Translocation of ambient black carbon to different organs: implications for accerated ageing

EFCA, July 3rd 2024, Brussels

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Disclaimer: *I will show real-life data and associations. Do not worry, it is all perfectly normal in the wild world of epidemiology!*

"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 5*s*. with 2*s*. 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 ½*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-

The Lancet, 1903

Le Soir Illustré, 13 Dec 1930, N° 147

Nemery B et al. *Lancet* 2001

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 bu... re- sp... s in th... lous pa...

Spanish flu?

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.

Special Cable to THE NEW YORK TIMES.

... deaths attributed to the dense fog ... Belgium of the last three days were due in reality only to natural causes, the peasants refuse to relinquish the theory of poison. They point to the ... hens of cattle killed as sup...

Microbes from the Sahara?

8 Dec 1930

BELGIAN FOG DEATHS LAID TO POISONOUS GAS

Doctor Who Perfórms Autopsy Unable to Identify It— Brussels Inqairy 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 Liége. 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 ... 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.

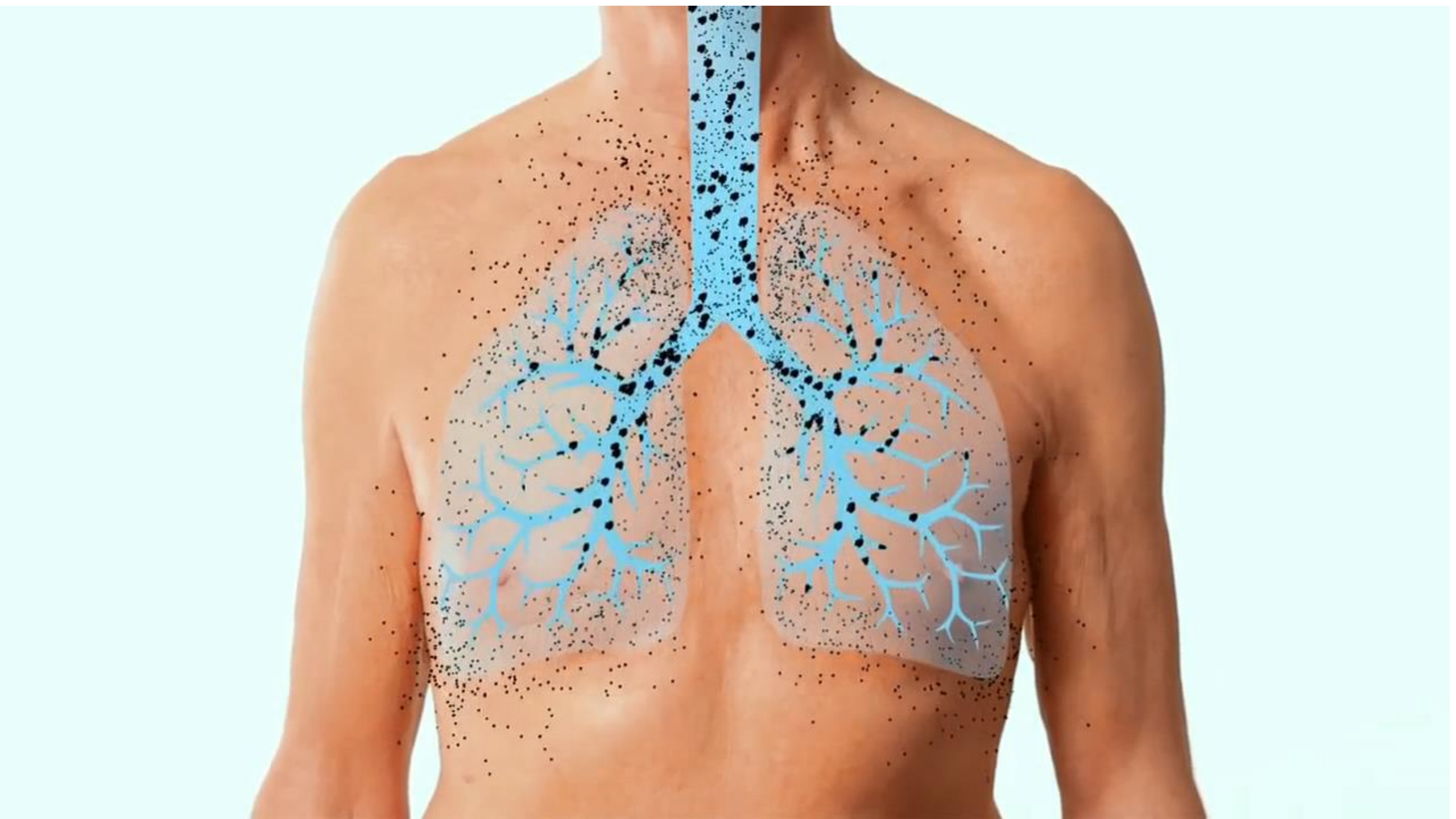
Chemical warfare?

Courtesy of B. Nemery, KU Leuven

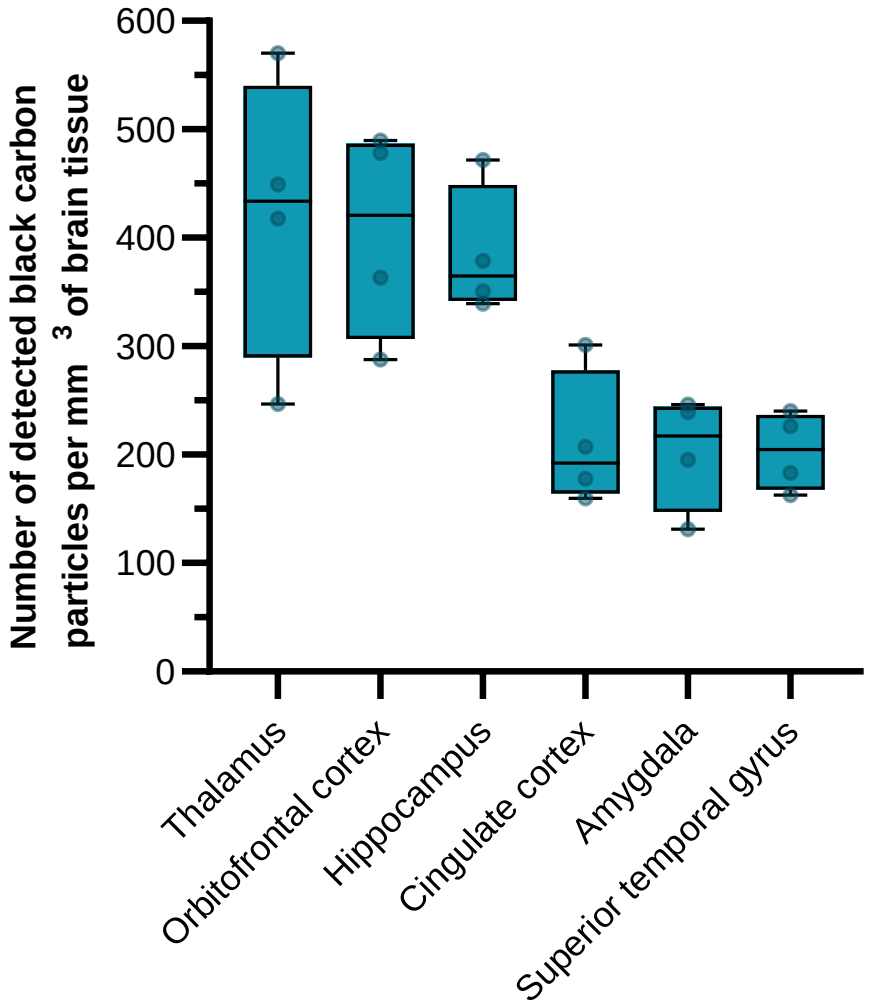
Questions I like to address

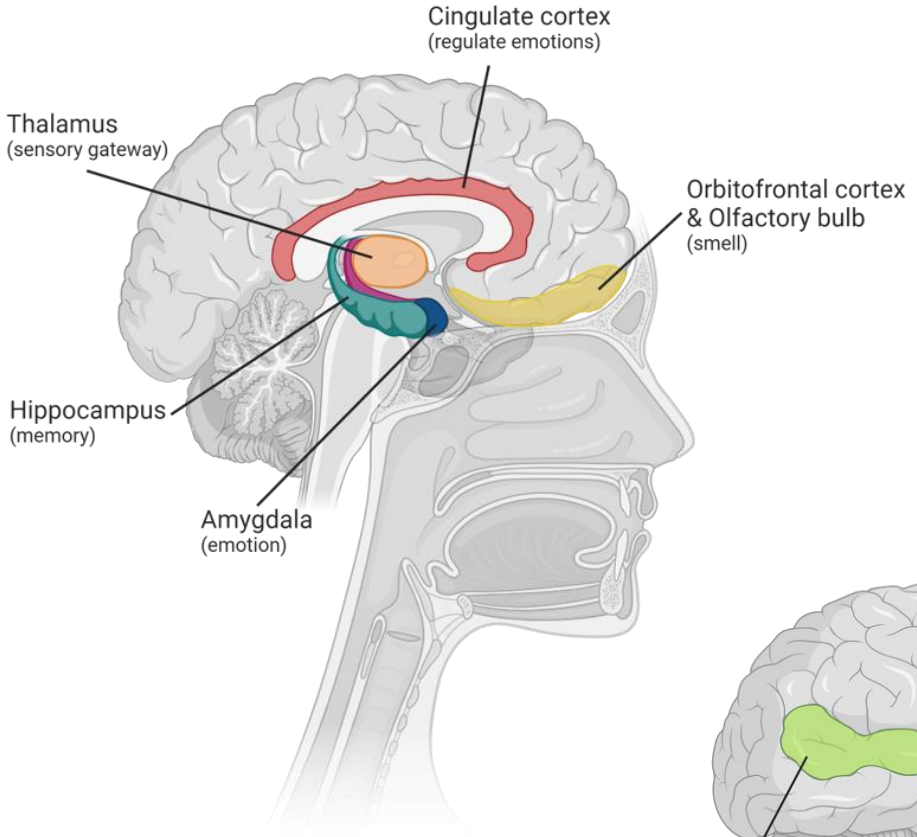
- Are particles translocating from mother to fetus at low ambient cocentrations?
- Does early life exposure to particles influence the molecular longevity potential?
- Can we protect the general population from molecular ageing by air pollution?
- Black carbon and disease progression in hospitalised COVID patients

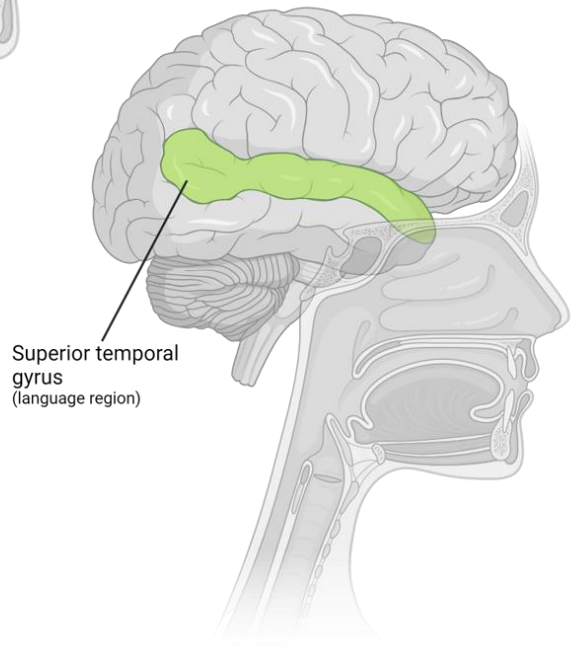
Nederlands longfonds



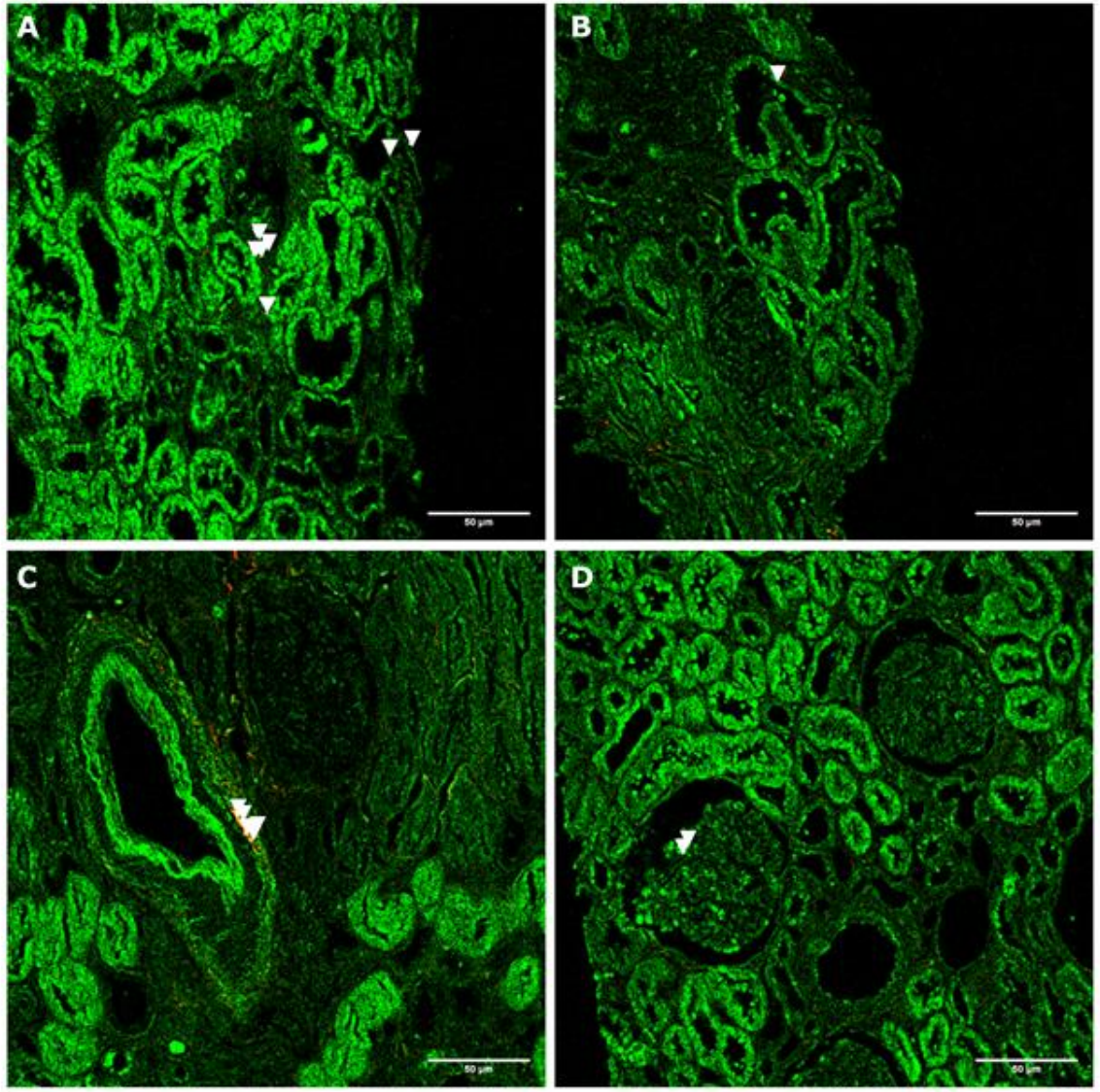
Accumulation of ambient black carbon particles within key memory related brain regions

