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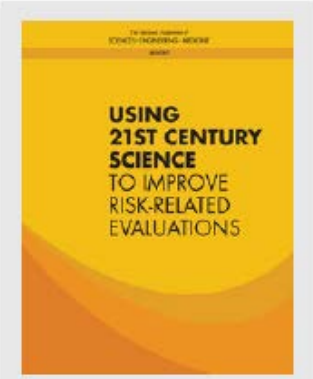
Environmental Gerogens in the AD Exposome
Air pollution & Cigarettes

Environmental Neuroscience: Advancing the Understanding of How Chemical Exposures Impact Brain Health and Disease

NAS Workshop, June 25, 2020

Exposome "record of all exposures, internal & external throughout the lifetime …molecules to populations"



NAS Press 2019
Niedswiecki et al 2019 *Ann Rev Pharm*

Air pollution & Cigarettes

- I, Adult AD exposome
- II, Developmental AD exposome
- III, Interactions and Strategies

Heritability of AD in twins: women, 45%; men 58% (Gatz 2006)

half of individual AD risk may be environmental

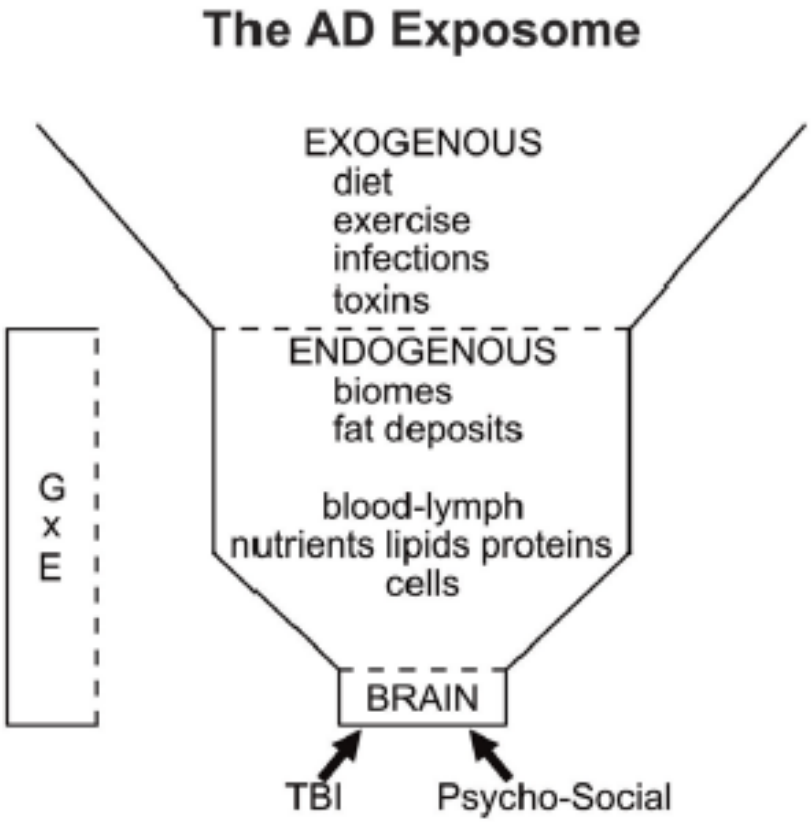
- **Airborne toxicants**

Air Pollution & Cigarettes

atherosclerosis

neurodegeneration

- Obesity
- Psycho-social stress
- Synergies



Finch & Kulminski, *Alz Dementia* 2019

Inflammation

Pathogen-driven inflam.

