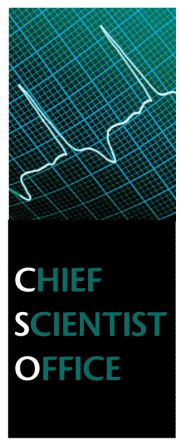


Maternal exposure to air pollution nanoparticles and adverse birth outcomes



Female Reproductive toxicity of EDCs: a human evidence-based screening and Identification Approach



Paul A. Fowler

Institute of Medical Sciences

Partnership for the Assessment of Risks from Chemicals



Horizon Europe - started Jan 2023
"Inflammation in human early life: targeting impacts on life-course health" (INITIALISE)

Air Pollution

- One or more chemicals or substances in high enough concentrations in the air to harm humans, other animals, vegetation, or materials. Such chemicals or physical conditions (such as excess heat or noise) are called air pollutants
- Ozone, CO, lead, sulphur & nitrogen dioxides etc, particulate matter

PM air pollution

- Mixture of solid and liquid droplets suspended in the air
- Complex mixture: acids (eg sulphuric acid), inorganic compounds (eg ammonium sulphate, ammonium nitrate, and sodium chloride), organic chemicals, soot, metals, soil or dust particles, and biological materials (eg pollen and mould spores)

Micro- and nano- particles

- Plastics
- **Black carbon** – product of incomplete combustion

Multiple adverse consequences for exposed children and adults

- **Include respiratory, pulmonary, immune function deficits**

Barcelona

Achieving WHO air quality interim targets for PM_{2.5} + NO₂ = **avoid 410 deaths** and **save €281 million annually**

Estimating ambient air pollution mortality and disease burden and its economic cost in Barcelona. Font-Ribera et al Environ Res. 2023 Jan 1;216(Pt 1):114485. doi: 10.1016/j.envres.2022.114485.

Pea Soupers



Pea Souper

Great Smog
December
1952
5 days
12,000
deaths



Wave of air quality
regulation and
enforcement

Piccadilly Circus,
Great Smog of
London

5 days exposure in-utero
= 8% ↑ childhood asthma

9 million globally

by "modern" pollution ↑ 66% in last 20 years

"chemical pollution"

"air pollution"

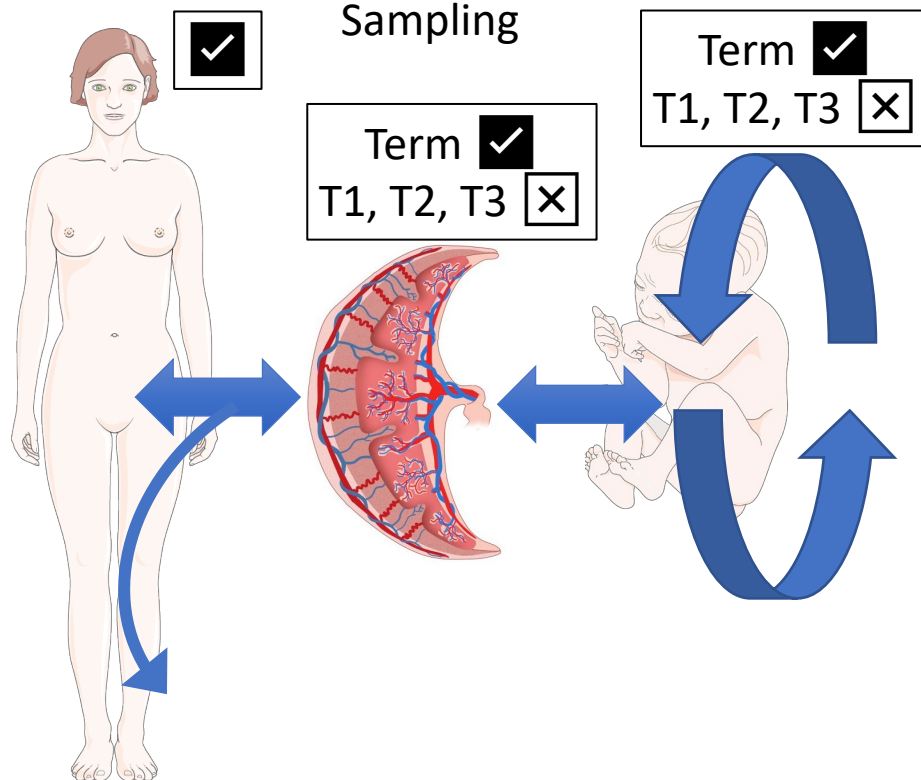
World Health Organisation

9 /10 people are breathing polluted air



HOW do adverse environmental factors affect human in-utero development?

