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Air pollution & dementia
in SES gradients of aging
GETA Symposium, Sacramento
October 19, 2023

Finch CE & Tanzi RE (1997)

The genetics of aging. *Science* 278:407-411

The role of genetics in determining life-span is complex and paradoxical.
The heritability of life-span is modest in humans and animal models (15-30%).
However, some genetic variants significantly modify senescence of mammals and invertebrates, with both positive and negative impacts on age-related disorders and life-spans. In certain examples, the gene variants alter metabolic pathways, which could thereby mediate interactions with nutritional and other environmental factors that influence life-span. *Given the relatively minor effect and variable penetrance of genetic risk factors that appear to affect survival and health at advanced ages,*
life-style & other environmental influences may profoundly modify outcomes of aging.
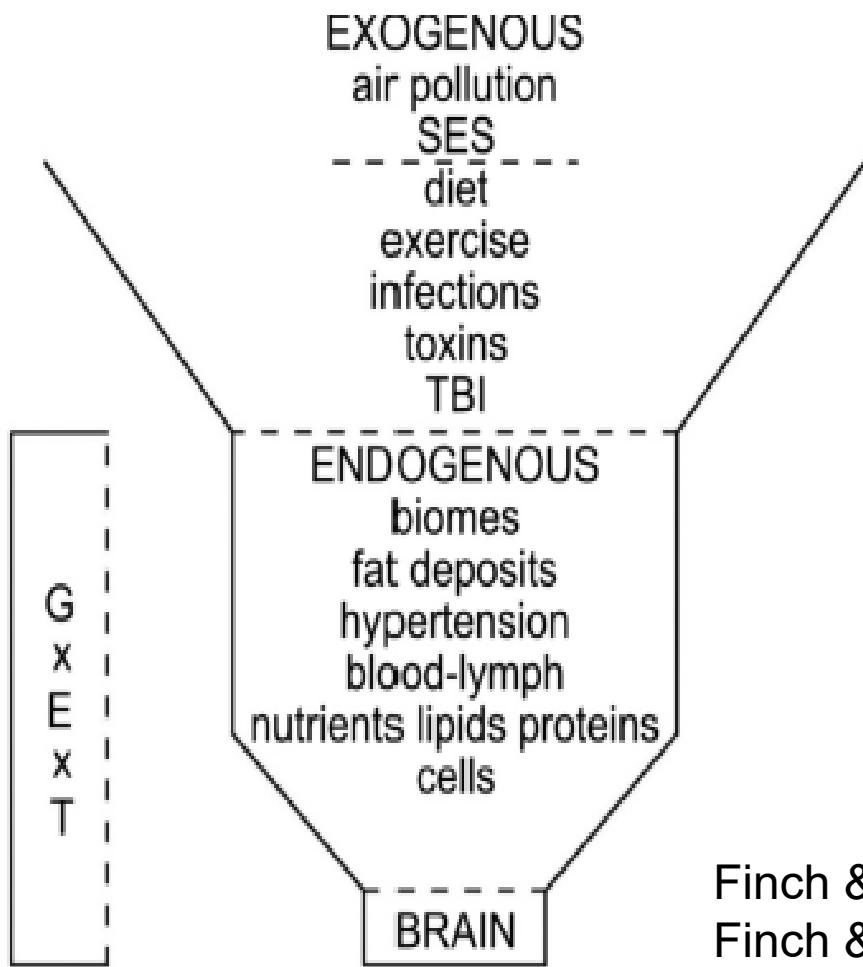
**2023: emerging role of
air pollution in dementia and aging processes**

