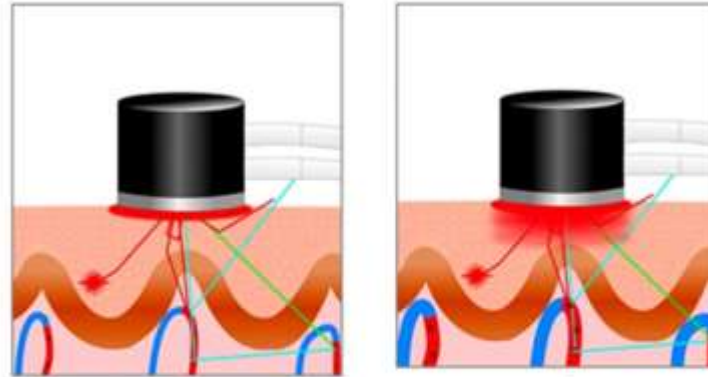
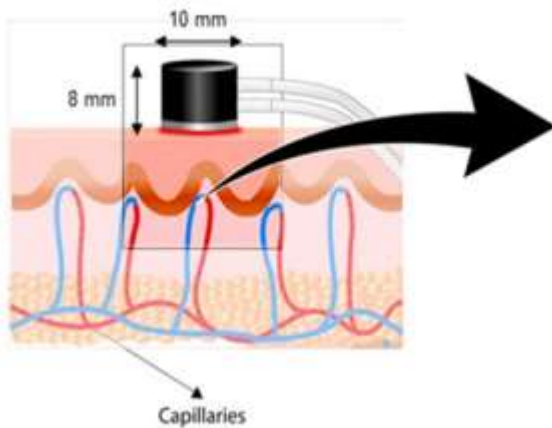
Luyten et al. JAMA Network open 2020



Seidelmann *et al.* Circulation 2016

Cardiovascular assessment

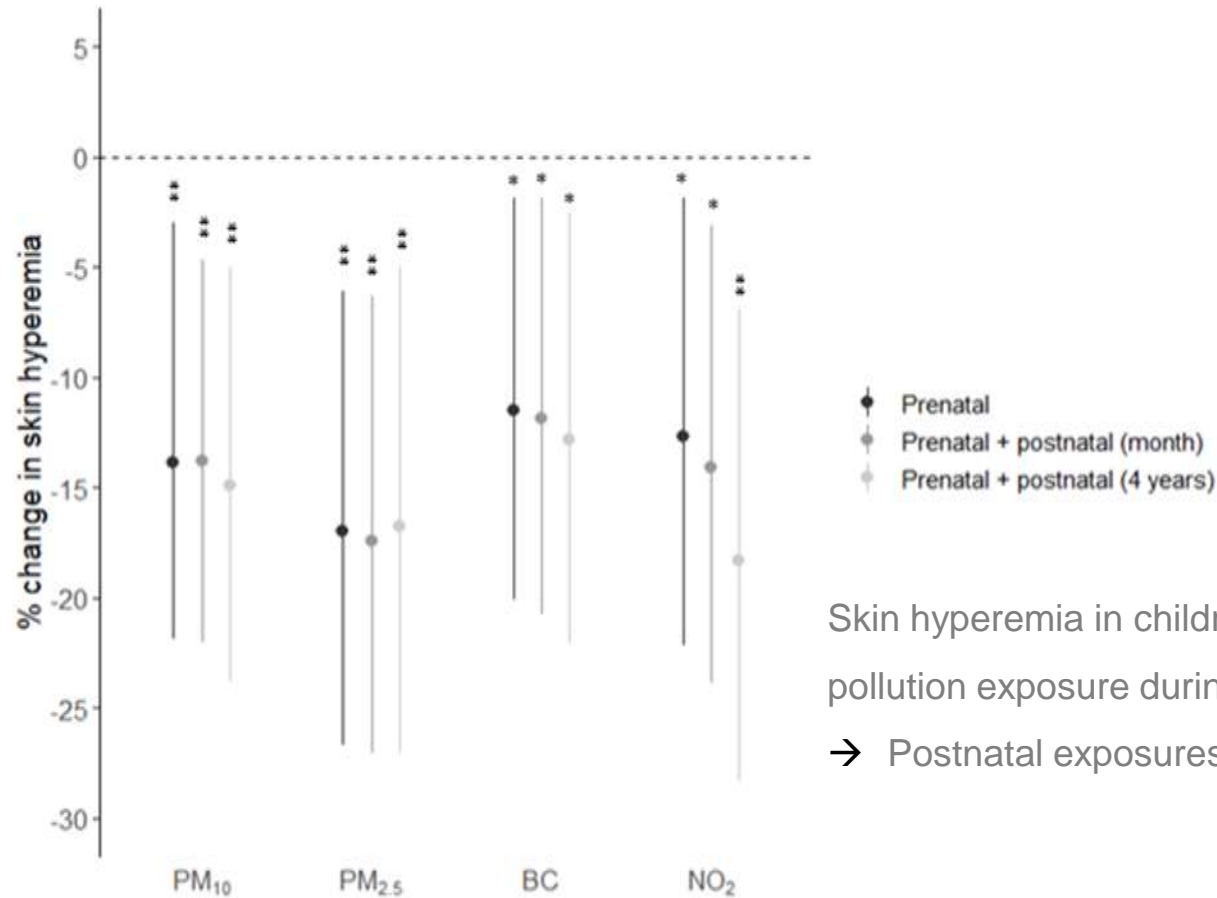
Skin perfusion was assessed using a laser Doppler system to detect blood flow changes