- "Normal" development in our own species
- Three-way communication & exchange underpinning successful pregnancy in all 3 trimesters



- Differences between T1, T2, T3 and term placenta
- Sex differences
 - sensitivity to exposures
 - development

The PRACTICAL problems include:

- Ethics – limited experimental opportunities
- How to link PRENATAL studies with POSTNATAL studies
- Numerous confounding factors
- Statistical power & Reproducibility

Sex differences in early and term placenta are conserved in adult tissues. Olney et al. Biol Sex Differ. 2022 Dec 22;13(1):74. doi: 10.1186/s13293-022-00470-y.

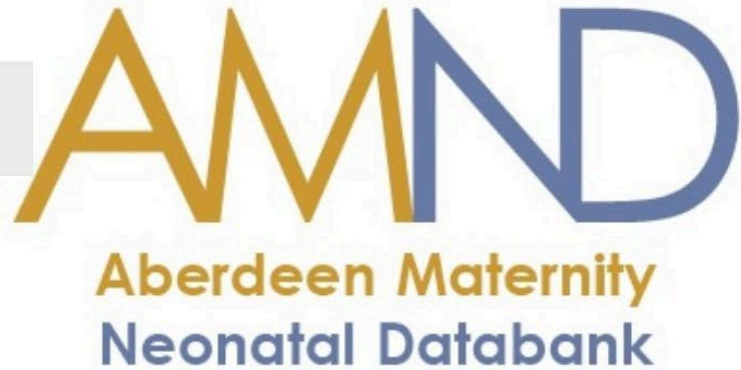
Fetal studies

Open access

Original research

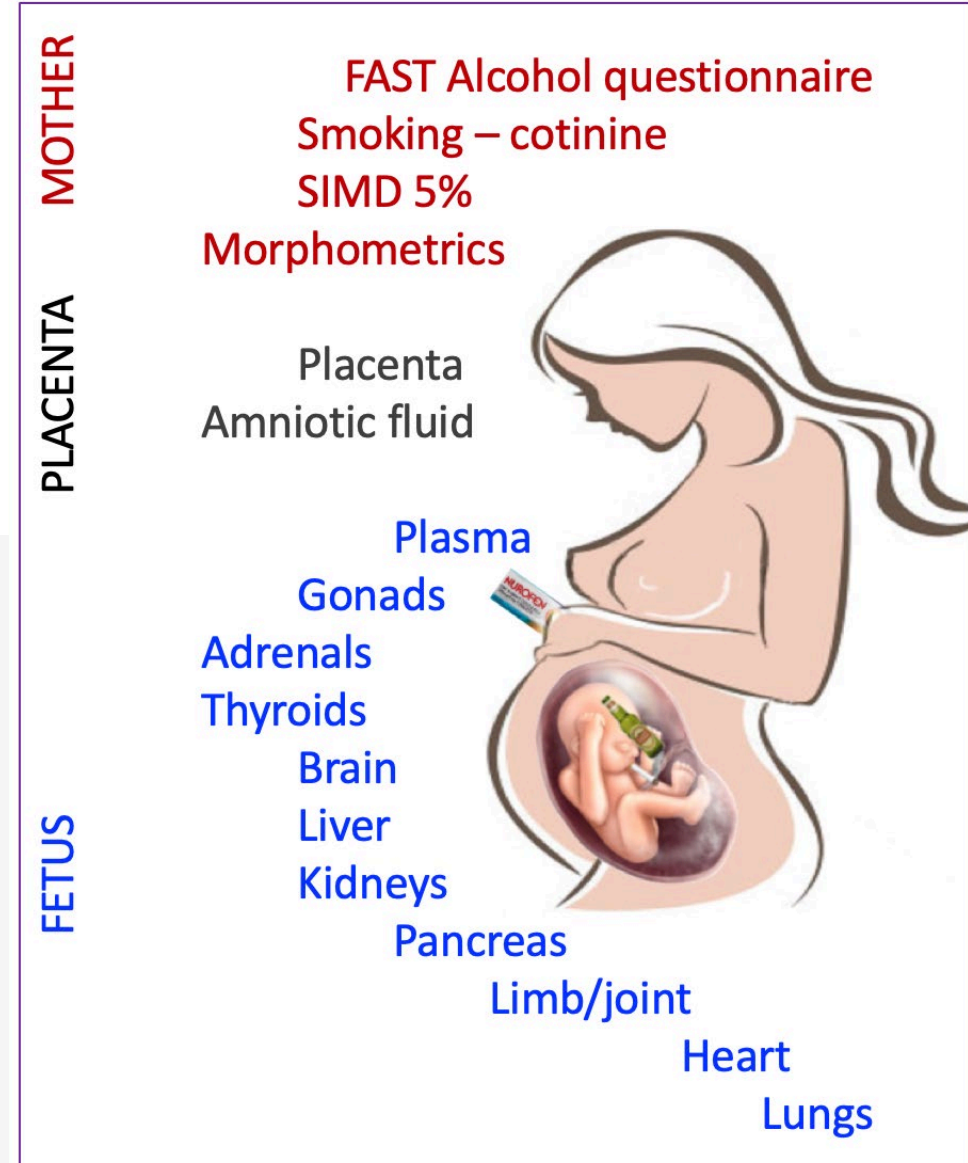
BMJ Open Maternal over-the-counter analgesics use during pregnancy and adverse perinatal outcomes: cohort study of 151 141 singleton pregnancies