# environmental influences on heart & brain aging
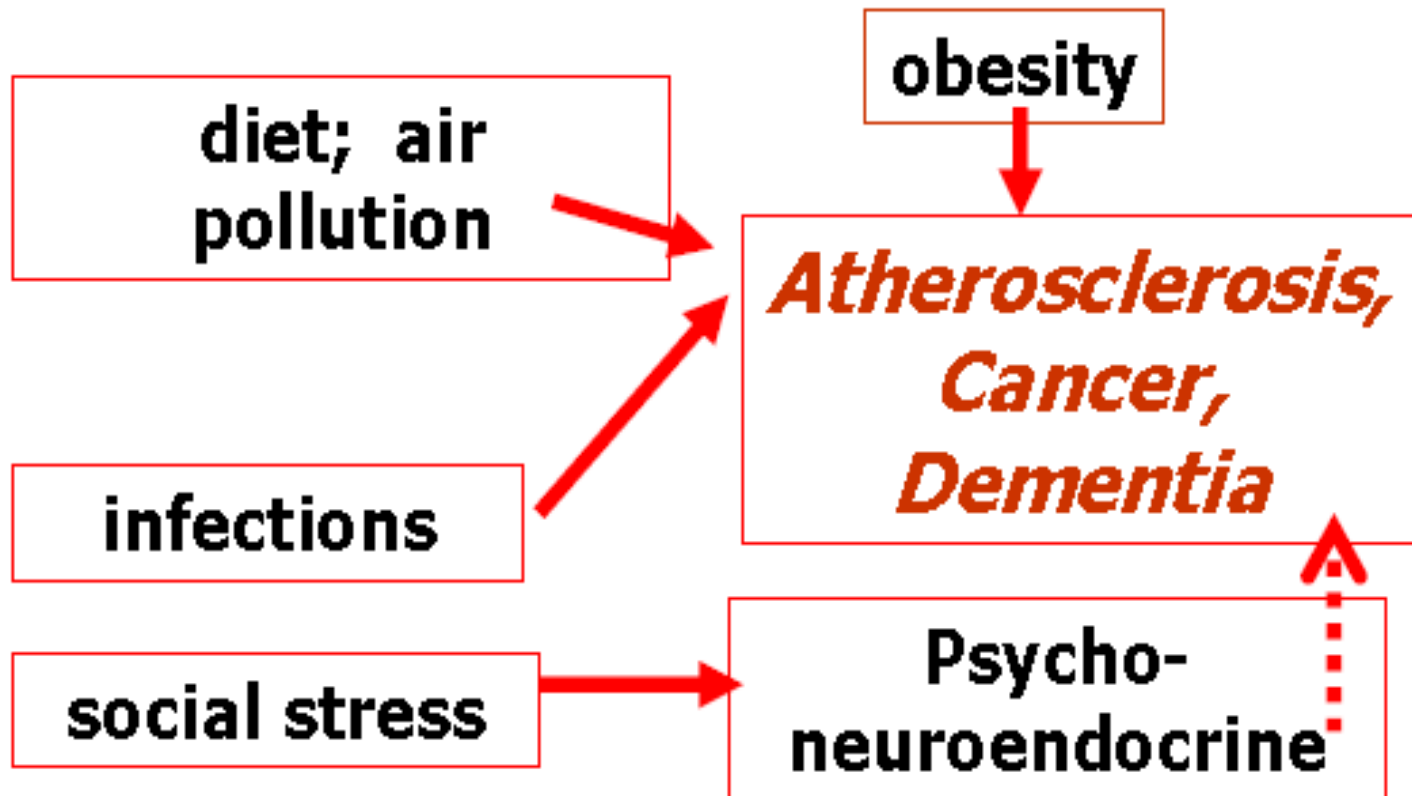
The Gero-Exposome: developmental framework for GxE & gerogens of aging
Gestation thru old age

EXOGENOUS
air pollution
SES
- - - - - - - - - -
diet
exercise
infections
toxins
TBI

ENDOGENOUS
biomes
fat deposits
hypertension
blood-lymph
nutrients lipids proteins
cells