- infections, acute/chronic
- Parasites

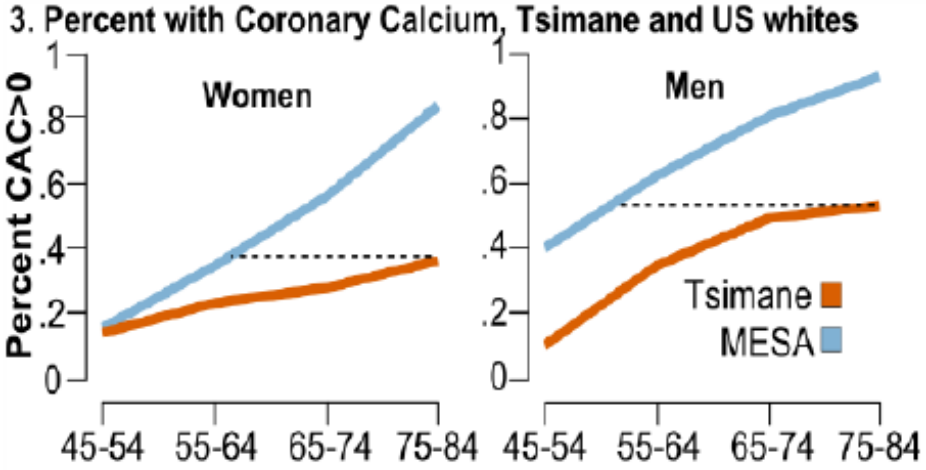
Sterile inflammogens

- fat tissue
- Air pollution
- Cigarettes
- Environmental toxins

High energy cost of fever and tissue repair

Lower energy cost

Bolivian Tsimane-
pathogen-driven chronic inflammation
strokes and heart attack 90% lower than US



Kaplan et al, *Lancet*, 2017

Coronary aging of Tsimane is 25 years slower than US

Is brain aging also slower?

Air pollution & cigarettes are

STERILE GEROGENS:

- shorten lifespan by 5-10 years
- accelerate diseases of aging

  arteries: heart attacks & strokes

  brain: Alzheimer's and brain atrophy

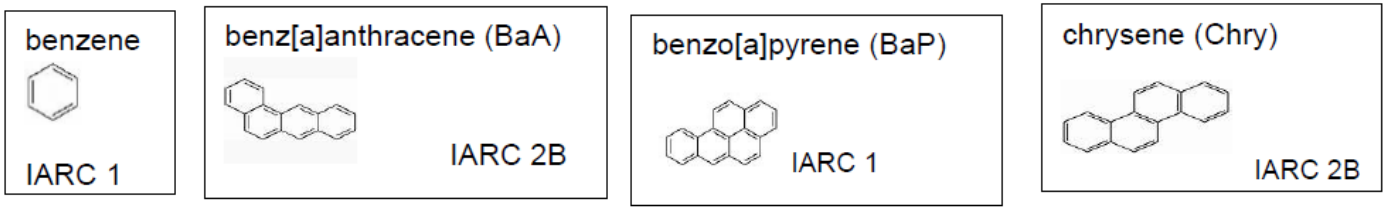
  cancers: lung, kidney
- oxidative stress & inflammation

shared pathology and accelerated aging

Fossil fuels and cigarettes
shared toxins and gerogens

- Fine particles (PM2.5u) deposited in lungs
- Incompletely burned carbon particles

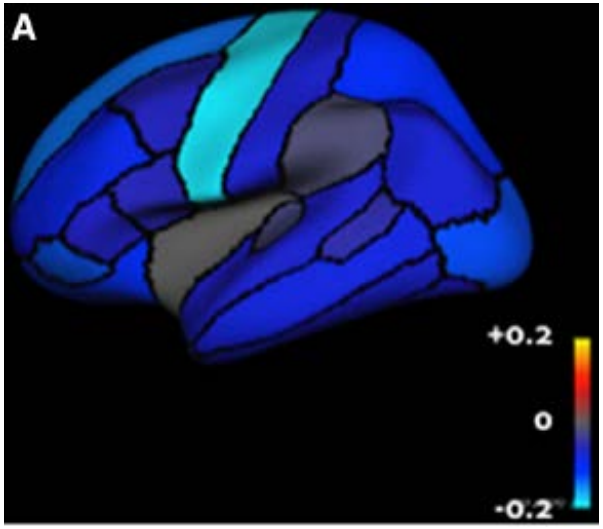
  carcinogens: polyaromatic hydrocarbons (PAH)