Aikaterini Zafeiri ¹, Edwin Amalraj Raja, ² Rod Thomas Mitchell, ³ David C Hay, ⁴ Sohinee Bhattacharya ⁵, Paul A Fowler ¹



This unique database

holds data for all Aberdeen City births from 1949 to the present day, making the AMND a valuable resource for research



Fetal studies

Normal development
Maternal lifestyle
Environment

- **Cigarette smoke (common chemicals with air pollution)**
- Obesity/overweight
- Chemical exposures
- Endocrine disruption

J Clin Endocrinol Metab, February 2008, 93(2):619–626 jcem.endojournals.org ORIGINAL ARTICLE
Endocrine Research

Maternal Smoking during Pregnancy Specifically Reduces Human Fetal Desert Hedgehog Gene Expression during Testis Development

Paul A. Fowler, Sarah Cassie, Stewart M. Rhind, Mark J. Brewer, J. Martin Collinson, Richard G. Lea, Paul J. Baker, Siladitya Bhattacharya, and Peter J. O'Shaughnessy

Filis et al. BMC Medicine (2018) 16:194
https://doi.org/10.1186/s12916-018-1183-7 BMC Medicine

RESEARCH ARTICLE Open Access

Maternal smoking and high BMI disrupt thyroid gland development

Panagiotis Filis^{1*}, Sabine Hombach-Klonisch³, Pierre Ayotte⁴, Nalin Nagrath¹, Ugo Soffientini², Thomas Klonisch³, Peter O'Shaughnessy² and Paul A. Fowler¹

ORIGINAL ARTICLE
Endocrine Research

Maternal Smoking and Fetal Sex Significantly Affect Metabolic Enzyme Expression in the Human Fetal Liver

Peter J. O'Shaughnessy, Ana Monteiro, Siladitya Bhattacharya, and Paul A. Fowler

Conclusions: The human fetal liver expresses a wide array of metabolic enzymes, with sex differences apparent in 44% of the transcripts measured. Exposure of the fetus to pollutants/toxicants is associated with significantly altered transcript expression, with the more marked response in the male potentially affecting levels of endogenous factors involved in fetal growth. (*J Clin Endocrinol Metab* 96: 2851–2860, 2011)

PLOS BIOLOGY

Alternative (backdoor) androgen production and masculinization in the human fetus

Peter J. O'Shaughnessy¹, Jean Philippe Antignac², Bruno Le Bizec², Marie-Line Morvan², Konstantin Svechnikov³, Olle Söder³, Iuliia Savchuk³, Ana Monteiro¹, Ugo Soffientini¹, Zoe C. Johnston¹, Michelle Bellingham^{1*}, Denise Hough¹, Natasha Walker⁴, Panagiotis Filis⁴, Paul A. Fowler^{1,4*}

Johnston et al. BMC Medicine (2018) 16:23
DOI 10.1186/s12916-018-1009-7 BMC Medicine

RESEARCH ARTICLE Open Access

The human fetal adrenal produces cortisol but no detectable aldosterone throughout the second trimester

Zoe C. Johnston¹, Michelle Bellingham¹, Panagiotis Filis², Ugo Soffientini¹, Denise Hough¹, Siladitya Bhattacharya³, Marc Simard⁴, Geoffrey L. Hammond⁴, Peter King⁵, Peter J. O'Shaughnessy¹ and Paul A. Fowler^{2*}

Human Reproduction, Vol.29, No.7 pp. 1471–1489, 2014
Advanced Access publication on May 20, 2014 doi:10.1093/humrep/deu117

human reproduction ORIGINAL ARTICLE Reproductive biology

In utero exposure to cigarette smoke dysregulates human fetal ovarian developmental signalling

Paul A. Fowler^{1*}, Andrew J. Childs², Frédérique Courant³, Alasdair MacKenzie⁴, Stewart M. Rhind^{5,†}, Jean-Philippe Antignac³, Bruno Le Bizec³, Panagiotis Filis¹, Fergus Evans¹, Samantha Flannigan¹, Abha Maheshwari⁶, Siladitya Bhattacharya⁶, Ana Monteiro⁷, Richard A. Anderson², and Peter J. O'Shaughnessy⁷

ORIGINAL ARTICLE J Clin Endocrinol Metab. December 2009, 94(12):4688–4695
Endocrine Care