G x E x T

BRAIN

- **Exo**genous macrolevel

- **Exo**genous individual

- **Endo**genous individual

Finch & Kulminski, *Alz Dement* 2019
Finch & Haghani, *J Gerontol* 2021
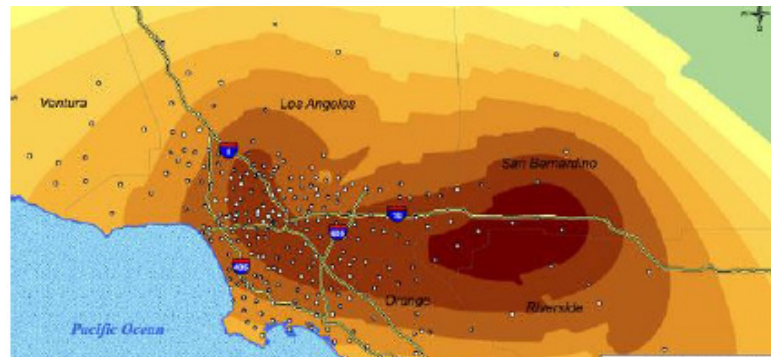
- PM2.5 & with lower verbal learning (β=-0.32 per 10 µg/m^3 PM2.5).
- NO$_2$ >20 ppb, lower logical memory.
- O$_3$ >49 ppb, lower executive function

Gatto et al Components of air pollution and cognitive function in middle-aged & older adults in Los Angeles. _Neurotoxicology,_ 2014.

Ambient air pollution, ApoE4 increased cognitive decline of older adults in northern Manhattan
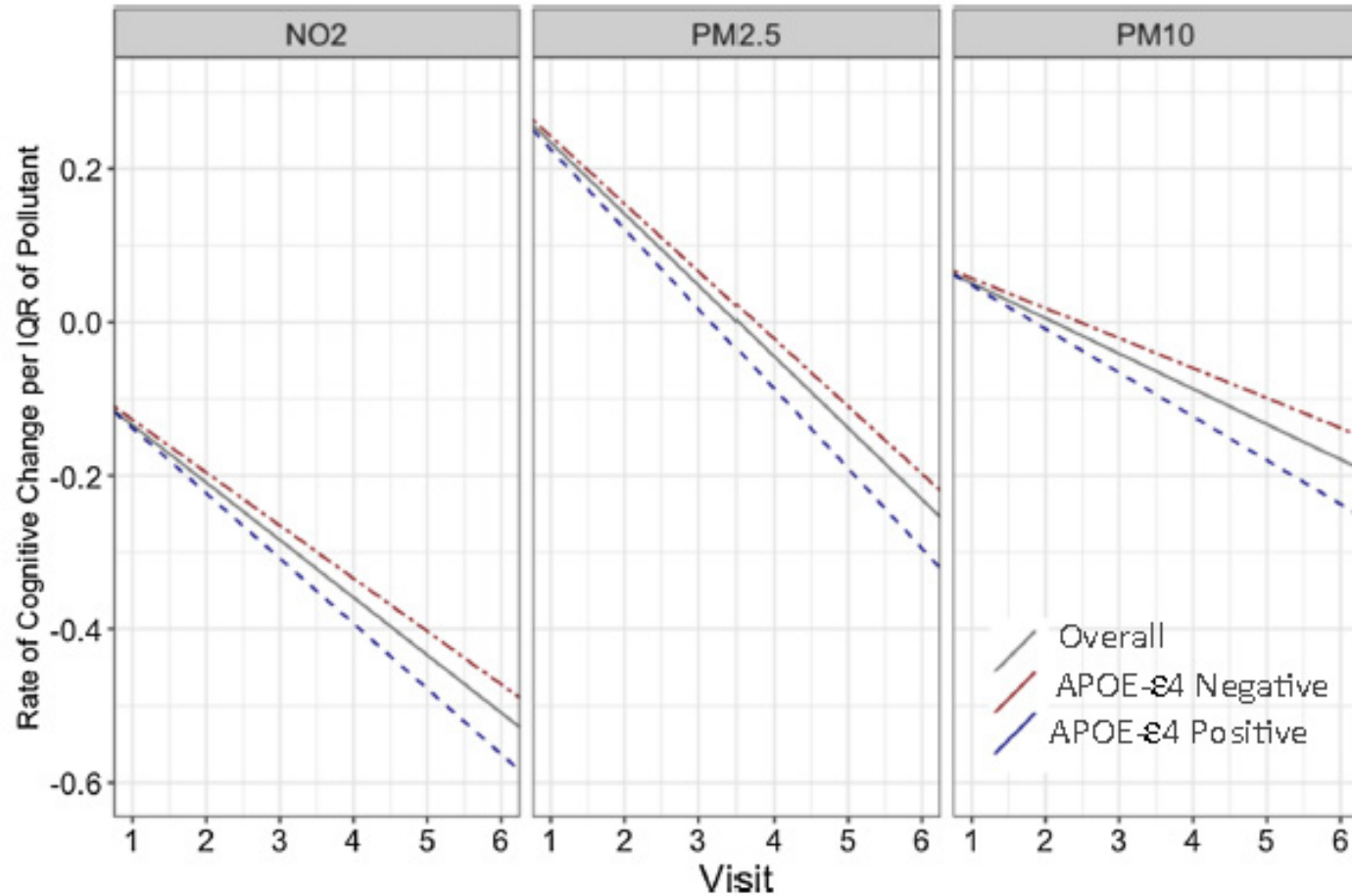
Kulick *Environ Int,* 2020