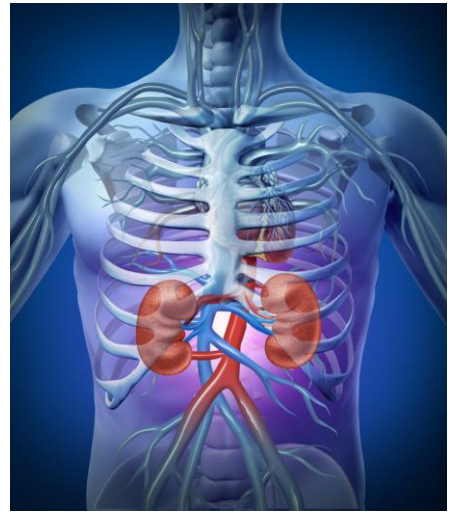






Vanbrabant K, *et al.* Jama network open, 2024





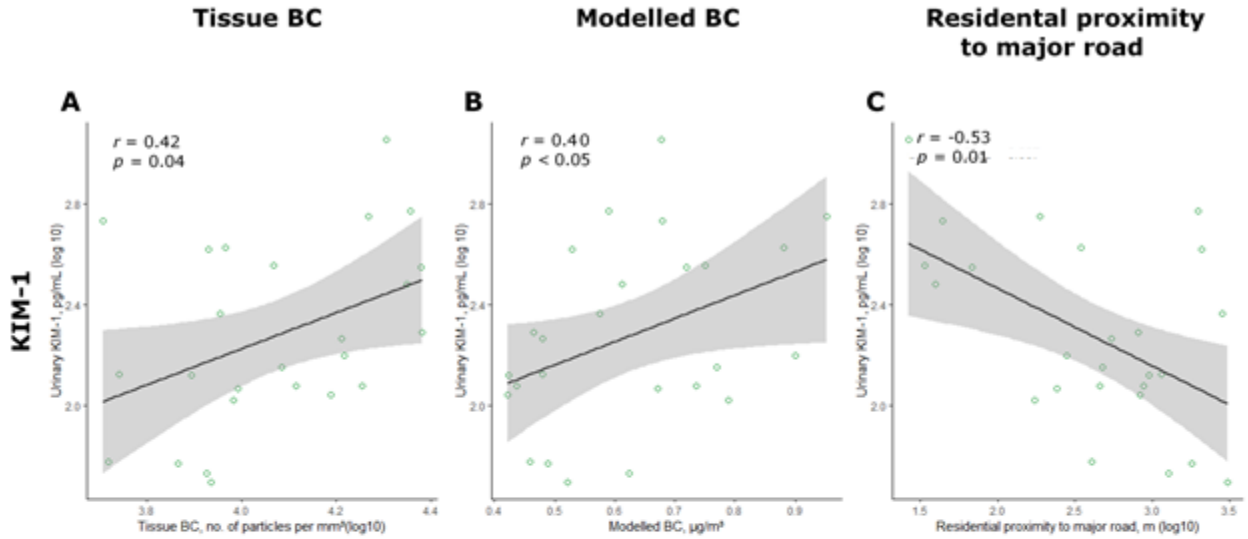
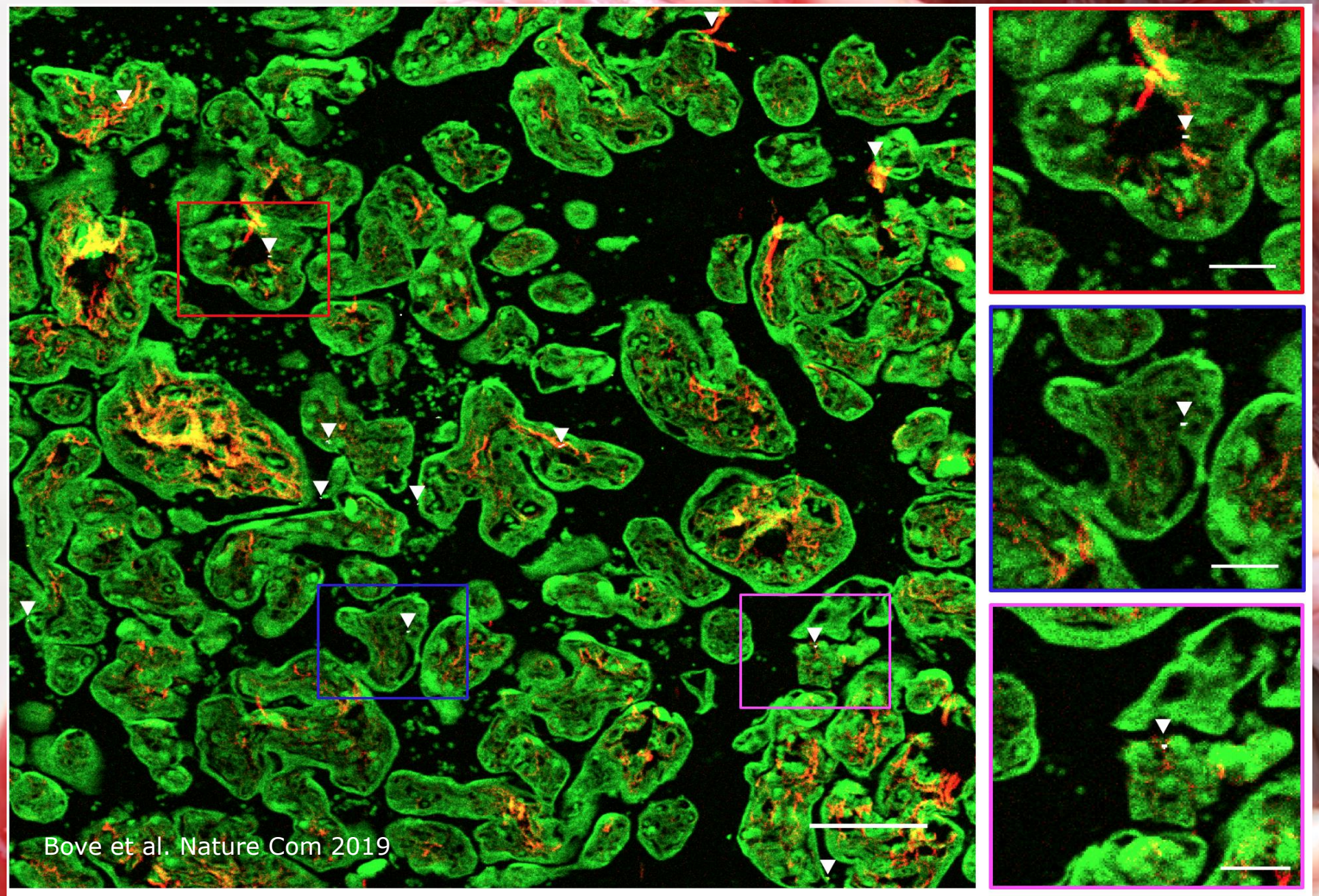


Figure 2. BC particles are observed in major structural components of kidney biopsy tissue from transplant recipients one-year post-transplant. The white light generation originating from the BC particles (depicted in white and indicated with white arrowheads) under femtosecond-pulsed laser illumination can be observed in multiple renal structures: **A)** in the interstitial region surrounding tubule(s), **B)** in the epithelial lining of the tubule(s), **C)** in the smooth muscle surrounding a blood vessel, and **D)** in the capillaries of the glomerular tuft.

Rasking *et al.* 2023. Environmental Health.

Fetal exposure to black carbon



Bove et al. Nature Com 2019

MATTERS ARISING

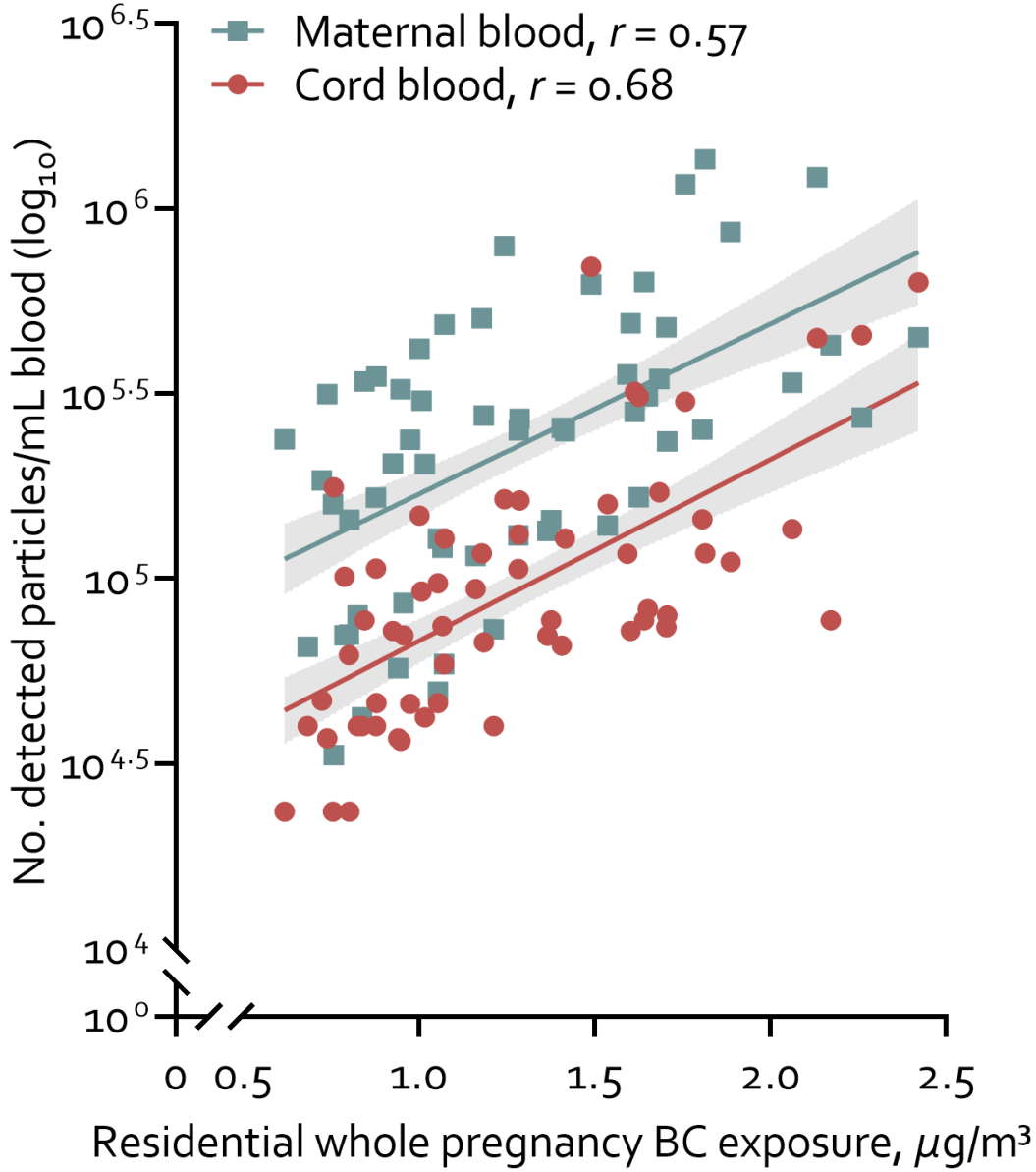
https://doi.org/10.1038/s41467-021-26437-y OPEN

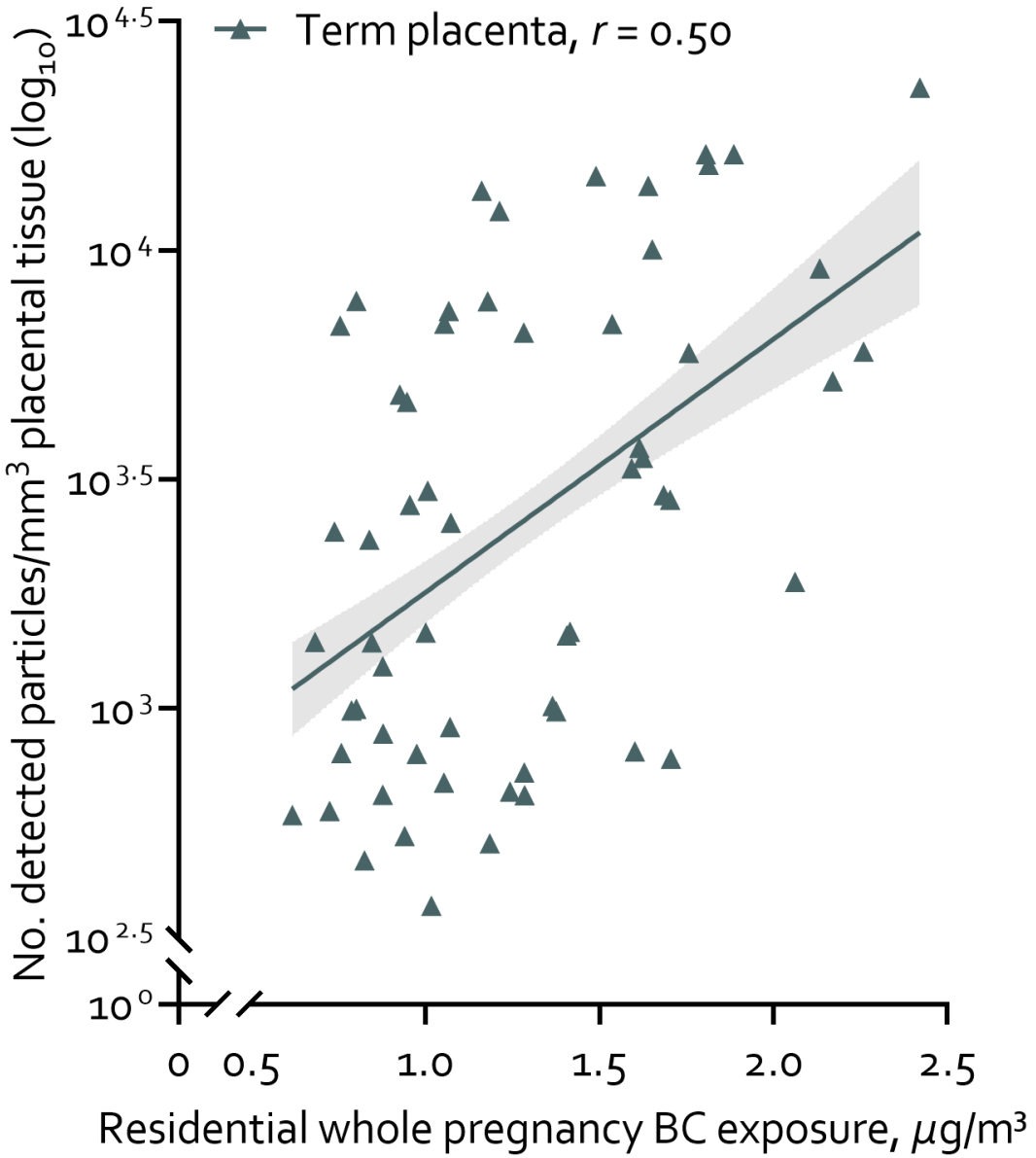
'Fetal side' of the placenta: anatomical mis-annotation of carbon particle 'transfer' across the human placenta

Beth Holder[1,11✉], John D. Aplin[2], Nardhy Gomez-Lopez[3], Alexander E. P. Heazell[2], Joanna L. James[4], Carolyn J. P. Jones[2,11], Helen Jones[5], Rohan M. Lewis[6], Gil Mor[7], Claire T. Roberts[8], Sarah A. Robertson[9] & Ana C. Zenclussen[10]

To definitively demonstrate penetration of the placental barrier, certain criteria must be met. Specifically, higher magnification images are required to enable proper visualisation of the location of particles within cell layers other than the syncytiotrophoblast such as the stroma or capillary endothelium; regions that are not mentioned in the entirety of the paper. The interpretation of potential transfer across the placental barrier towards the fetus would be justified if particles were clearly demonstrated to have crossed the syncytiotrophoblast and to be present within the villous stroma and/or the endothelium of fetal blood vessels (or in cord blood), substantiated by co-localisation of cell lineage-specific markers.