Maternal Smoking and Developmental Changes in Luteinizing Hormone (LH) and the LH Receptor in the Fetal Testis

Paul A. Fowler, Siladitya Bhattacharya, Jörg Gromoll, Ana Monteiro, and Peter J. O'Shaughnessy

Drake et al. BMC Medicine (2015) 13:118
DOI 10.1186/s12916-014-0251-x BMC Medicine

RESEARCH ARTICLE Open Access

In utero exposure to cigarette chemicals induces sex-specific disruption of one-carbon metabolism and DNA methylation in the human fetal liver

Amanda J Drake^{1*}, Peter J O'Shaughnessy², Siladitya Bhattacharya³, Ana Monteiro², David Kerrigan¹, Sven Goetz⁴, Andrea Raab⁴, Stewart M Rhind⁵, Kevin D Sinclair⁶, Andrew A Meharg⁷, Jörg Feldmann⁴ and Paul A Fowler^{8*}

Placenta 78 (2019) 10–17
Contents lists available at ScienceDirect
Placenta
journal homepage: www.elsevier.com/locate/placenta

Nutrient transporter expression in both the placenta and fetal liver are affected by maternal smoking

Natasha Walker^{a,*}, Panagiotis Filis^a, Peter J. O'Shaughnessy^b, Michelle Bellingham^b, Paul A. Fowler^a

Air pollution, PM, pregnancy outcomes

- 81 eligible cohort studies
- Every 10 $\mu\text{g}/\text{m}^3$ increase of exposure:

PM _{2.5} = 9%	PM ₁₀ = 12%	increase pre-term birth
PM _{2.5} = 26%	PM ₁₀ = 4%	increase stillbirth
PM _{2.5} = 10%	PM ₁₀ = 4%	increase small for gestational age

Increased risk for adverse offspring consequences:

- Heart disease, hypertension
- Diabetes, obesity
- Pulmonary disease, asthma
- Allergies
- Boys risk of ASD
- Maternal thyroid
- Reduced cognitive function
- Changes to fetal and neonatal DNA repair capacity

human
reproduction
open

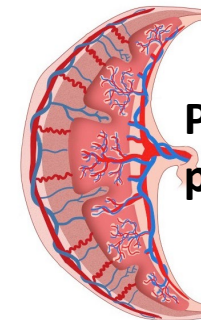
ORIGINAL ARTICLE

Effects of maternal smoking on offspring reproductive outcomes: an intergenerational study in the North East of Scotland

Sam Tweed^{1,*}, Sohinee Bhattacharya², and Paul A. Fowler³

“Women exposed to cigarette smoke in utero were significantly more likely to have a miscarriage than those not exposed; adjusted OR = 1.16 (95% CIs: 1.01-1.32)”

Ambient black carbon particles reach the fetal side of human placenta. Bové et al **Nawrot TS**. Nat Commun. 2019 Sep 17;10(1):3866. doi: 10.1038/s41467-019-11654-3.



Placental protection?

Black Carbon PM

ENVIRONAGE birth cohort (n=60)

- Mother + child pairs
- Maternal & cord blood, term placenta
- Whole pregnancy exposure
 - LOW $\leq 25^{\text{th}}$ percentile
 - INTERMEDIATE 25-75th percentile
 - HIGH $\geq 25^{\text{th}}$ percentile
- Based on residential address + validated spatial-temporal interpolation method
- Genk, Belgium



SAFeR study (n=36)

- 10-19 weeks gestation, mean = 14 weeks
- Sex balanced
- Placenta, liver, lung, brain from SAME fetuses
- Aberdeen, Scotland