Measurement of the Doppler shift that occurs in light that has been scattered by moving red blood cells



Changes in the microvasculature and prenatal exposure



Skin hyperemia in children is **inversely associated** with air pollution exposure during the **third trimester** of pregnancy
→ Postnatal exposures did not alter these associations



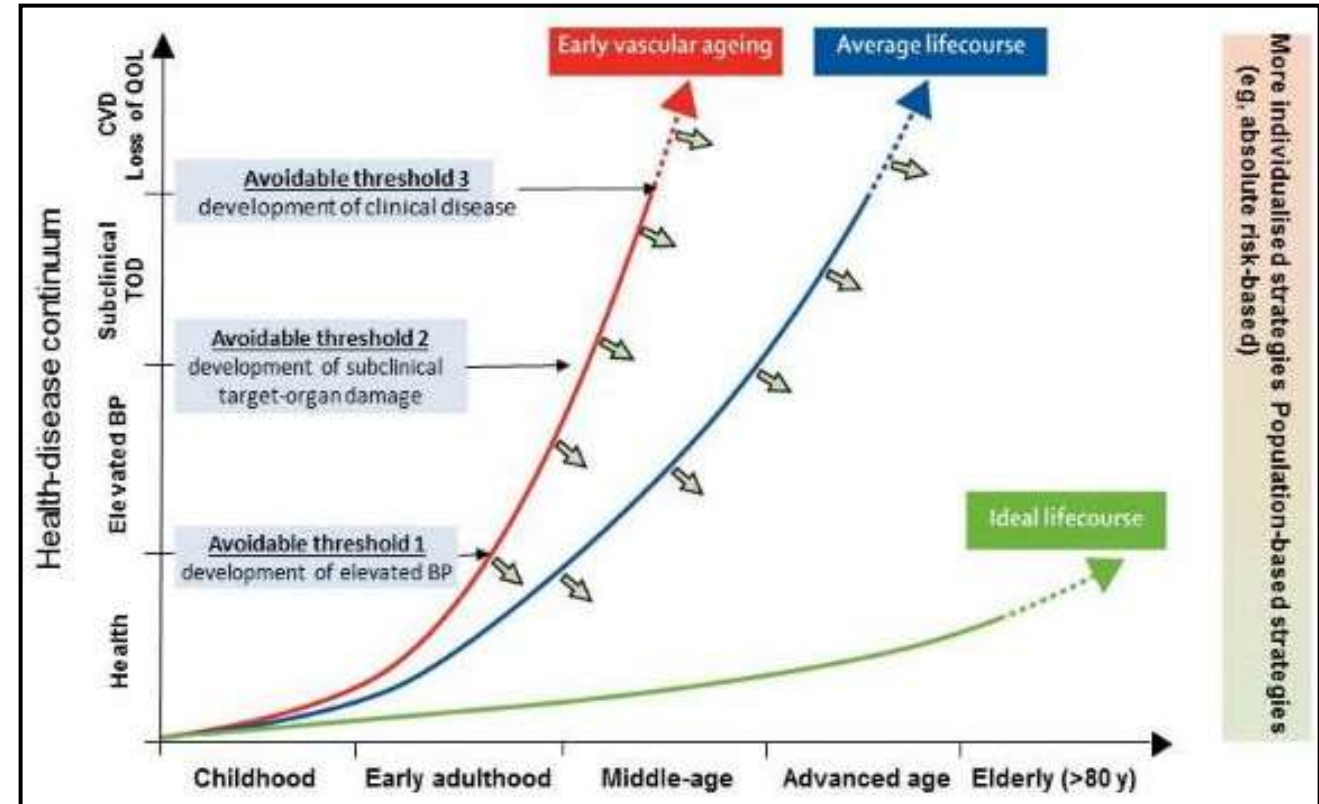
Estimates are given as percentage change (95% CI) for every IQR increase in PM₁₀, PM_{2.5}, BC, or NO₂. Prenatal models were adjusted for the year of skin perfusion assessment, date of delivery, age of the child at the house visit, sex, child's birth weight, parity, age of the mother at birth, pre-pregnancy BMI, gestational age, gestational weight gain, maternal smoking, newborn ethnicity, and maternal education. For the described models, n = 139. * p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001

Suggests a role for prenatal air pollution exposures in the microvascular origin of cardiovascular disease development later in life

Why is the early life important?

EARLY LIFE as a key target period for solid, cost-effective preventive actions and policies related to multiple adverse environmental exposures

- ✓ Vulnerable periods of rapid organ development
- ✓ Chronic diseases have part of their origin in early life
- ✓ Lifetime influence
- ✓ Effective prevention



Air pollution is linked with health effects over the life span

Environmental exposures in early life are relevant for disease development throughout the life span

Telomere is a marker for the exposome and integrates environmental conditions with molecular ageing

Healthy air is a major determinant of molecular longevity of the next generation

Current EU PM_{2.5} standard is not protective to prevent air pollution induced molecular and organ ageing



Acknowledgment



Research Foundation
Flanders
Opening new horizons



European Research Council
Established by the European Commission

Kom op
tegen Kanker

Next lectures

February 8th, **Greener cities good for cognitive function ?**



February 22nd, **Air pollution and brain health**



February 15th, **Climate change and health**



March 1st, **Is Environment and Health still relevant in Europe?**