ENVIRONAGE
Maternal-perinatal BC load

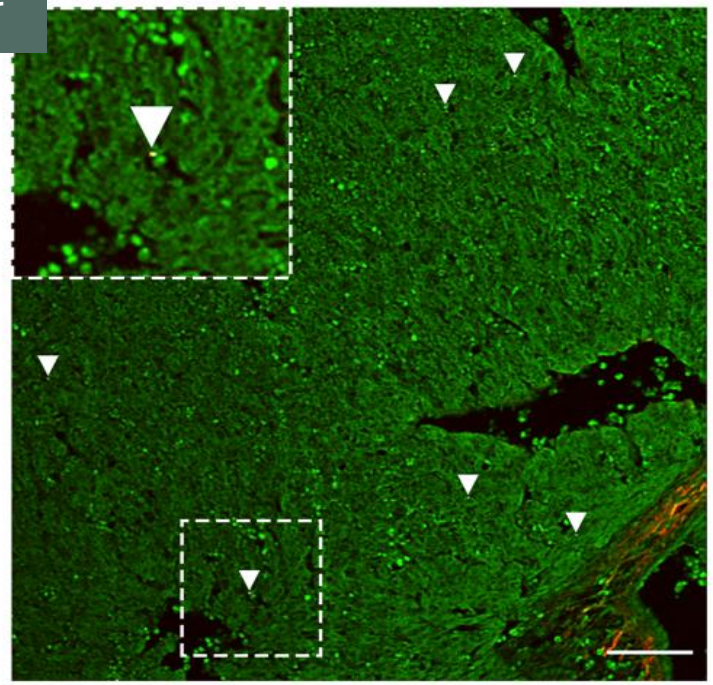




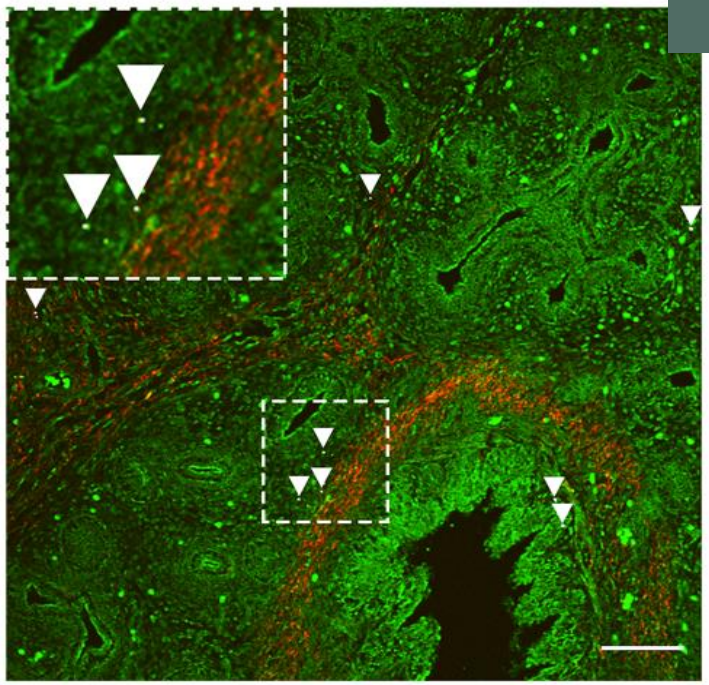
Bongaerts E, *et al.* Lancet Planetary Health, 2022

SAFeR
Fetal BC load

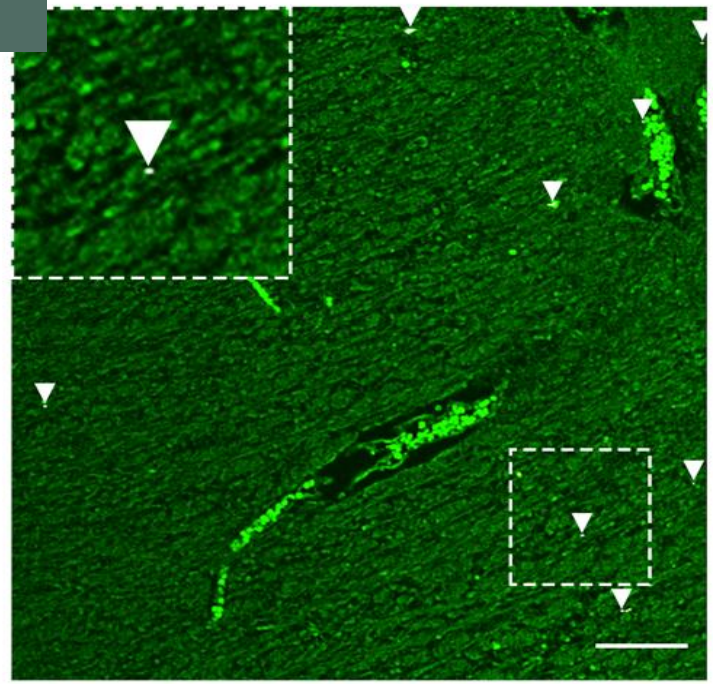
Fetal liver



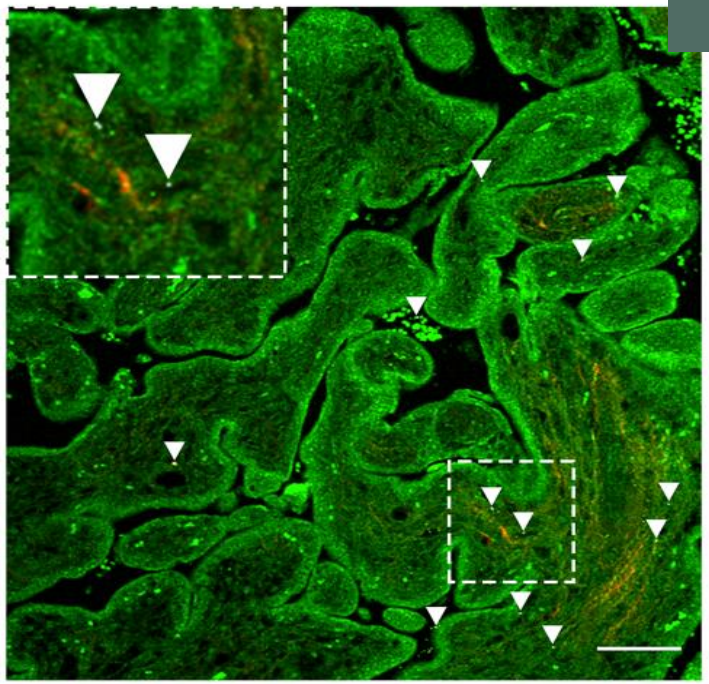
Fetal lung



Fetal brain



Preterm placenta



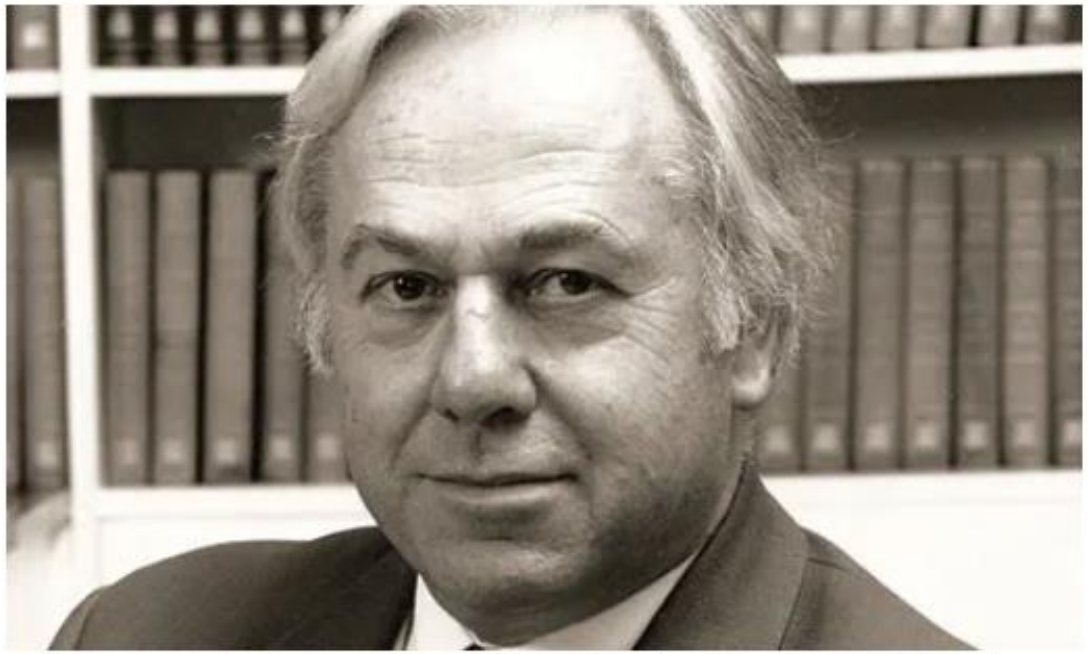
Bongaerts E, et al. Lancet Planetary Health, **2022**

Paracelsus (1493-1541)

“The dose makes the poisson”

David Barker obituary

Epidemiologist who proposed the idea that common chronic diseases result from poor nutrition in the womb



'The next generation does not have to suffer from heart disease or osteoporosis. These diseases ... barely existed 100 years ago,' said David Barker

The physician and epidemiologist David Barker, who has died aged 75, posited the initially controversial but now widely accepted idea that common chronic illnesses such as cancer, cardiovascular disease and diabetes result not always from bad genes and an unhealthy adult lifestyle, but from poor intrauterine and early postnatal health. In one of his last public speeches, he argued: "The next generation does not have to suffer from heart disease or osteoporosis. These diseases are not mandated by the human genome. They barely existed 100 years ago. They are unnecessary diseases. We could prevent them had we the will to do so."

The fetal and infant origins of adult disease

The womb may be more important than the home

A hundred years ago, when tuberculosis and rheumatic heart disease were common, the proposition that the childhood environment affects adult health would have been self evident. This proposition may still hold, even though infective disease has given place to degenerative disease.

Studies in Norway, Finland, Britain, and the United States have shown that death rates from cardiovascular disease are inversely related to adult height, and geographical differences in cardiovascular mortality are related to past differences in infant mortality.[1-7] These findings have been interpreted as evidence that adverse living conditions during childhood, such as poor housing and diet, increase the risk of ischaemic heart disease.[4] Case-control studies have generally supported this[8-12]: patients with myocardial infarction have higher infant death rates among their siblings,[8,9] are more likely to come from larger families, and are more likely to have fathers who were unemployed.[10] Now studies in Finland show that men with ischaemic heart disease had worse socioeconomic conditions in childhood (p 1121)[12]—an observation also made in Britain.[9]

The completeness of infant mortality records in England and Wales from 1911 onwards has allowed detailed geographical comparisons of the relation between infant mortality 70 years ago and mortality from cardiovascular disease today. Differences in the death rates from cardiovascular disease among the 212 local authority areas of England and Wales are closely related to past differences in neonatal mortality.[6,13] Most neonatal deaths were associated with low birth weight, and rates were high in areas where mothers had poor health and high death rates during childbirth.[14,15] These findings suggested that research should be redirected towards the intrauterine environment rather than the environment in later childhood—housing, family income, diet, and other influences. The Medical Research Council employed a historian to search for old records of birth baboons. Knowledge of the fetal processes that may determine programming is beginning to emerge.[20] A recent symposium heard evidence that diseases other than cardiovascular disease may also be determined by the maternal environment.[21] Schizophrenia and obstructive lung disease are two examples.

The old model of adult degenerative disease was based on the interaction between genes and an adverse environment in adult life. The new model that is developing will include programming by the environment in fetal and infant life.

D J P BARKER

Director,
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University of Southampton,
Southampton General Hospital,
Southampton SO9 4XY

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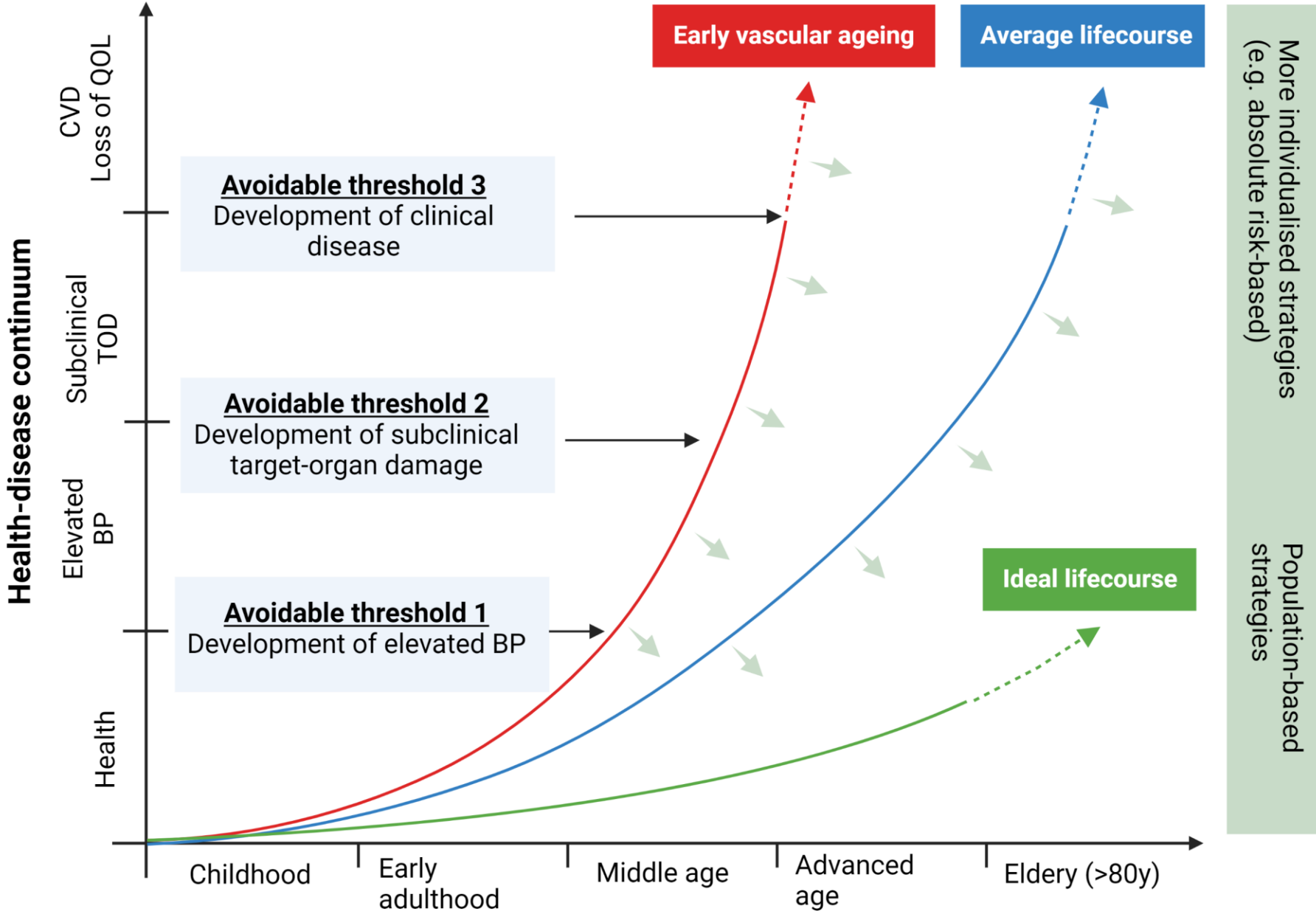
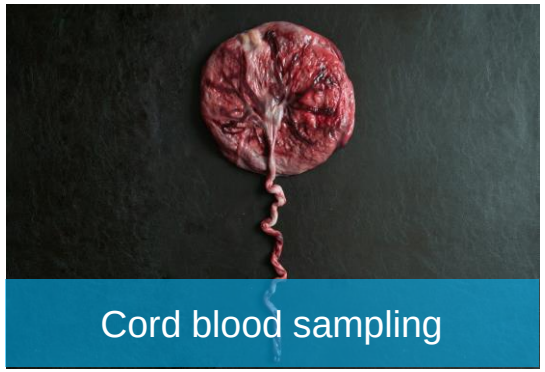

Health-disease continuum
CVD
Loss of QOL
Subclinical
TOD
Elevated
BP
Health
Avoidable threshold 3
Development of clinical disease
Avoidable threshold 2
Development of subclinical target-organ damage
Avoidable threshold 1
Development of elevated BP
Early vascular ageing
Average lifecourse
Ideal lifecourse
Childhood
Early adulthood
Middle age
Advanced age
Eldery (>80y)
More individualised strategies (e.g. absolute risk-based)
Population-based strategies

ENVIRONAGE

Investigating children's health one step at a time!