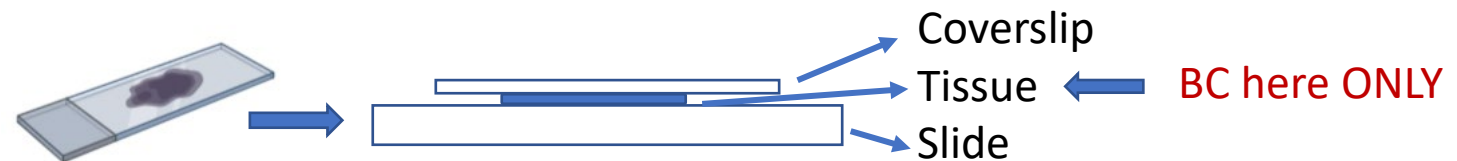
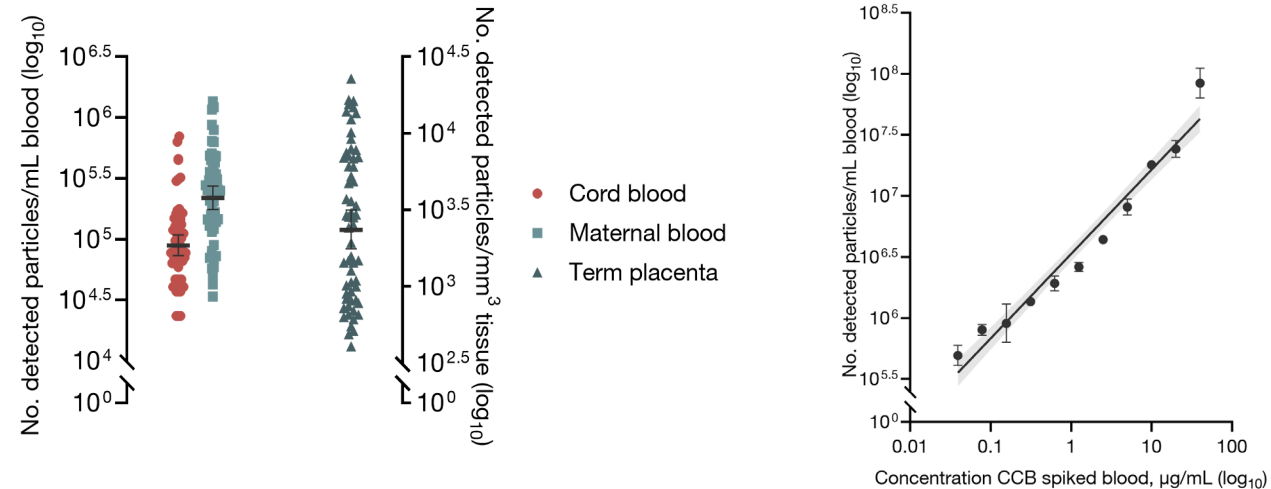


Maternal exposure to ambient black carbon particles and their presence in maternal and fetal circulation and organs: an analysis of two independent population-based observational studies

Eva Bongaerts MSc^a, Laetitia L Lecante PhD^c, Hannelore Bové PhD^a, Prof Maarten B J Roeffaers PhD^d, Prof Marcel Ameloot PhD^b, Prof Paul A Fowler PhD^c, Prof Tim S Nawrot PhD^{a, e, g, h}

Black Carbon PM

- Black Carbon particle analysis based on 2 of the characteristic white light features of carbonaceous materials
- 5 random of 5 μm tissue sections for each tissue sample

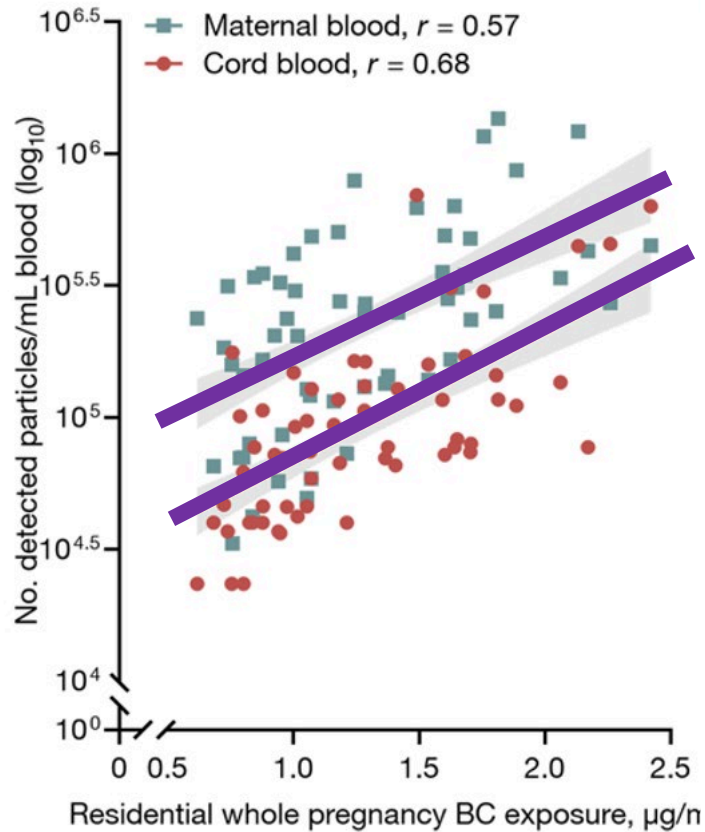


- Scotland's air quality one of best in Europe
- **PM_{2.5}** levels in Aberdeen 4.9 - 8.2 $\mu\text{g}/\text{m}^3$
- No BC data available).