- Toxic metals: iron and lead
- 45% of US children incur 2nd hand smoke

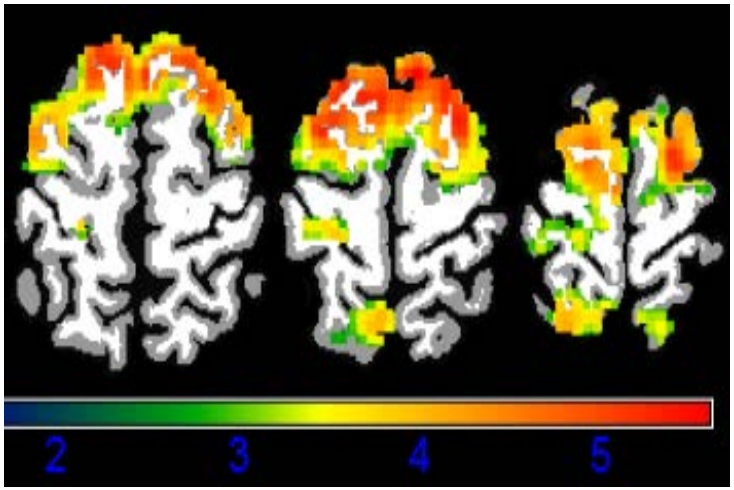
Cerebral atrophy

- Smoking, pack yr



VETSA cohort, men, 56 y
Prom-Wormley et al.
Behav Genet, 2015

air poll, PM2.5

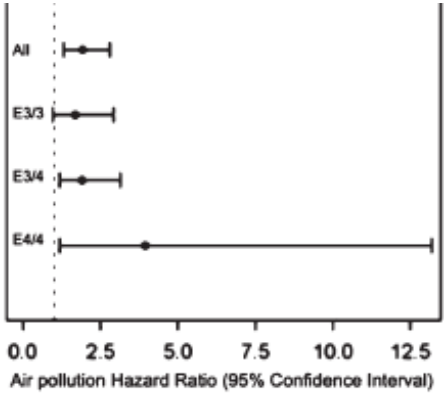


white matter loss 5 cm^3/3.5 µg$PM2.5/m^3$

WHIMS cohort, women, 70 y
Casenova *FHN,* 2019

air pollution accelerates cognitive aging in ApoE4

WHIMS



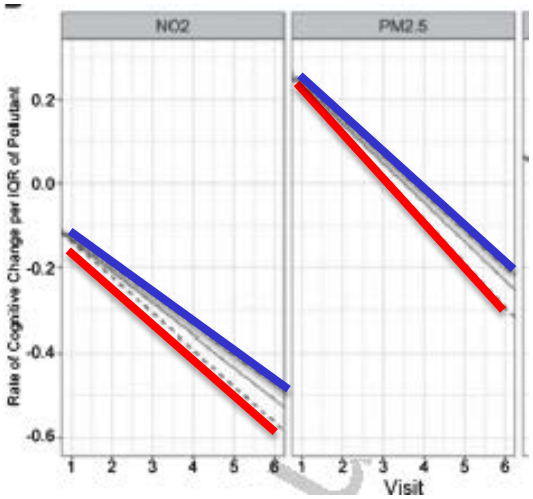
Cacciottolo *Trans Psych* 2017;