Microbiome sampling


Cord blood sampling


Cognitive tests

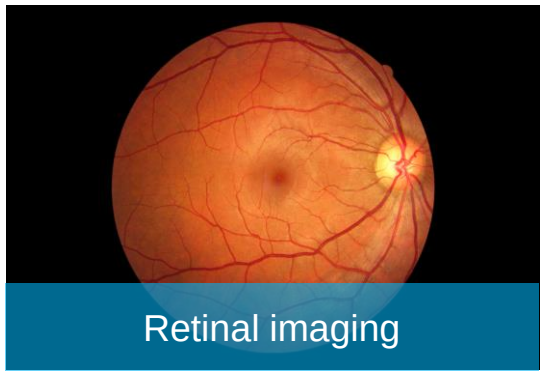

Bone density


Anthropometrics

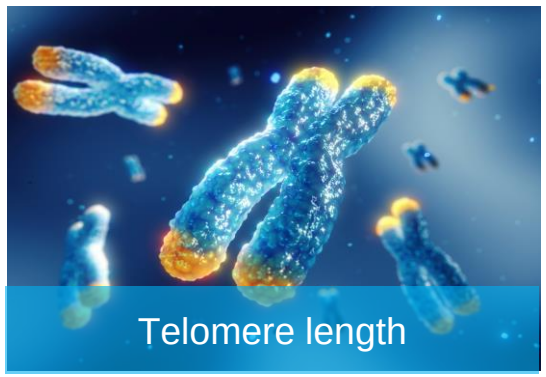
Questionnaire data

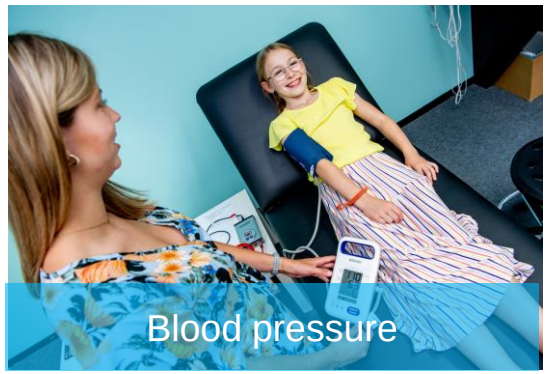

Physical activity


Ultrasound imaging


Retinal imaging


Blood sampling

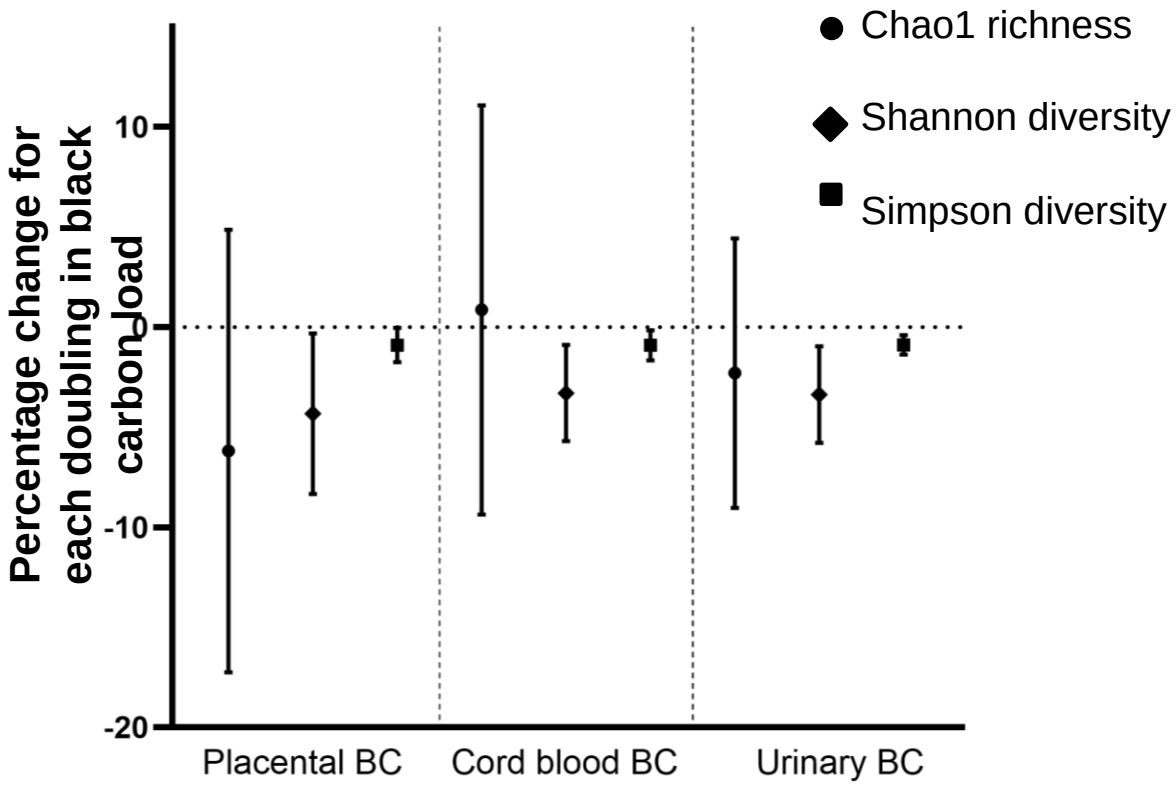

Telomere length

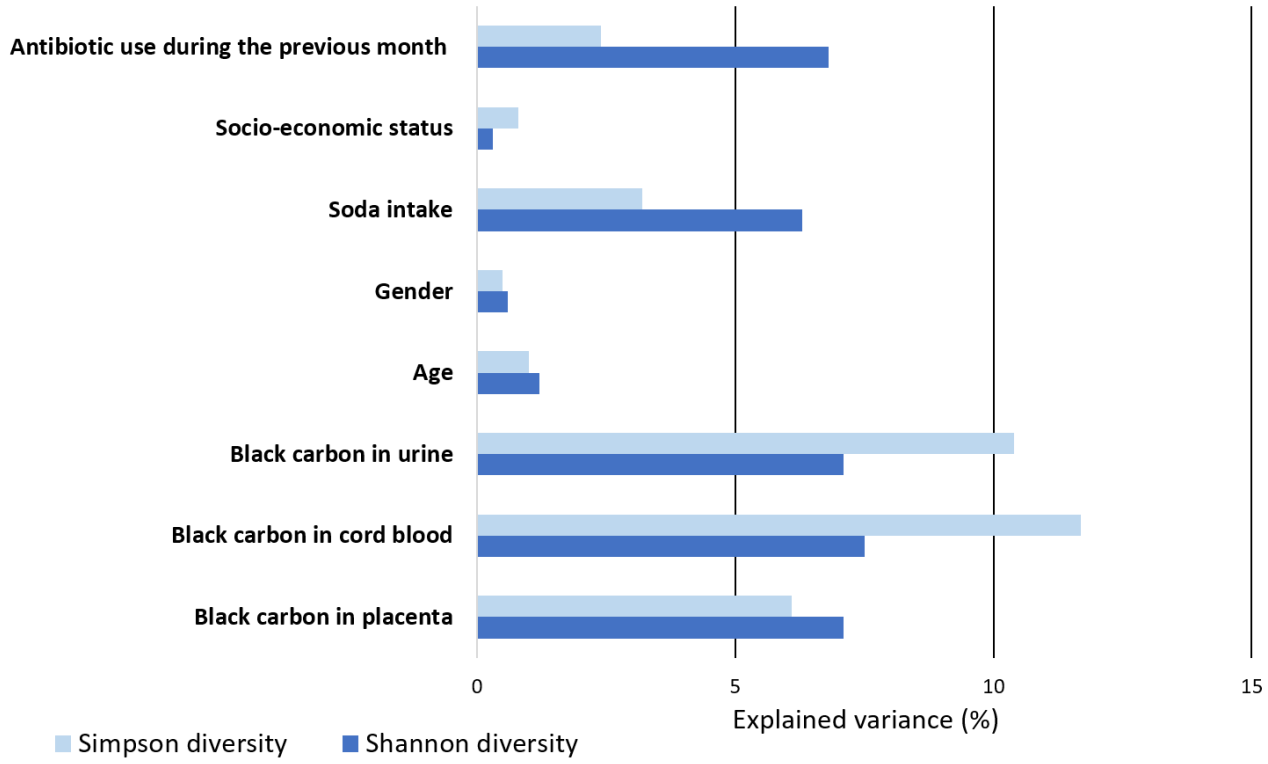

Blood pressure

Research

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP11257.

Accumulation of Black Carbon Particles in Placenta, Cord Blood, and Childhood Urine in Association with the Intestinal Microbiome Diversity and Composition in Four- to Six-Year-Old Children in the ENVIRONAGE Birth Cohort

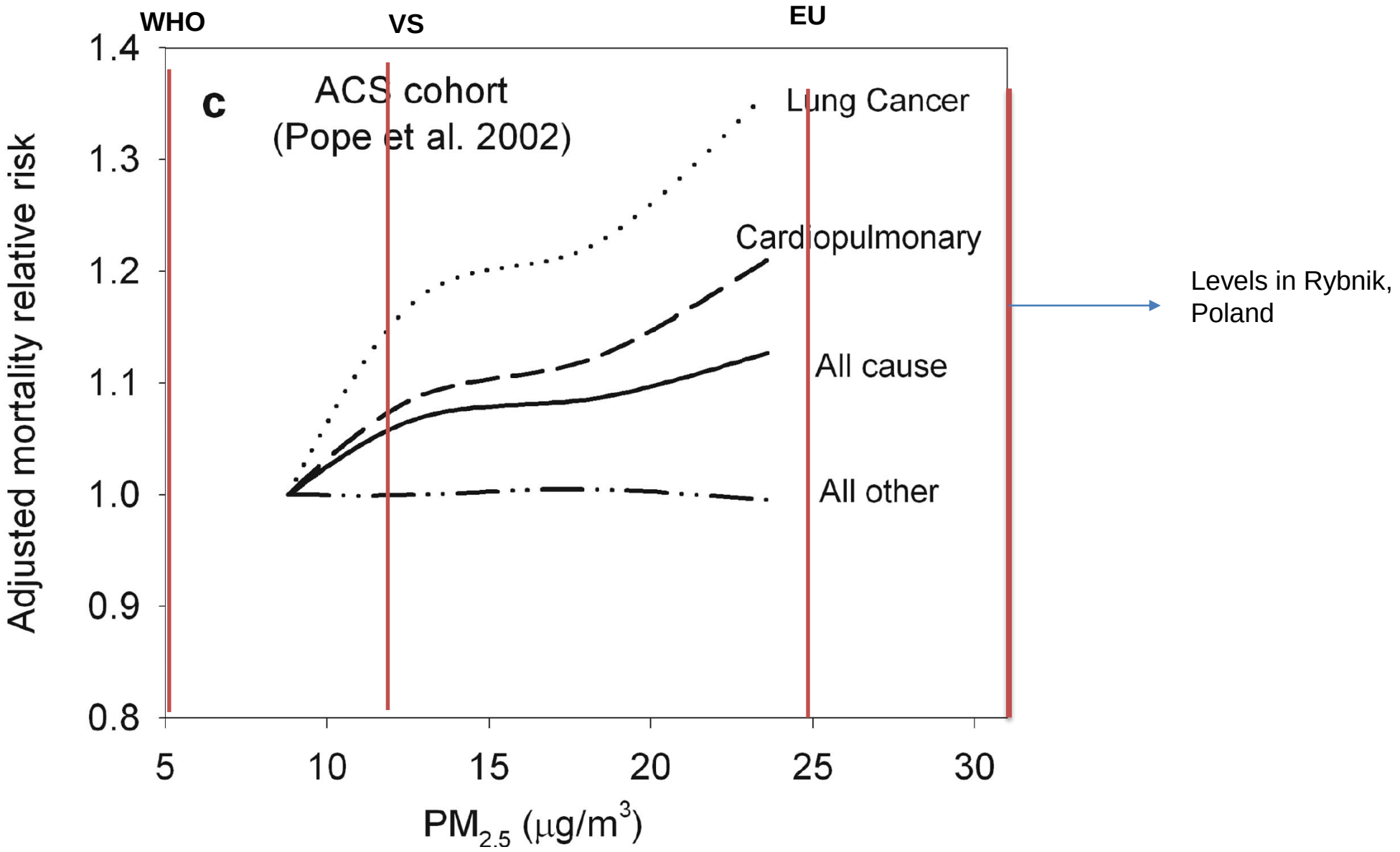




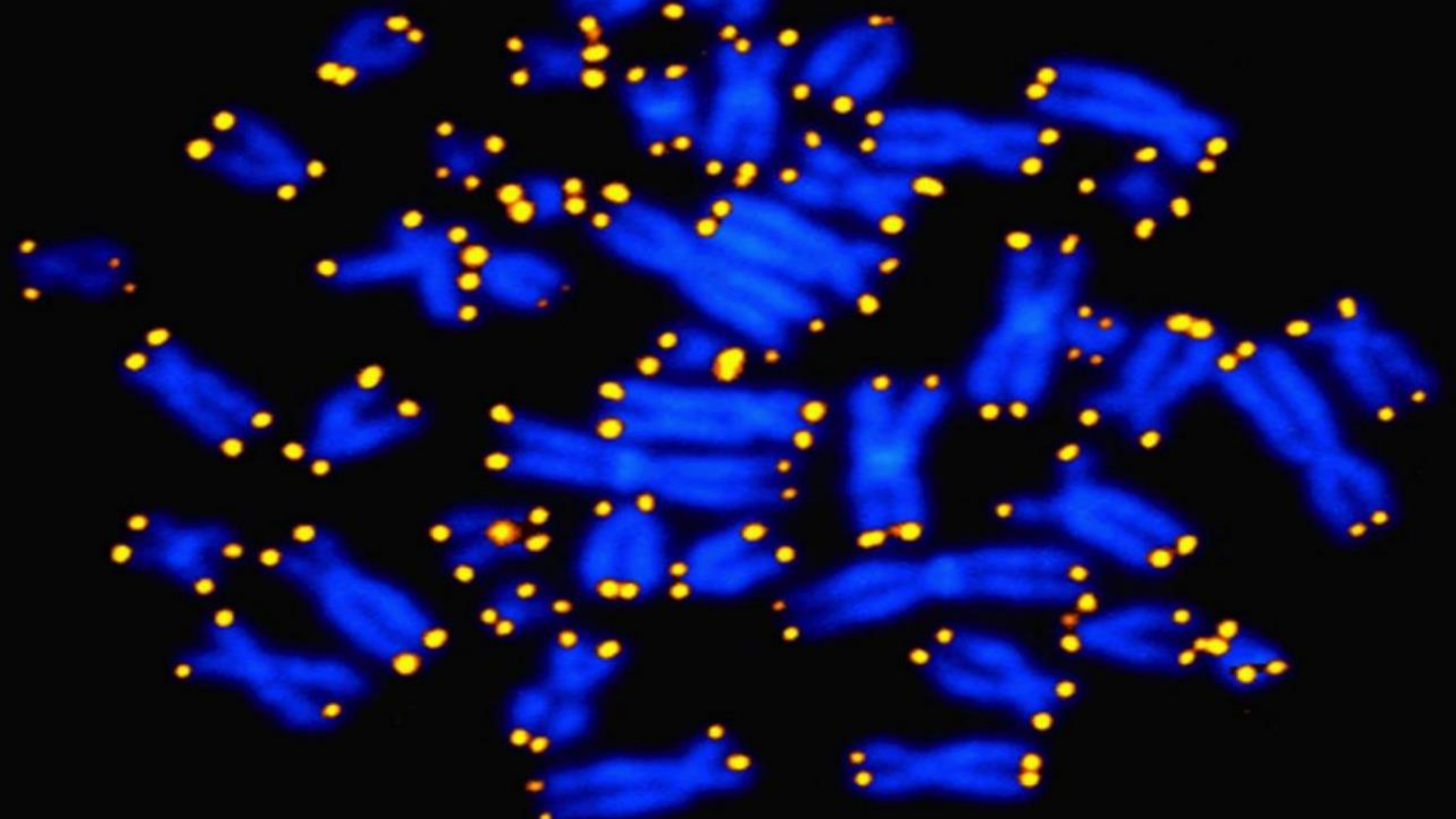
Adjusted for parity, season of delivery (winter, spring, summer, or autumn), sequencing batch (first or second), child's age (year), gender (boy or girl), weight (kg), length (cm), and maternal education (low, middle, or high)

Van Pee et al. EHP 2023

Dose response association and thresholds / guidelines



Pope *et al.* JAMA 2002



The Nobelprize in Medicine (2009)