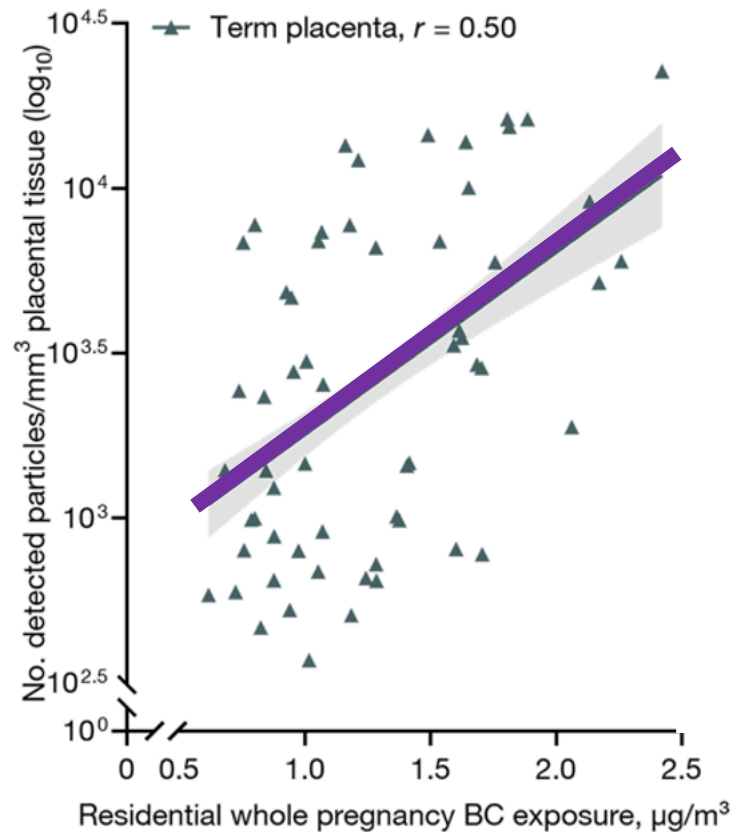
- Belgian mothers' residential exposure over the entire pregnancy
- **BC** levels 0.63 - 2.34 $\mu\text{g per m}^3$

Do Black Carbon PM reach fetal organs?