WHICAP

NO2 PM2.5

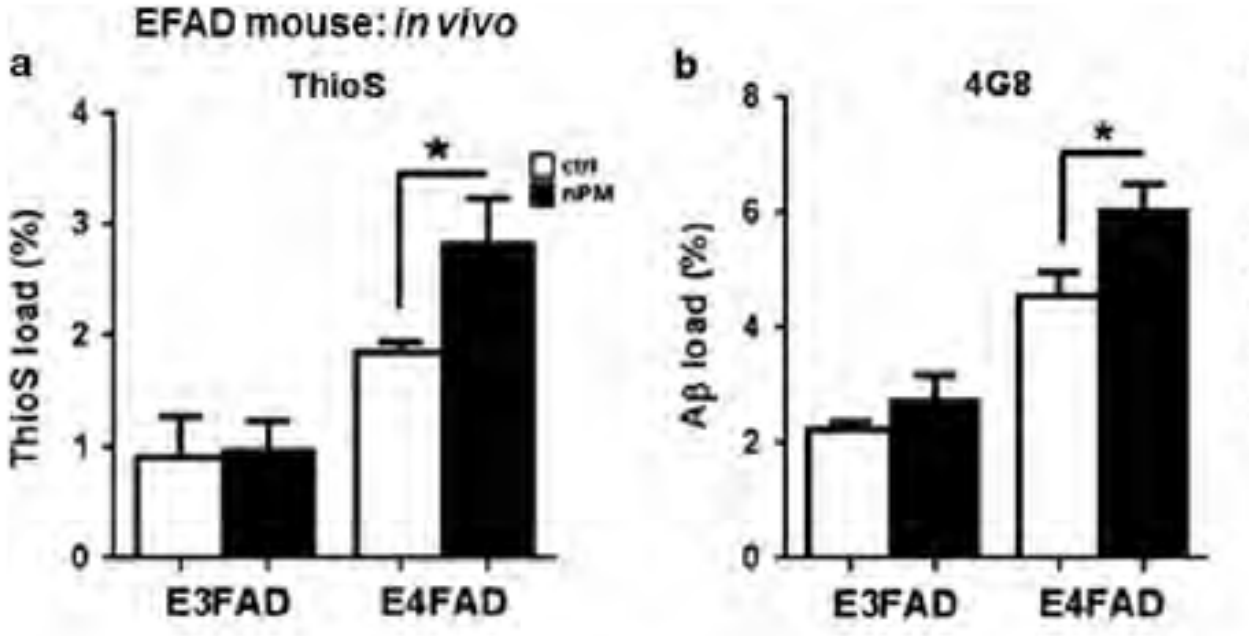
E4

E3



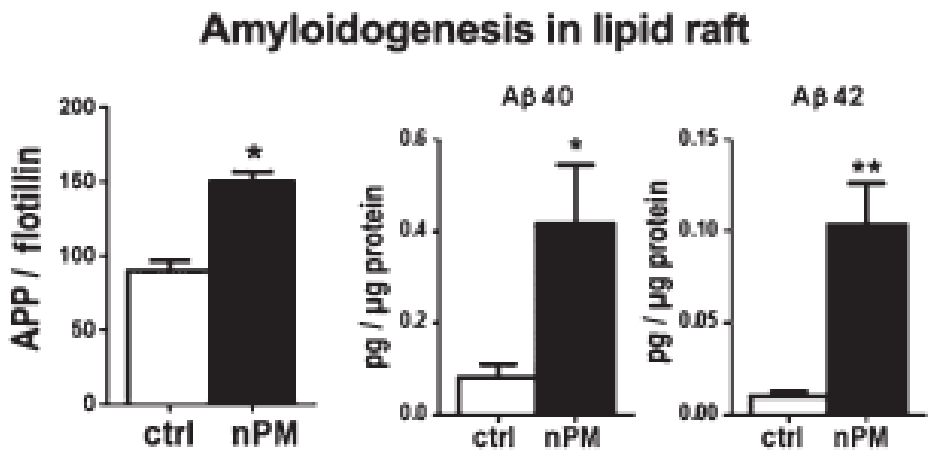
Kulick *Environ Int* 2020

Air Poll increases brain amyloid more in E4FAD mice

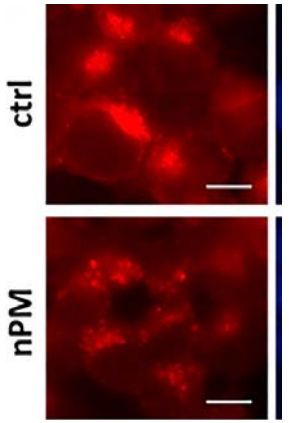


Cacciottolo et al 2017, *Transl Psych*

nPM alters APP processing in lipid rafts pro-amyloidogenic pahways

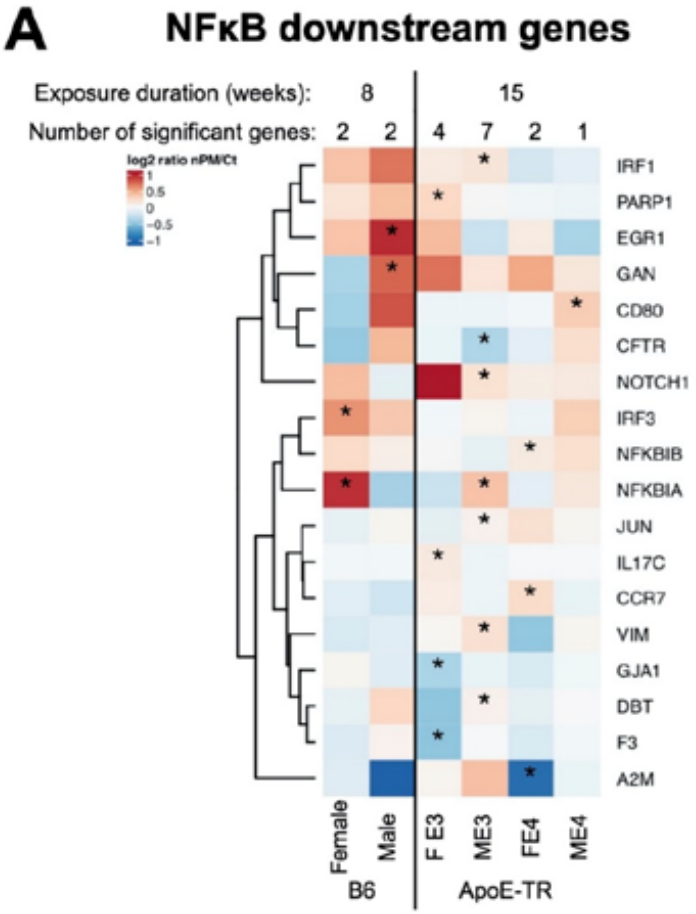


Lipid ganglioside



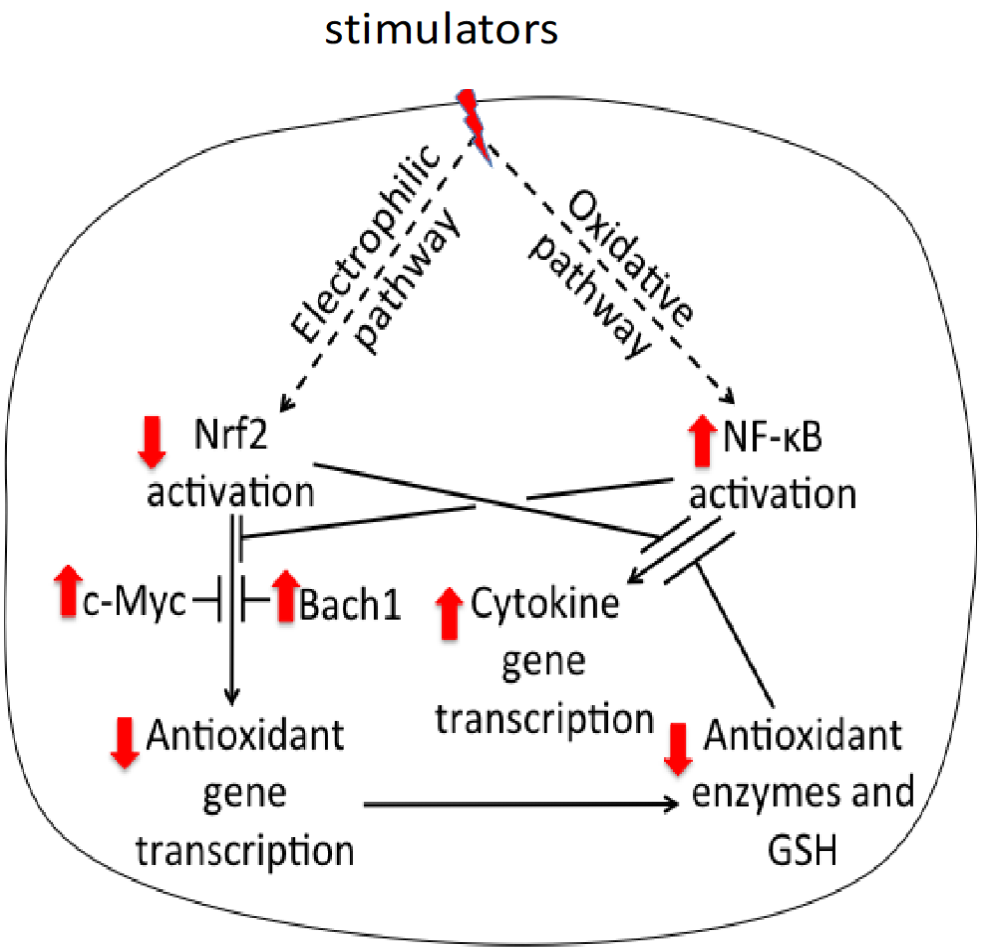
Cacciottolo 2020 *FREBM*

NFkB path gene response to nPM differ by sex and ApoE



Haghani et al. *eLIFE*, in press

AirPoll and CigS pathways



Forman & Finch *FREBM* 2018