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

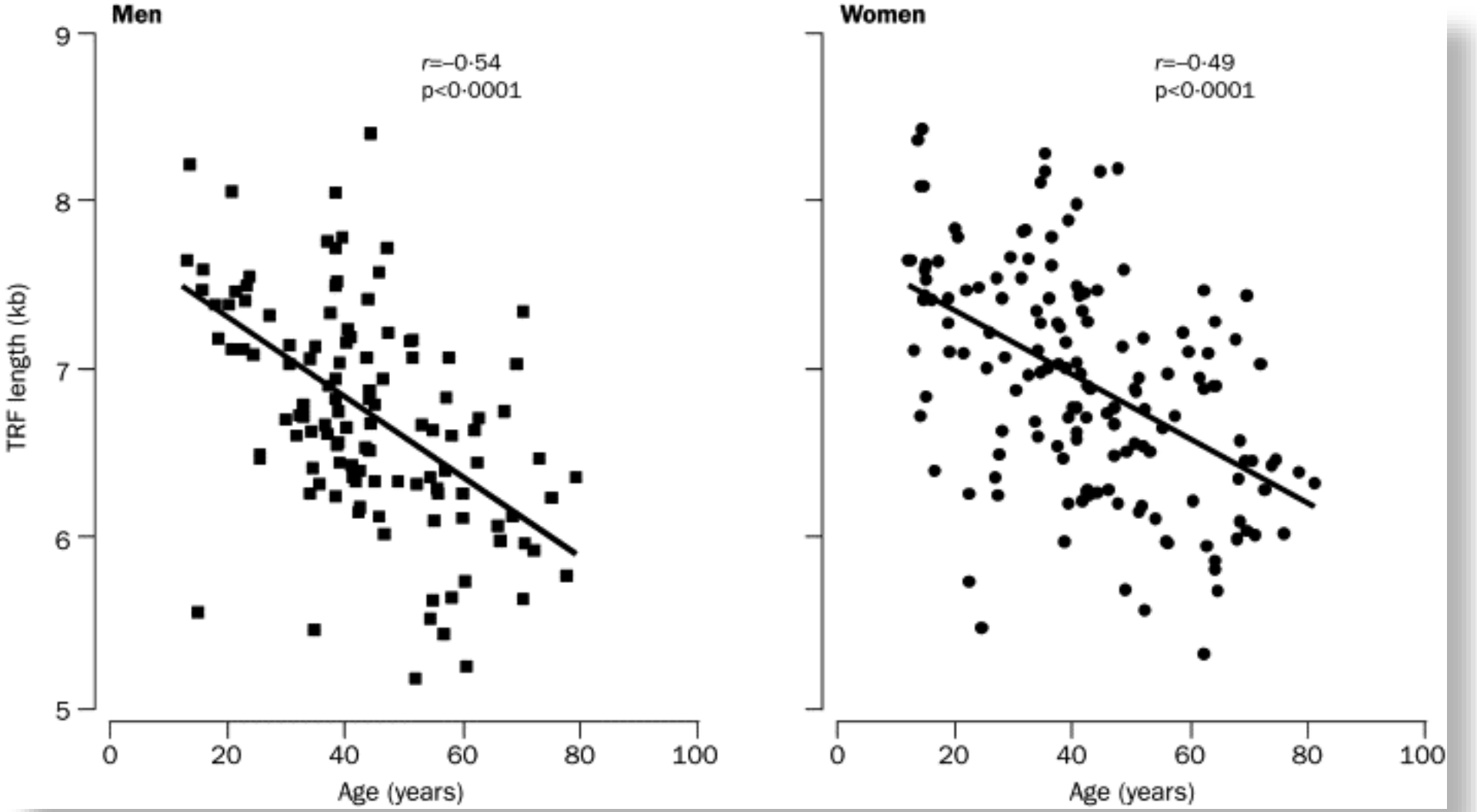
Elizabeth Blackburn

Jack Szostak

Carol Greider

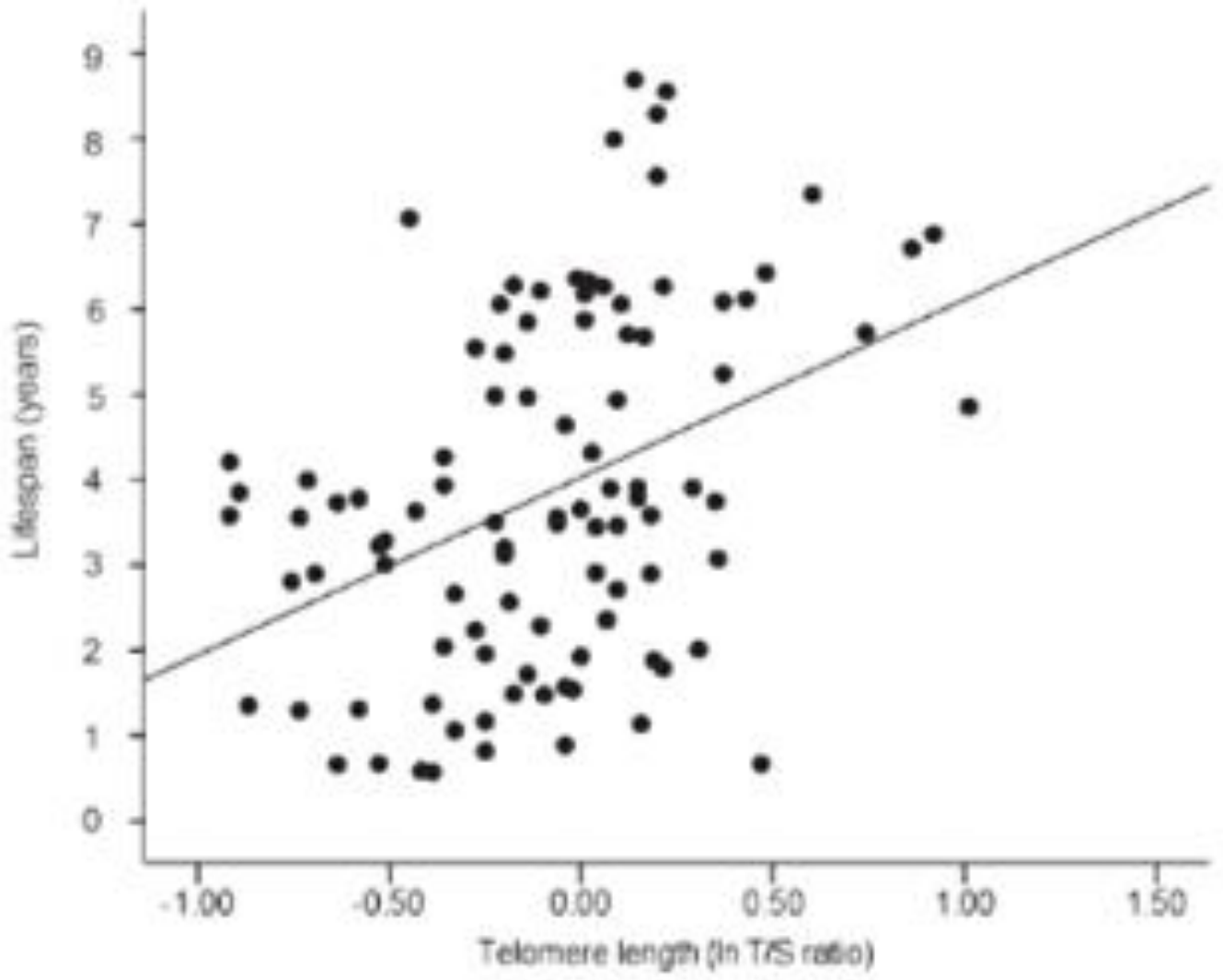
UHASSELT
KNOWLEDGE IN ACTION

Telomere length and ageing



Nawrot et al., Lancet, 2004

Telomere length early in life and life expectancy

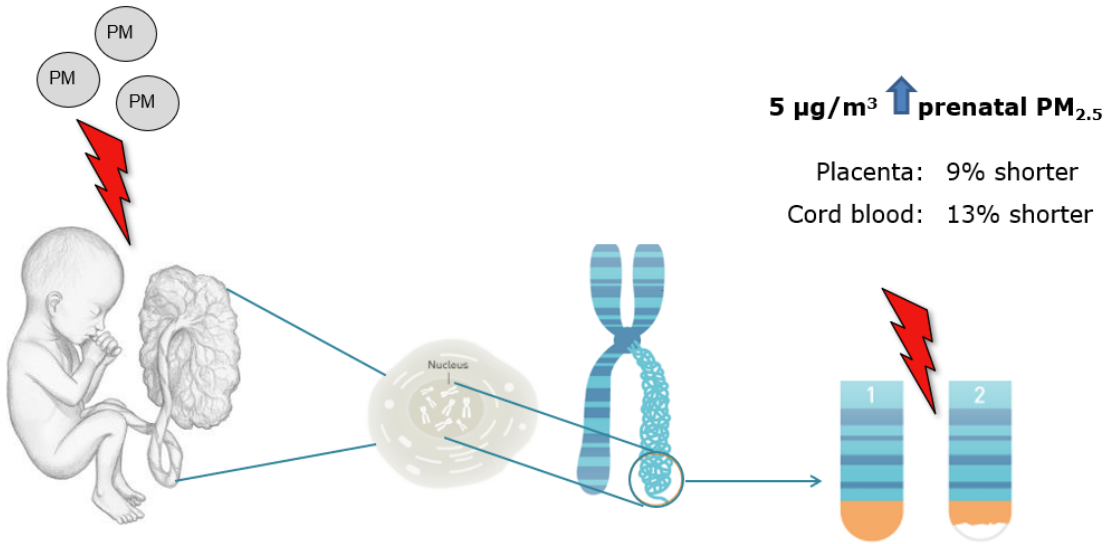


Heidinger B *et al.* PNAS 2012

JAMA Pediatrics | Original Investigation

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 Gasparrini, 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.

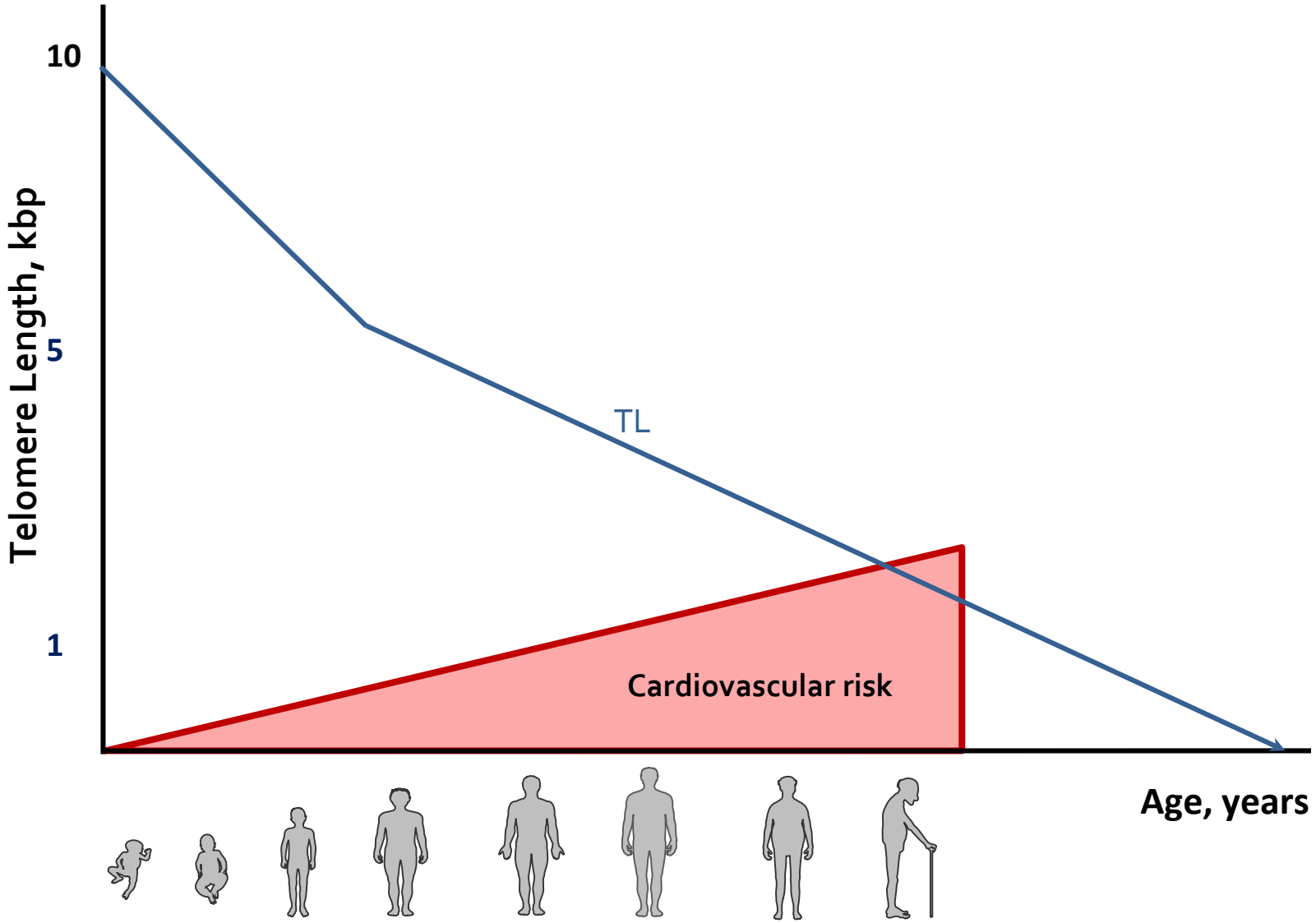
Key Points

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

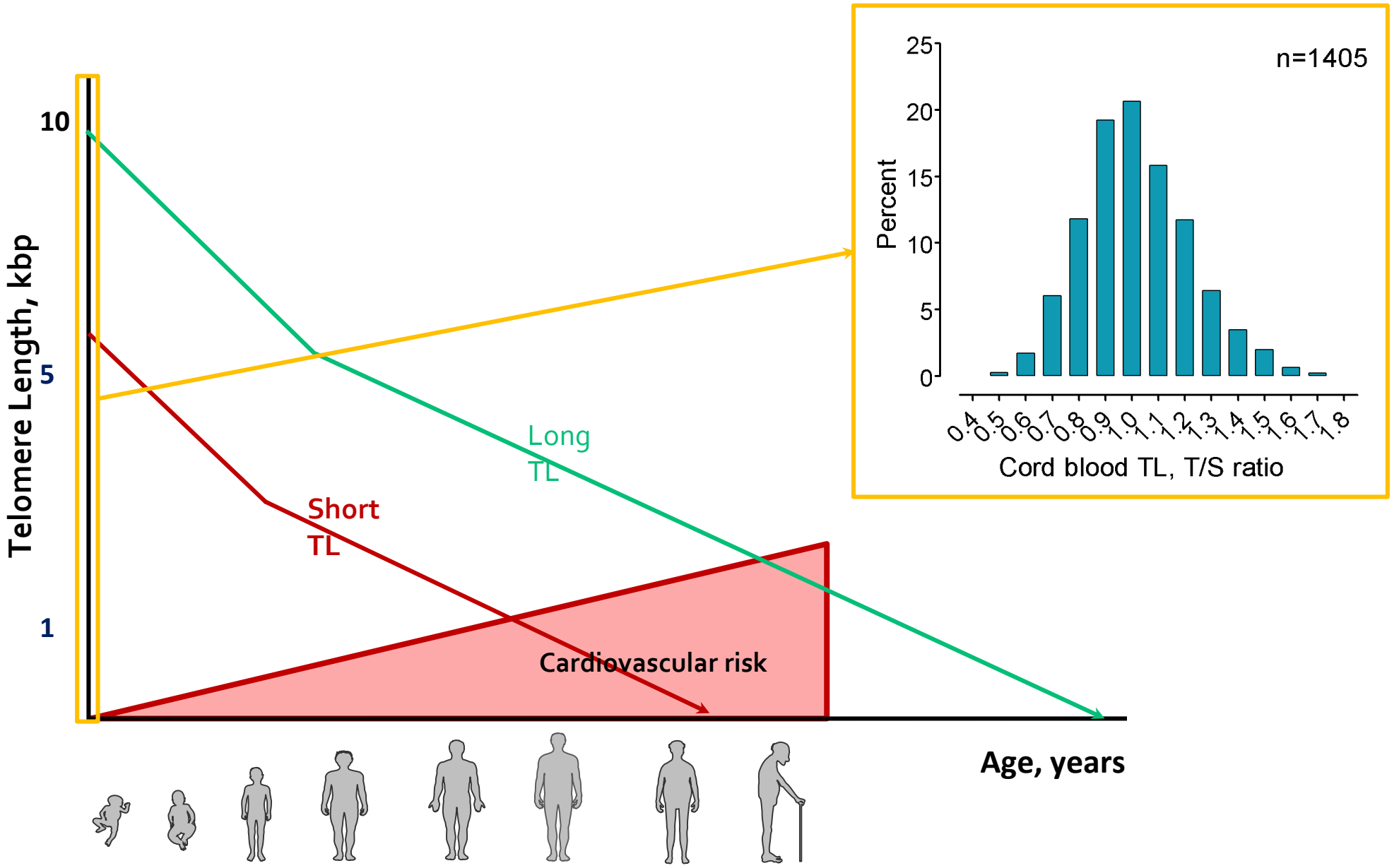
Findings In this birth cohort study of 641 mother-newborn pairs, mothers with higher residential exposure to $PM_{2.5}$ (particulate matter with an aerodynamic diameter ≤2.5 µm air pollution) gave birth to newborns with significantly lower telomere length that could not be explained by other factors including socioeconomic class. For a 5-µg/m^3 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.