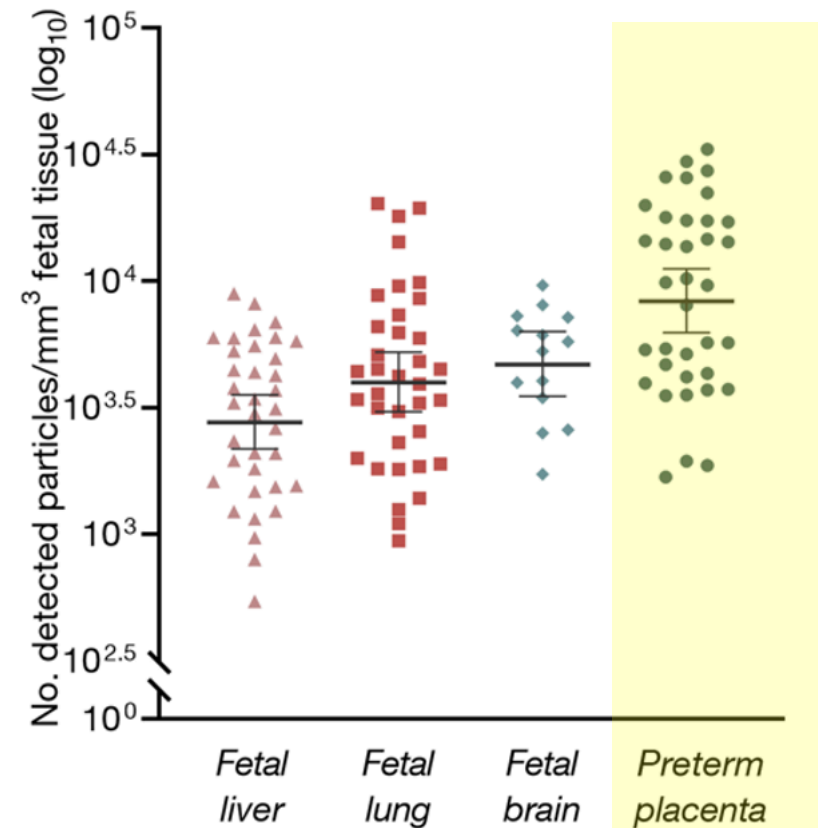
Maternal + Cord blood



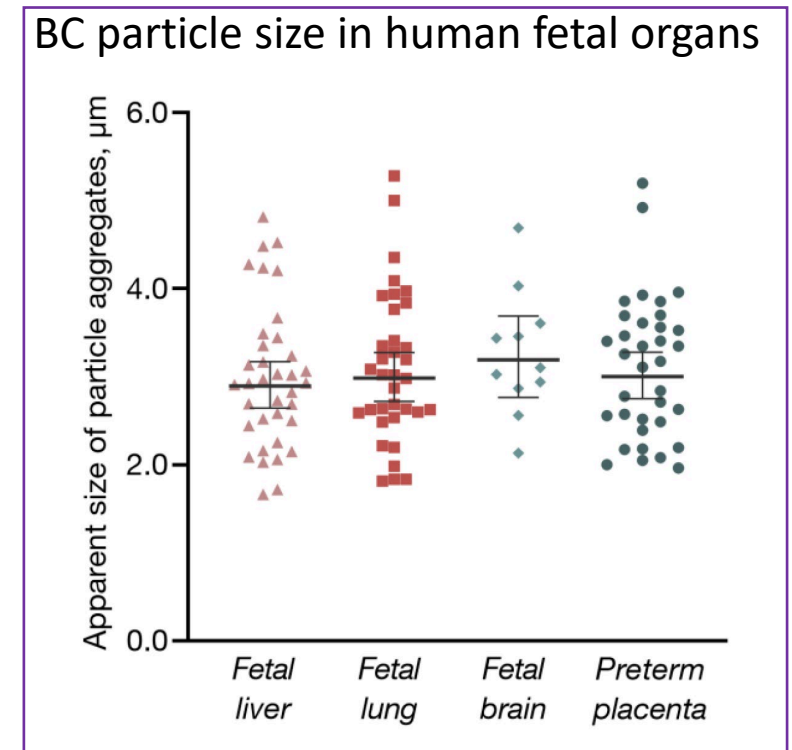
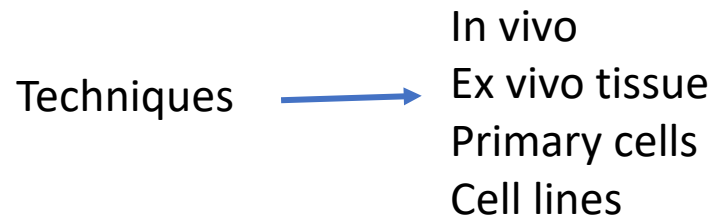
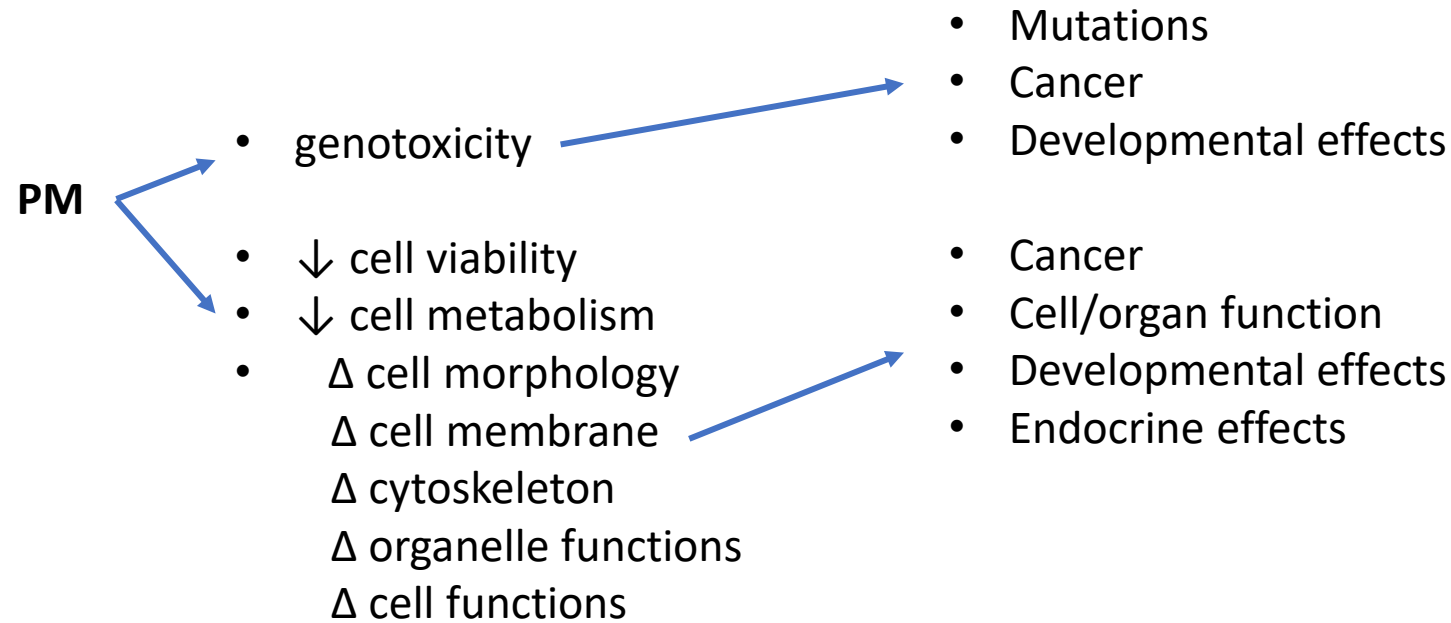
Term Placenta