Chen JC et al 2015. Ambient air pollution and neurotoxicity on brain structure: Evidence from Women's Health Initiative Memory Study (WHIMS). <u>Ann Neurol</u>. 2015.
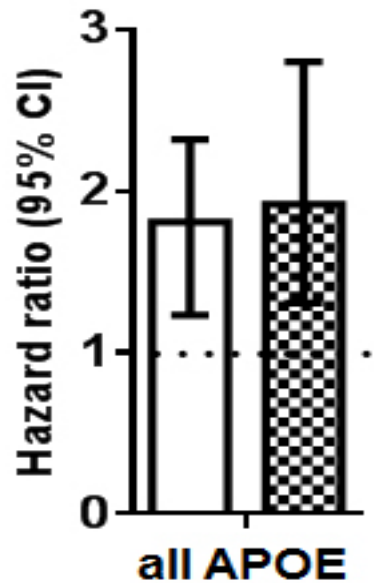
"JC" Jiu-Chiuan Chen,
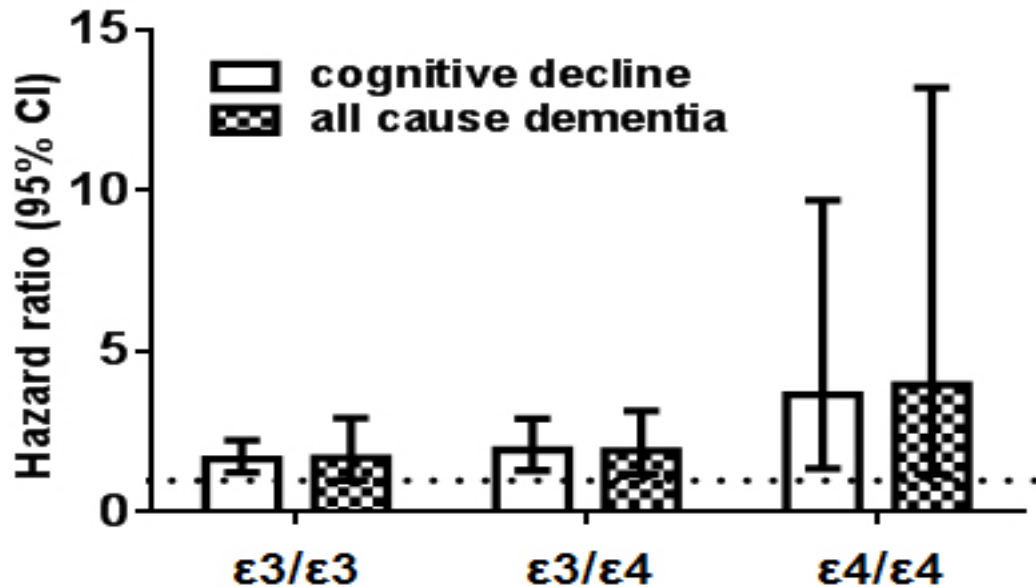Assoc Prof Preventive Medicine, USC