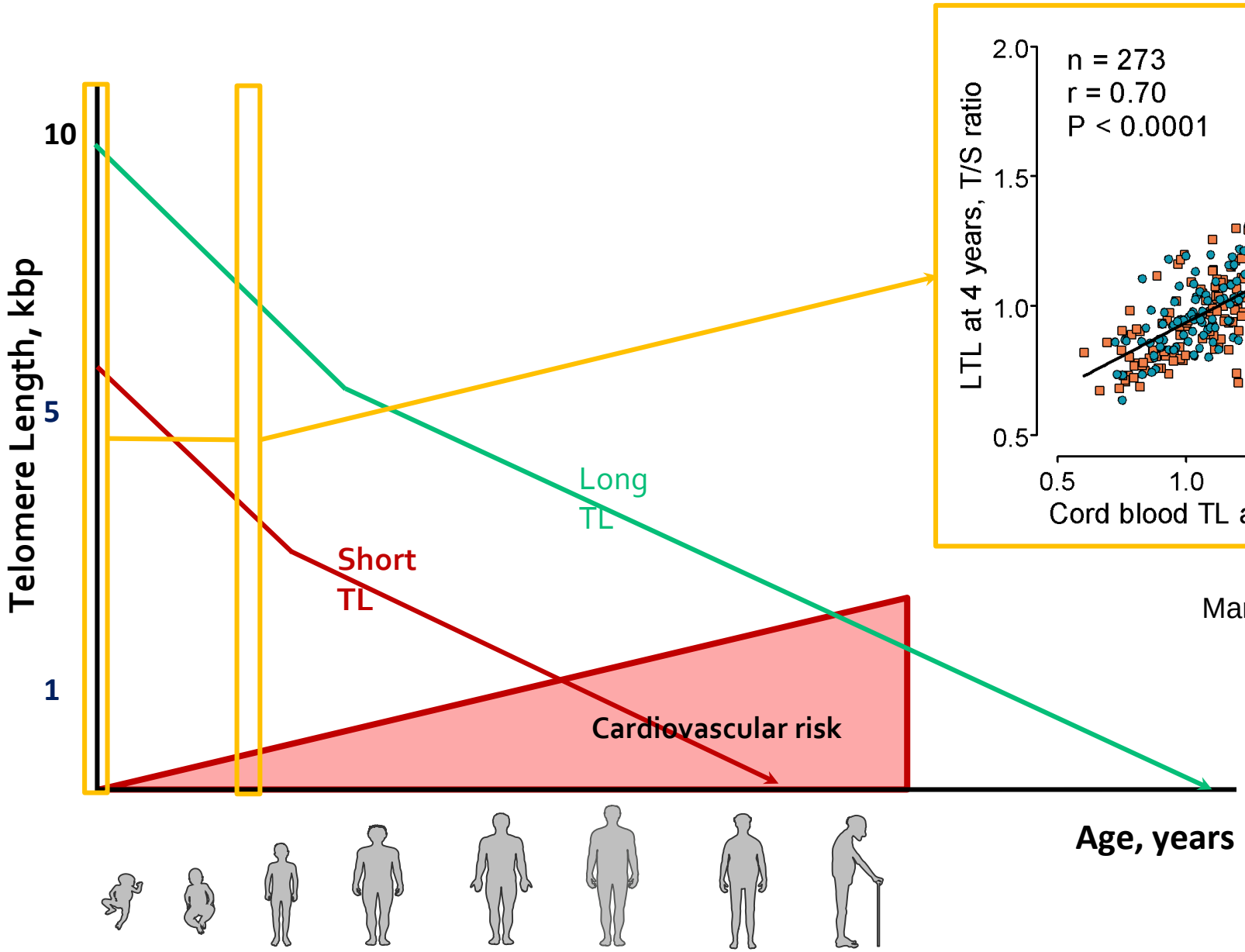
Telomere length at birth



Telomere length at birth



Telomere length at birth



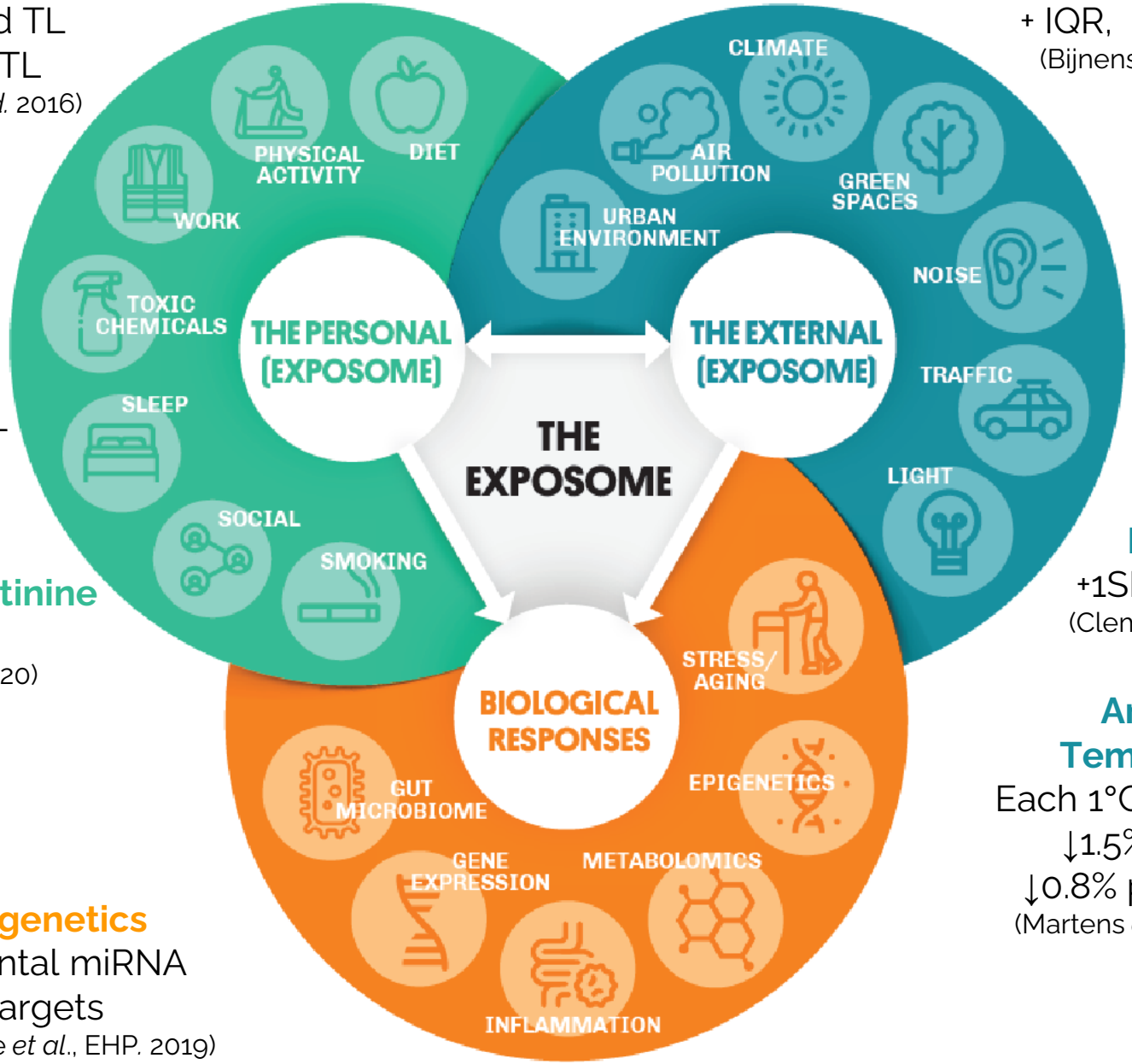
Martens *et al*. eBiomedicine *2022*

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
(Bijnens *et al.*, *Environ Int.* 2015)

Distance to major road
2-forld ↑, ↑ 5.3% placenta TL
(Bijnens *et al.*, *Environ Int.* 2015)

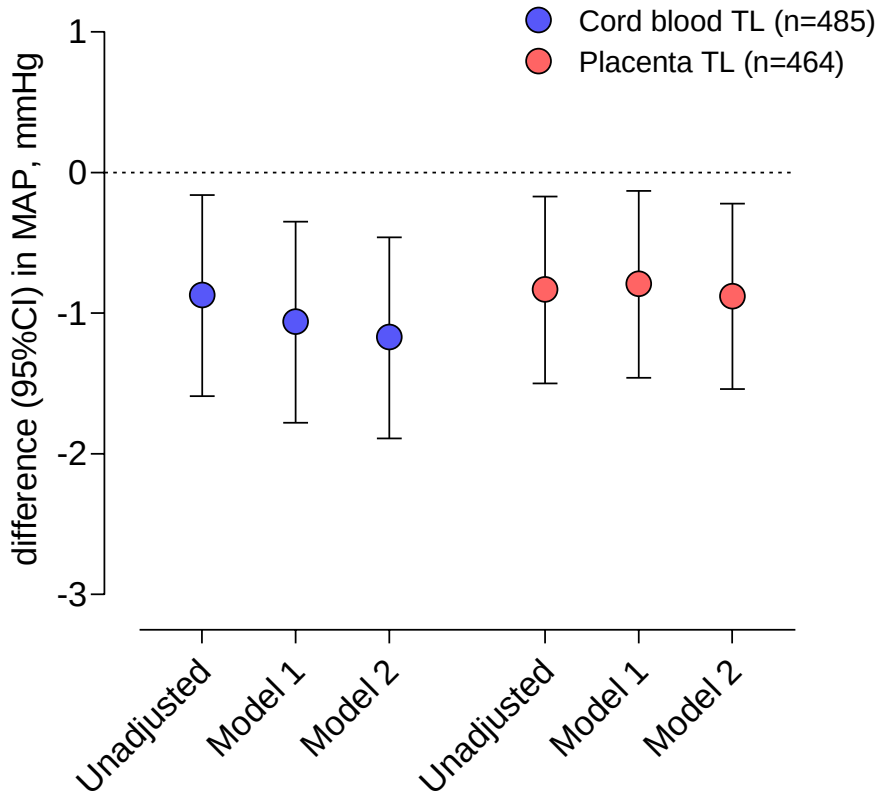
Prenatal $PM_{2.5}$
+ 5 μg/m^3; ↓8.8% cord TL
↓13.2% placenta TL
(Martens *et al.*, *JAMA Ped.* 2017)

Prenatal NO_2
+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)

Newborn TL and later-life cardiovascular health ?

Mean arterial bp (continuous)



High blood pressure (AAP2017)
Clinical relevance

AAP 2017 for Children 1-13 y	
Classification	**SBP/DBP Percentile**
Normal	<90th
Elevated BP	≥90th to <95th Or 120/80 mm Hg to <95th (whichever is lower)
Stage 1 hypertension	≥95th to <95th Plus 12 mm Hg or 130/80-139/89 mm Hg (whichever is lower)
Stage 2 hypertension	≥95th Plus 12 mm Hg or ≥140/90 mm Hg (whichever is lower)

Age-, sex-, height specific BP percentiles

Sharma *et al., JAMA Pediatrics,* 2018

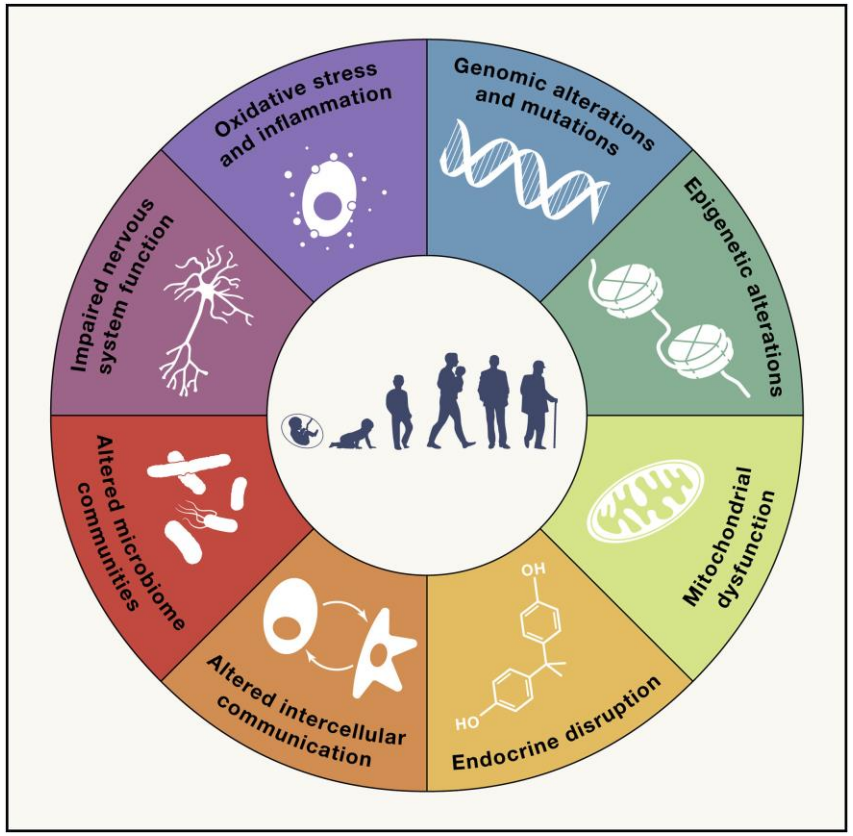
Model 1 adjusted for newborn sex, ethnicity, gestational age, birthweight, maternal age, maternal pre-pregnancy BMI, maternal education, maternal smoking during pregnancy and maternal gestational hypertension.
Model 2: Model 1 + child age, weight, height at follow-up and household smoke exposure

Questions I like to address

- Are particles translocating from mother to fetus at low ambient cocentrations?
- Does early life exposure to particles influence the molecular longevity potential?
- Can we protect the general population from molecular ageing by air pollution?
- Black carbon and disease progression in hospitalised COVID patients

Hallmarks of ageing *vs* hallmarks of environmental insults

Lopez-Otin et al. Cell 2013



Peters et al. Cell 2021

The urinary proteomic marker of ageing

1) Protein-wide analysis:

UPP data space
21,560 peptides; 4080 sequenced

↓

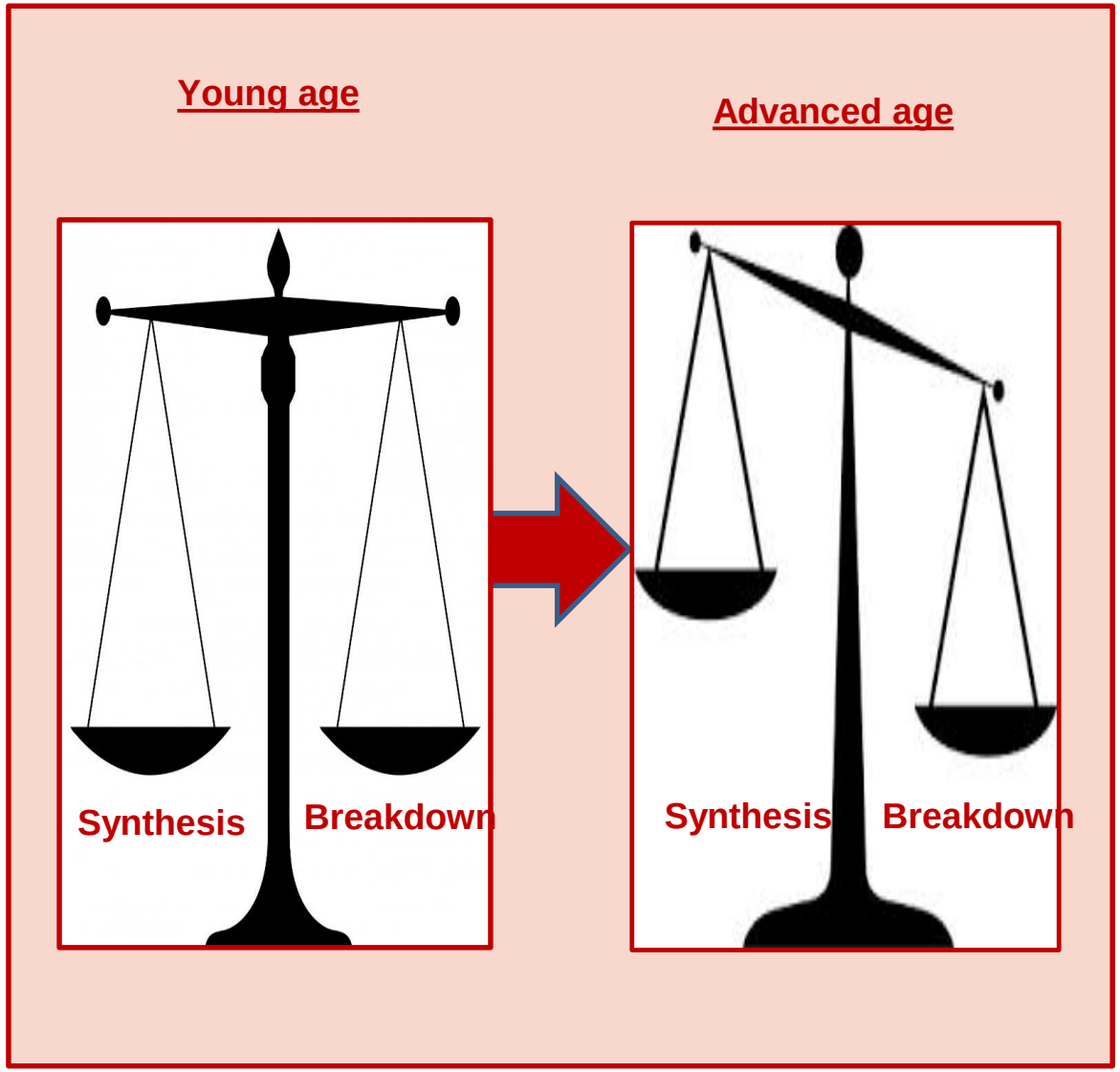
635 sequenced peptides (67 parental proteins)
with detectable signal in ≥70% of FLEMENGHO as start