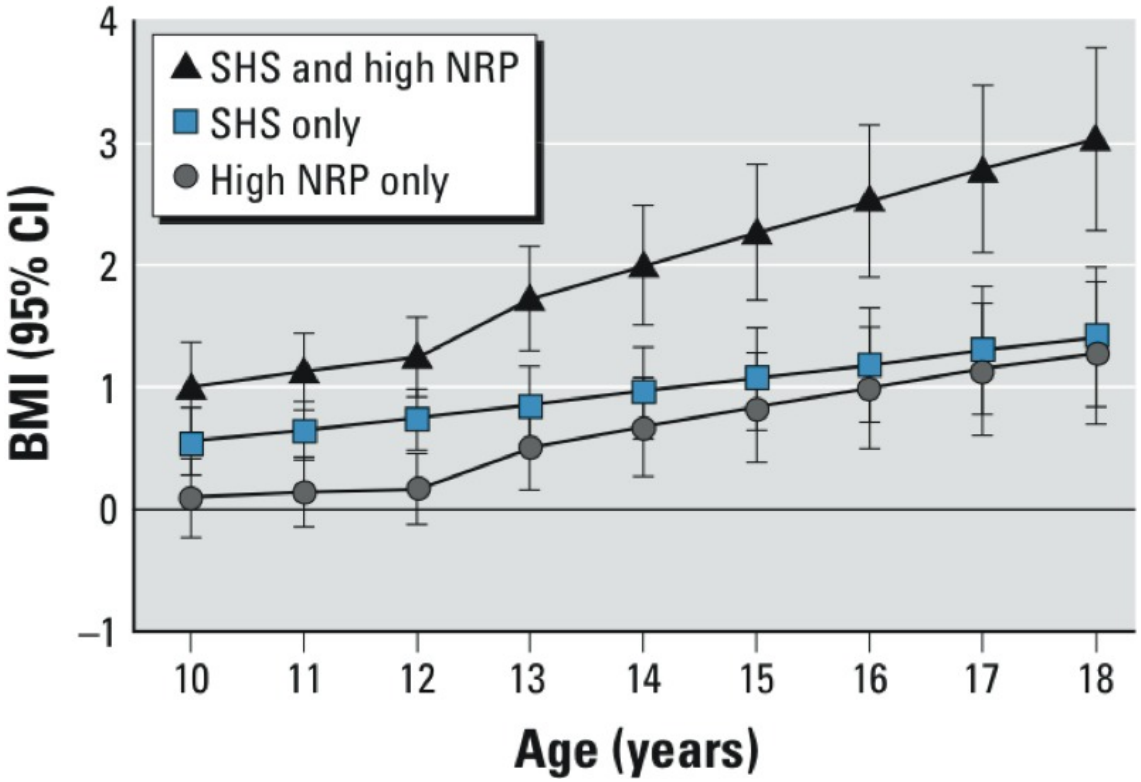
Developmental impact with potential impact on brain aging

	Air Pollution	Cigarettes	Lead (Pb)
prematurity	+	++	++
autism spectrum	++		++
childhood obesity	++	++	
brain grey matter deficit	++		++
Atherosclerosis	++	++	
blood pressure, systolic	++	+++	+
DNA methylation	++	++	++

+, only human ; ++, human & rodent

Finch & Morgan *Ann Rev Devel Psych* 2020

Synergies: Childhood obesity greater than additive effects of secondhand tobacco smoke (SHS) & near roadway air pollution (NRP)



McConnell *Environ Health Perspect.* April, 2015

Synergies of PM2.5 and CigS

	Synergy	
Childhood BMI	1.3-fold	McConnell *EHP* 2105
Cancer of lung	2.3	Turner *AJE* 2015
Cognitive aging	1.9	Ailshire *AJE* 2014

Forman and Finch FRBM 2018

Defining the personal exposome

- Residence level monitoring of air pollution

  Oakland Study Apte *Env Sci Technol,* 2018

- Wearable detectors Michael Snyder (Stanford)

  Personal aging markers & ageotypes by deep longitudinal profiling.
  Ahadi *Nature Med* 2020

Issues ahead

- Is impact on brain direct vs systemic
- SES and multiple morbidities on vulnerability
- Multigenerational impact
- Cohorts with unique exposure, e.g. lead (Pb)