1. **White matter volume loss** **total brain of -5 cm^3 per +3.5 μg/m^3 of cumulative PM$_{2.5}$ exposure.**
2. **Frontal & temporal lobes and corpus callosum.**
3. **Equivalent 1-2 years of brain aging in high PM2.5.**

Womens Health Initiative Mental Studies (WHIMS)

a Main Effect

Hazard ratio (95% CI)

all APOE

b Stratified by APOE alleles

Hazard ratio (95% CI)

☐ cognitive decline
▦ all cause dementia

ε3/ε3   ε3/ε4   ε4/ε4
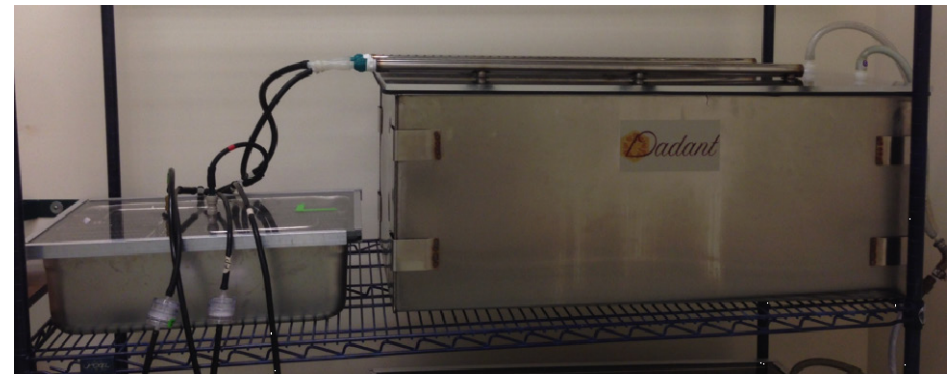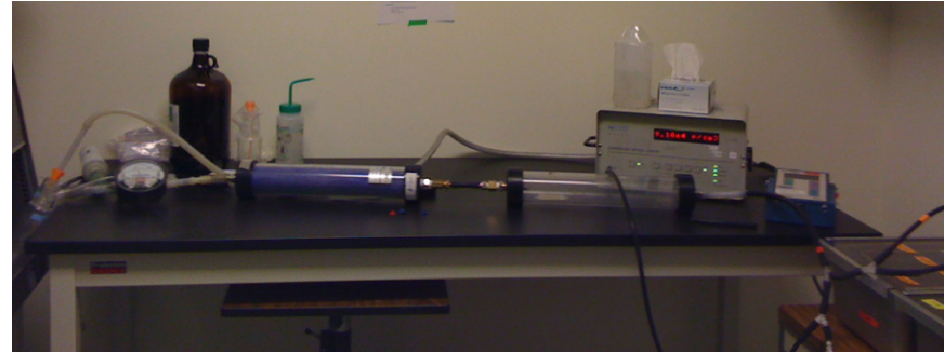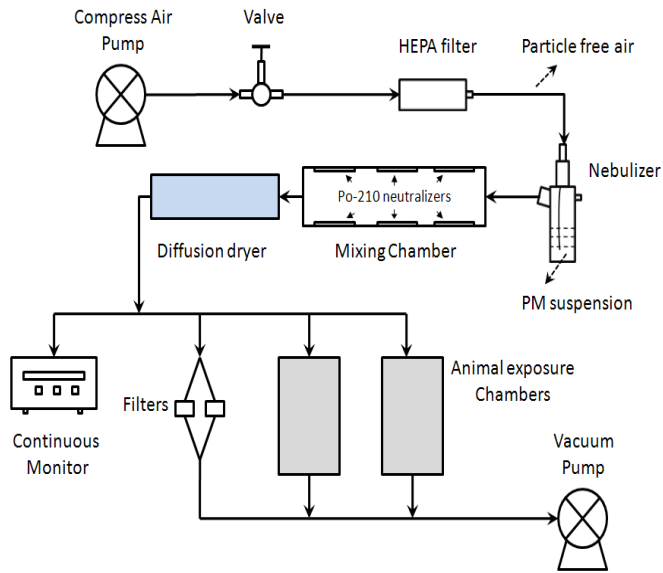
30% of older US women reside in PM2.5 > 12 ug/m^3.
10-20% of dementia in woman attributable to high $PM_{2.5}$