↓

Derivation data (n=559)
210 age-associated peptides (39 parental proteins)*
FDR-significance
Pathway analysis

↓

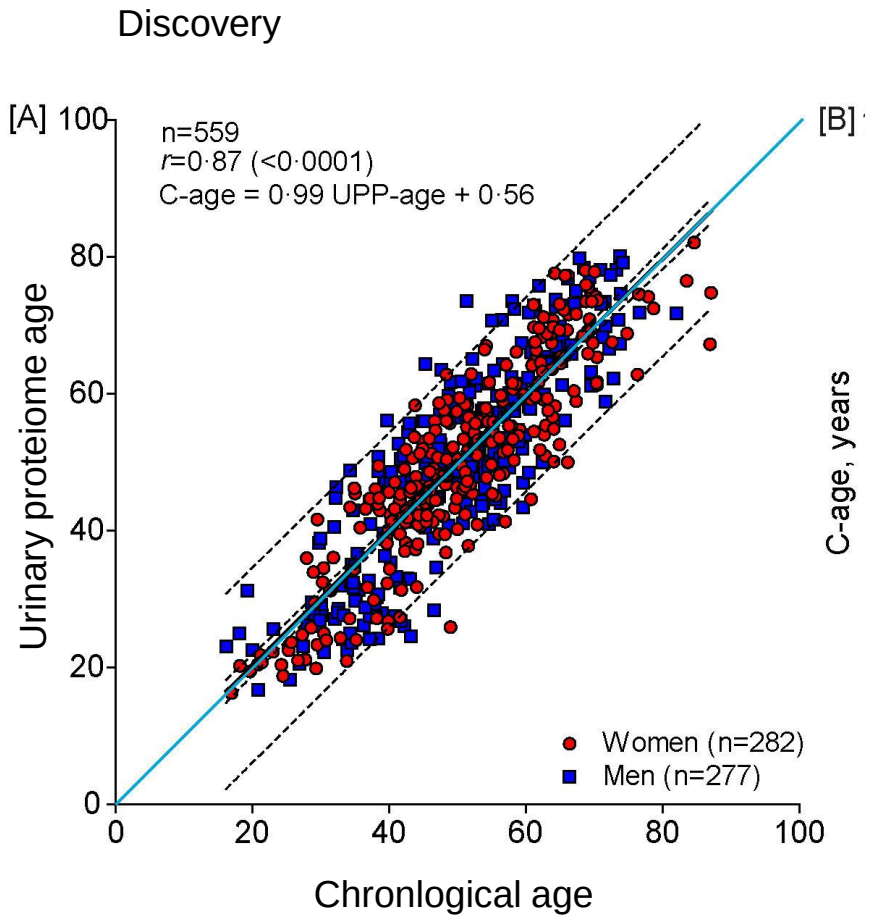
Time-shifted (n=559) and synchronous (n=219) validation
85% of (33/39) proteins confirmed
➔ COLLAGEN BREAKDOWN WITH AGE

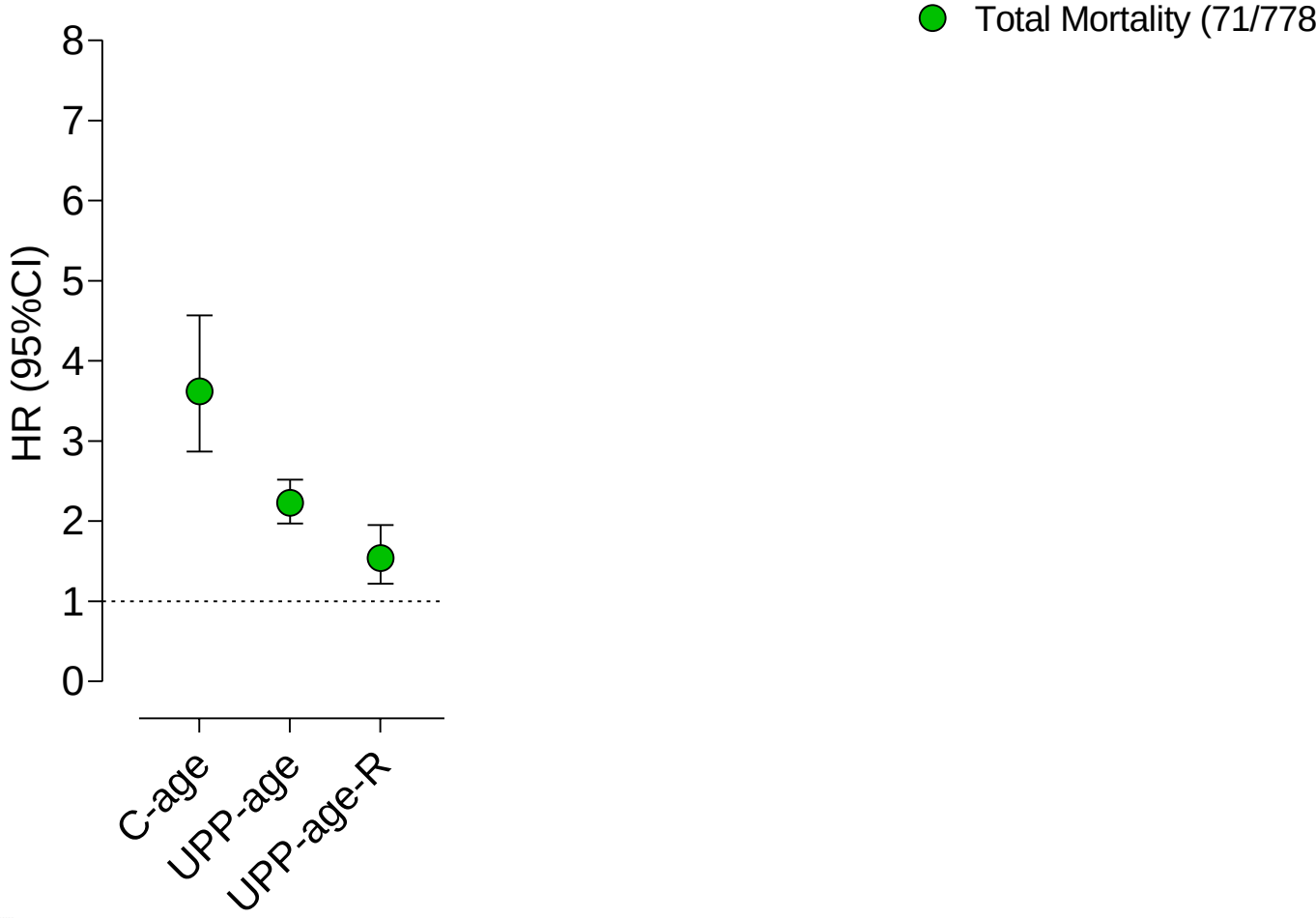


Martens et al. Lancet longevity 2021

Analyses adjusted for sex, MAP, BMI, plasma glucose, γ-glutamyltransferase, smoking, total-to-HDL ratio, and eGFR

The urinary proteomic marker of ageing

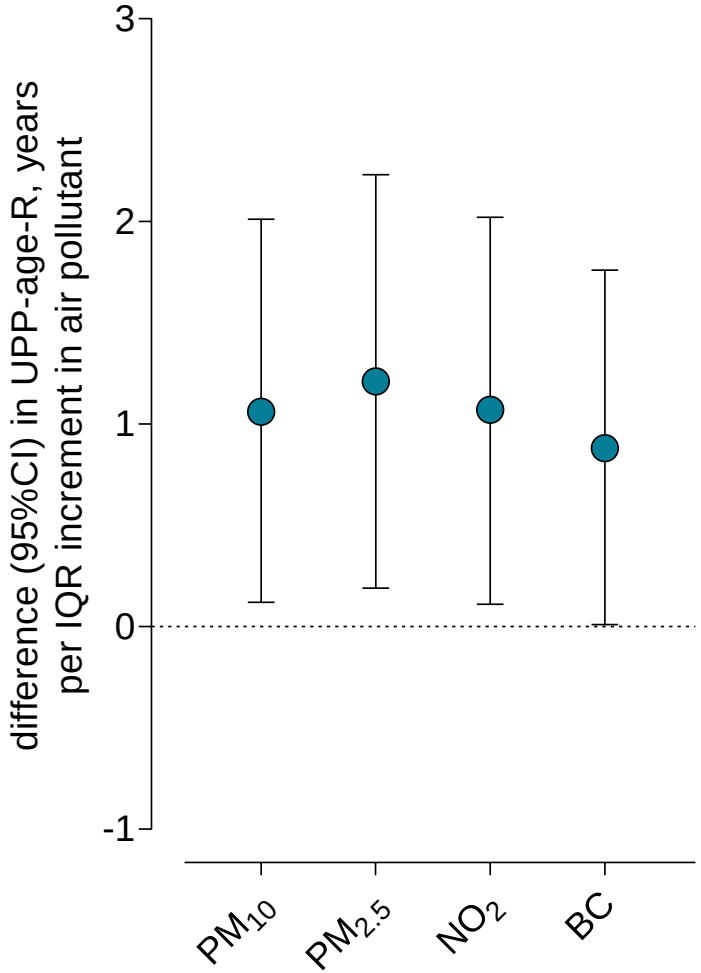




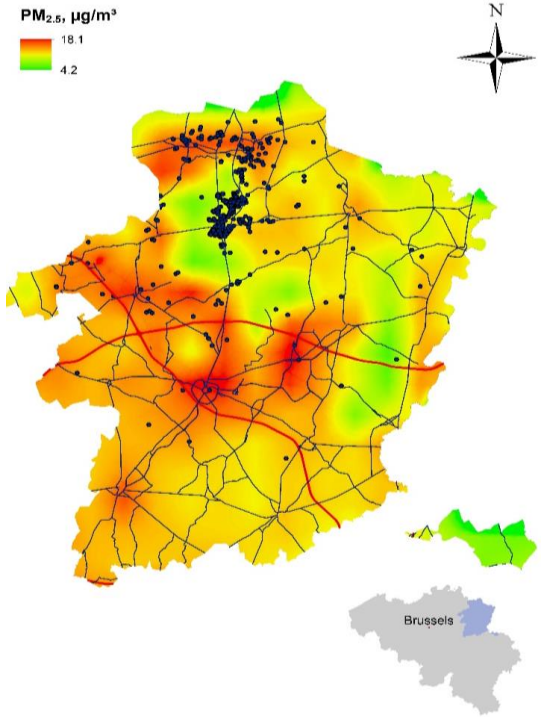
Martens et al. Lancet longevity 2021

The urinary proteomic marker of ageing

Proteomics clock: association with ambient air pollution exposure



~ 0.8 to 1.2 years higher



	Mean with (IQR)
PM_{10}, µg/m³	17.9 (3.9)
$PM_{2.5}$, µg/m³	12.9 (1.6)
NO_2, µg/m³	17.2 (5.2)
BC, µg/m³	0.74 (0.31)

Adjusted for age, sex, MAP, BMI, plasma glucose, γ-glutamyltransferase, smoking, total-to-HDL ratio, eGFR, socio-economic status

Proteomics clock: association with ambient air pollution exposure

- ➔ **Vitamin K** is essential for

  1) **Blood coagulation** (GLA proteins) → Bleeding (Vitamin K deficiency)

  2) **Bone mineralisation** (regulation of osteocalcin)→ Osteoporosis (Vitamin K deficiency)

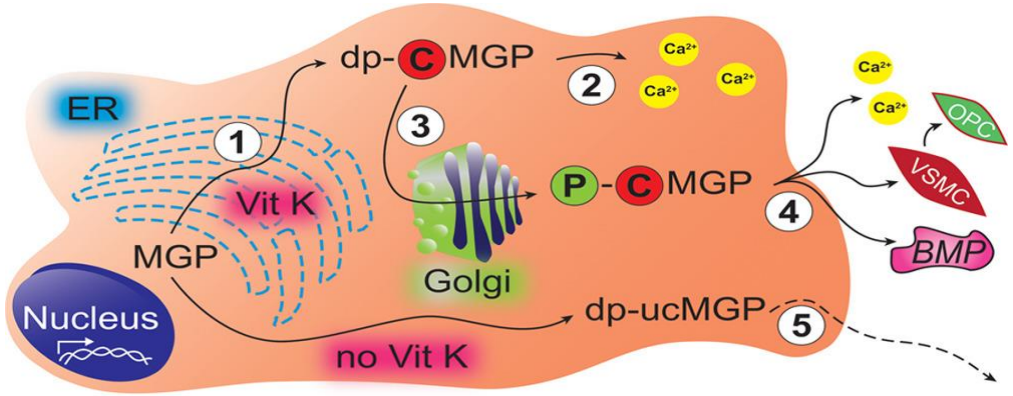
  3) Regulating **vascular stiffness and vascular calcification** → Increase CV (Vitamin K deficiency)

- Strong interaction with vitamin K status (more sensitive with poor vitamin K status)

- How do we measure this?

  Vitamin K is co-enzyme in conversion:

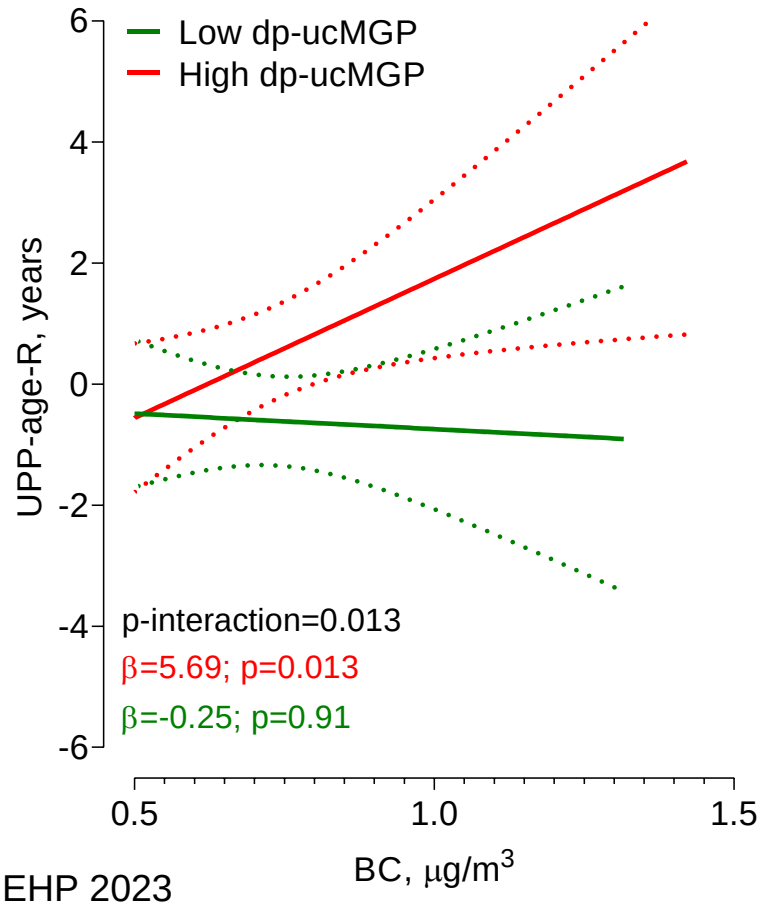
  dp-ucMGP to dp-cMGP ➔High dp-ucMGP reflects poor vitamin K status