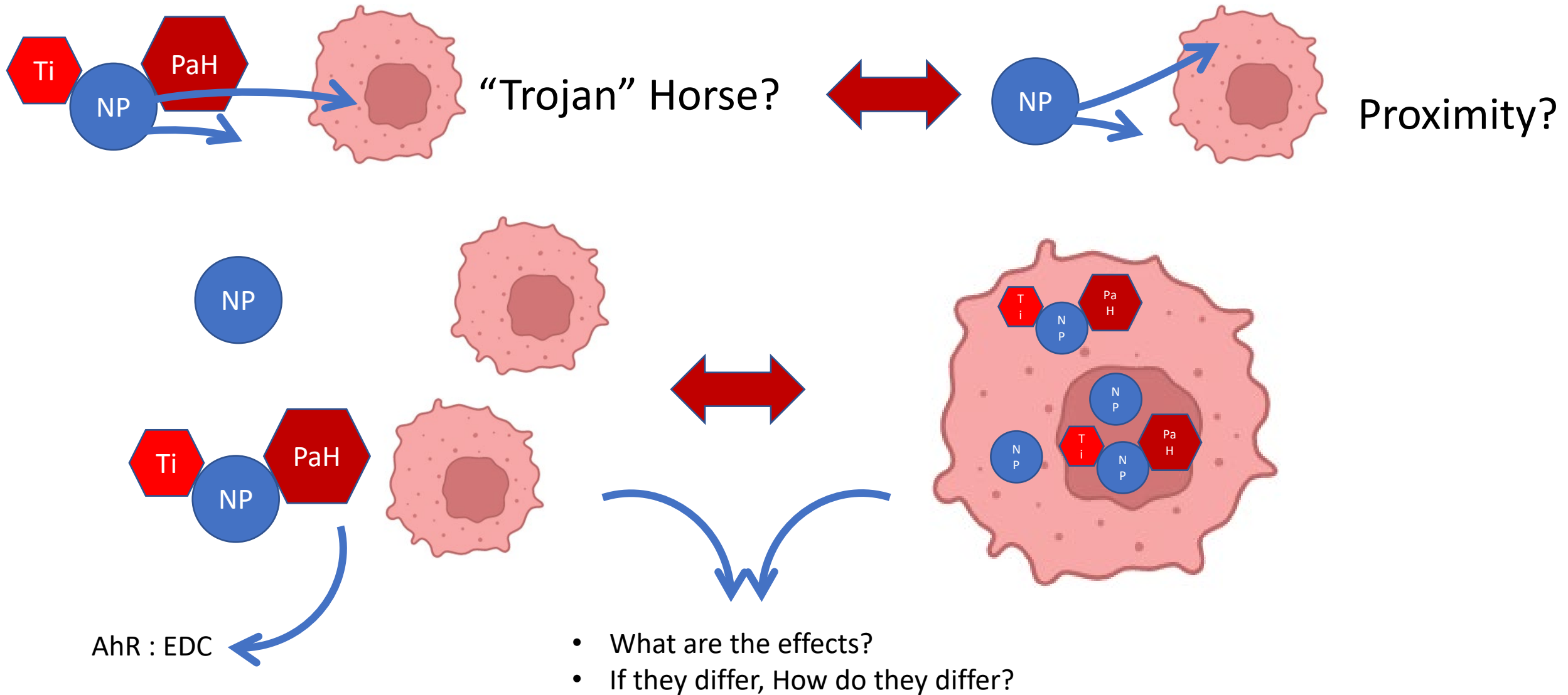
Fetus 10-19 WG



BC mechanisms?



BC mechanisms?



Conclusions

Opinion **Children have a right to clean air, and we must fight for it to become a reality**

BMJ 2022; 379 doi:

<https://doi.org/10.1136/bmj.o2425> **Camilla Kingdon**

From the existing research

- Substantial evidences that air pollution is an issue for the developing human fetus and pregnancy as a whole.
- Exposure to air pollution in-utero is associated with multiple adverse pregnancy and offspring outcomes, up to and including pregnancy loss (fetal death)
- PM_{2.5} especially, as well as PM₁₀, associated with stillbirth and other pregnancy/offspring risks

From our study

- Exposure to black carbon is proportional to environmental black carbon levels
- Black carbon air pollution particles reach into every fetus and fetal organ we have studied
- Placenta only minimally limits PM transfer to fetus
- Blood-brain barrier does not appear to protect the developing brain from invasion by PM

Approved work: Urban Outdoor Air quality

Published Thursday, 28 July, 2022

Work programme Environment



POST

This POSTnote will summarise the evidence for different measures to mitigate emissions from different sources of air pollution.