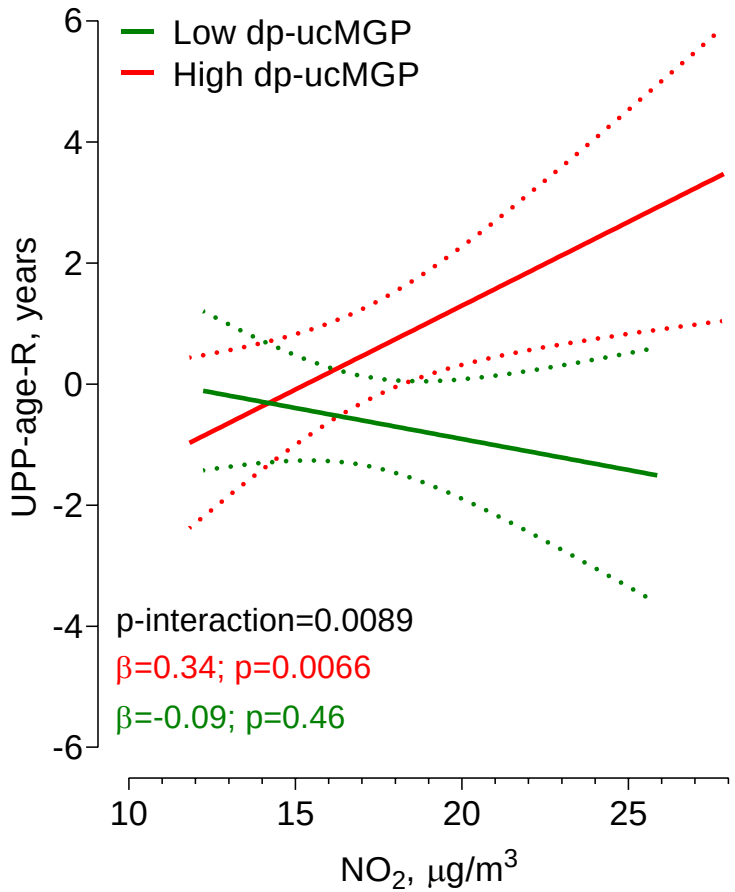


The urinary proteomic marker of ageing

Proteomics clock: association with ambient air pollution exposure

- Strong interaction with vitamin K status



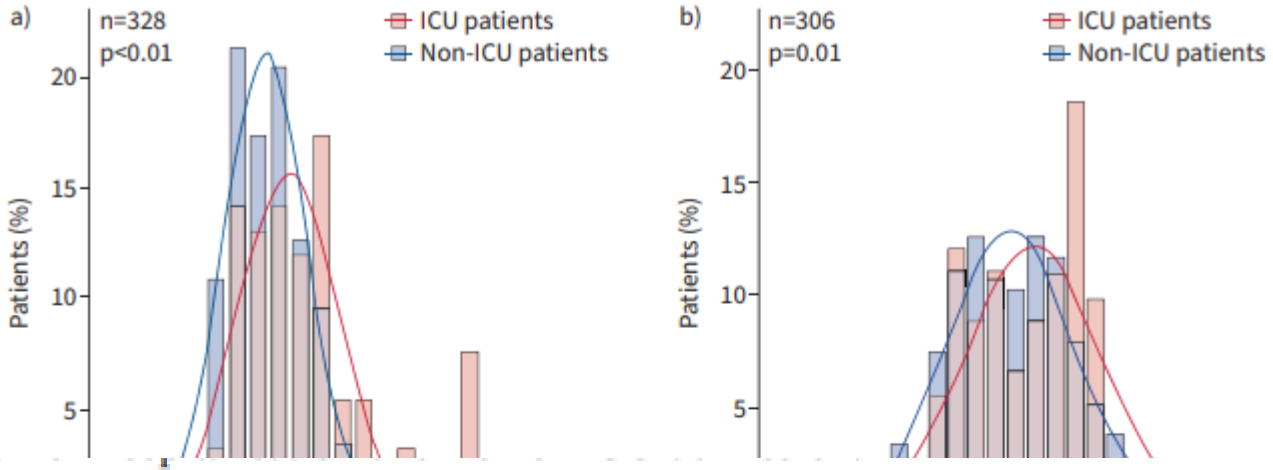


Martens et al. EHP 2023

Low= below median; high=above median

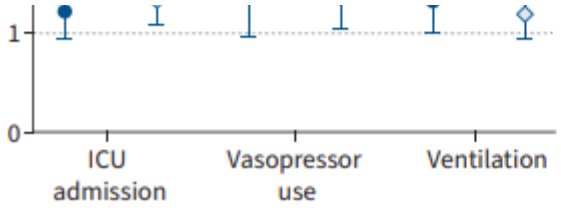
Adjusted for age, sex, MAP, BMI, plasma glucose, γ-glutamyltransferase, smoking, total-to-HDL ratio, eGFR, socio-economic status
Effects per IQR increment in air pollutant

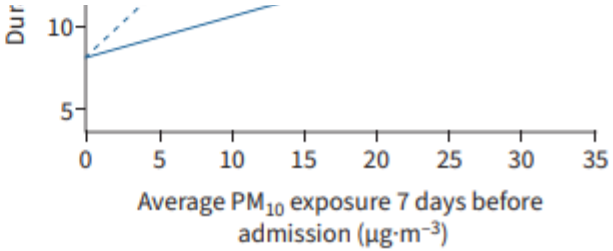
Pre-admission ambient air pollution predict hospitalisation outcomes in



Results Independent of potential confounders, an interquartile range (IQR) increase in exposure in the week before admission was associated with increased duration of hospitalisation ($PM_{2.5}$ +4.13 (95% CI 0.74–7.53) days, PM_{10} +4.04 (95% CI 1.24–6.83) days and NO_2 +4.54 (95% CI 1.53–7.54) days); similar effects were observed for long-term NO_2 and BC exposure on hospitalisation duration. These effect sizes for an IQR increase in air pollution on hospitalisation duration were equivalent to the effect of a 10-year increase in age on hospitalisation duration. Furthermore, for an IQR higher blood BC load, the OR for ICU admission was 1.33 (95% CI 1.07–1.65).

Conclusions In hospitalised COVID-19 patients, higher pre-admission ambient air pollution and blood BC levels predicted adverse outcomes. Our findings imply that air pollution exposure influences COVID-19 severity and therefore the burden on medical care systems during the COVID-19 pandemic.





Black carbon particles translocate to fetal organs even at low concentration
Healthy air is an important determinant of “molecular longevity”
Vitamin K2 might lower impact of air pollution on premature ageing
BC exposure influence COVID-19 severity in hospitalised patients
EU air quality improved during the last decade but further lowering will further improve public health

Acknowledgment

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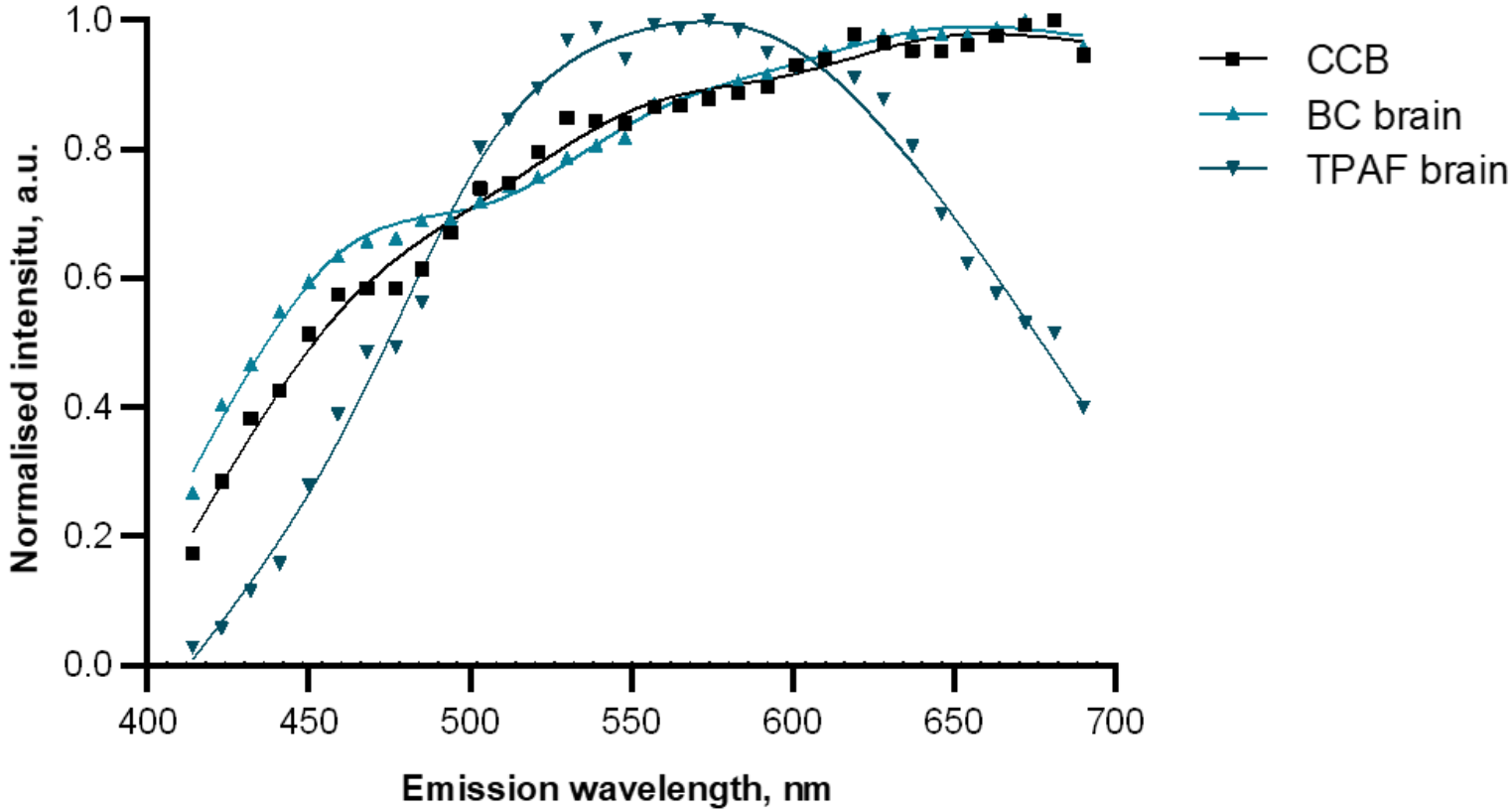
European Research Council
Established by the European Commission

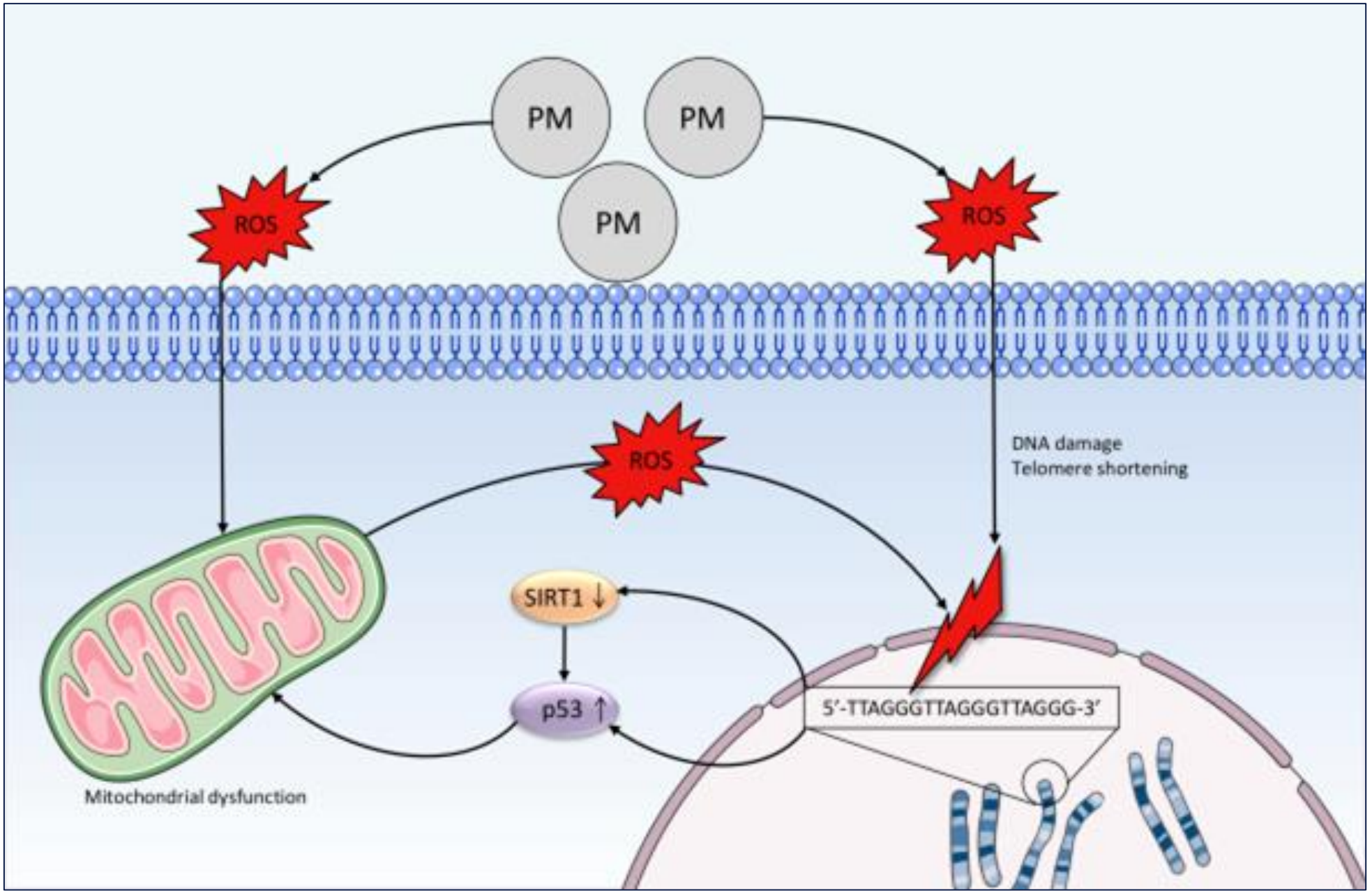
Bloomberg

Research Foundation Flanders
Opening new horizons

Kom op tegen Kanker



BC = black carbon, CCB = conductive carbon black, and TPAF = background signals



Martens & Nawrot, *Curr Environ Health Rep*, 2016

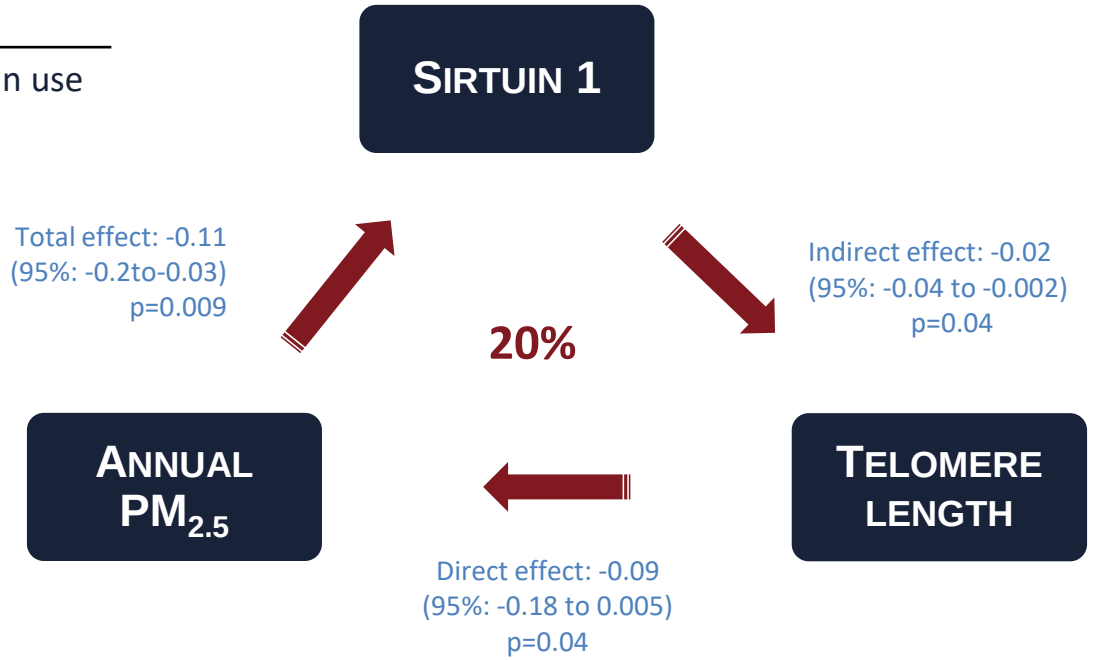
Air pollution and molecular core axis of ageing

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



Pieters N, *et al., Environ Health Perspect,* 2016

The urinary proteomic marker of ageing

Proteomics clock: association with ambient air pollution exposure

- What are the ageing effects in adjusted analyses?

	UPP-age-R		
Exposure	**Estimate (years)**	**p value**	**P-interaction**
PM_{10}			
Low dp-ucMGP	-0.08	0.90	0.0032
High dp-ucMGP	1.99	0.0075	
$PM_{2.5}$			
Low dp-ucMGP	-0.06	0.93	0.0075
High dp-ucMGP	2.18	0.0058	
BC			
Low dp-ucMGP	-0.06	0.93	0.012
High dp-ucMGP	1.95	0.0088	
NO_2			
Low dp-ucMGP	-0.47	0.46	0.0074
High dp-ucMGP	2.06	0.0028	

Adjusted for age, sex, MAP, BMI, plasma glucose, γ-glutamyltransferase, smoking, total-to-HDL ratio, eGFR, socio-economic status
Effects per IQR increment in air pollutant