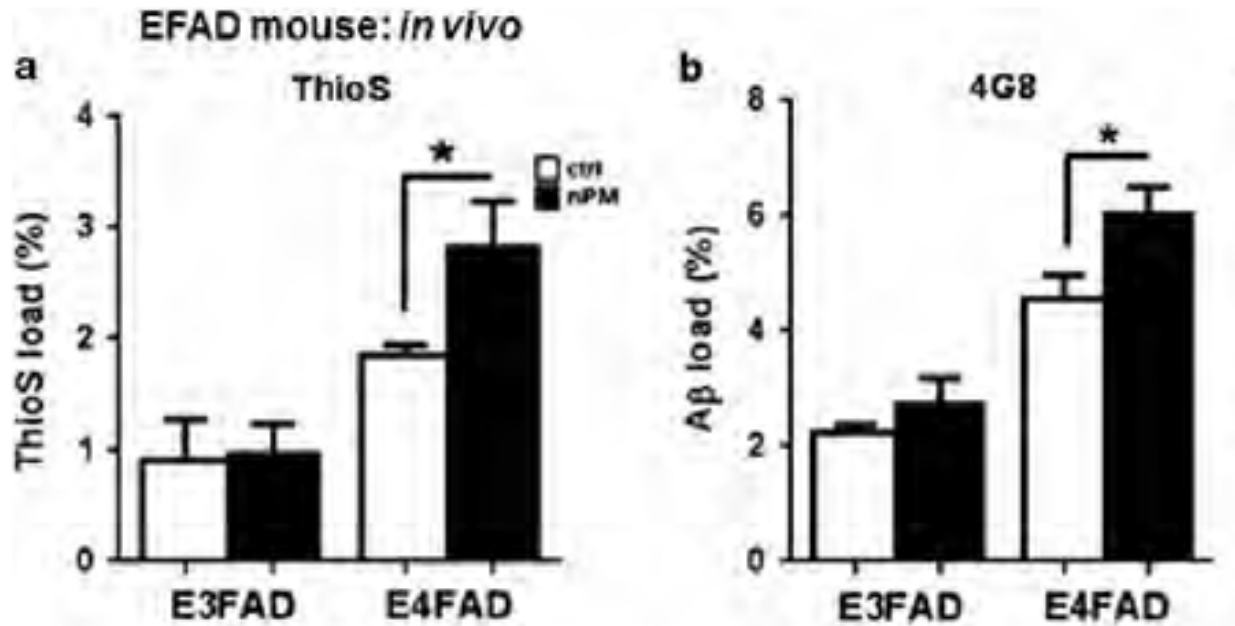Cacciottolo et al. *Transl Psych*, 2017

Re-aerosolized nanoscale particulate matter (nPM) for rodent exposure: 150 hrs during 10 weeks
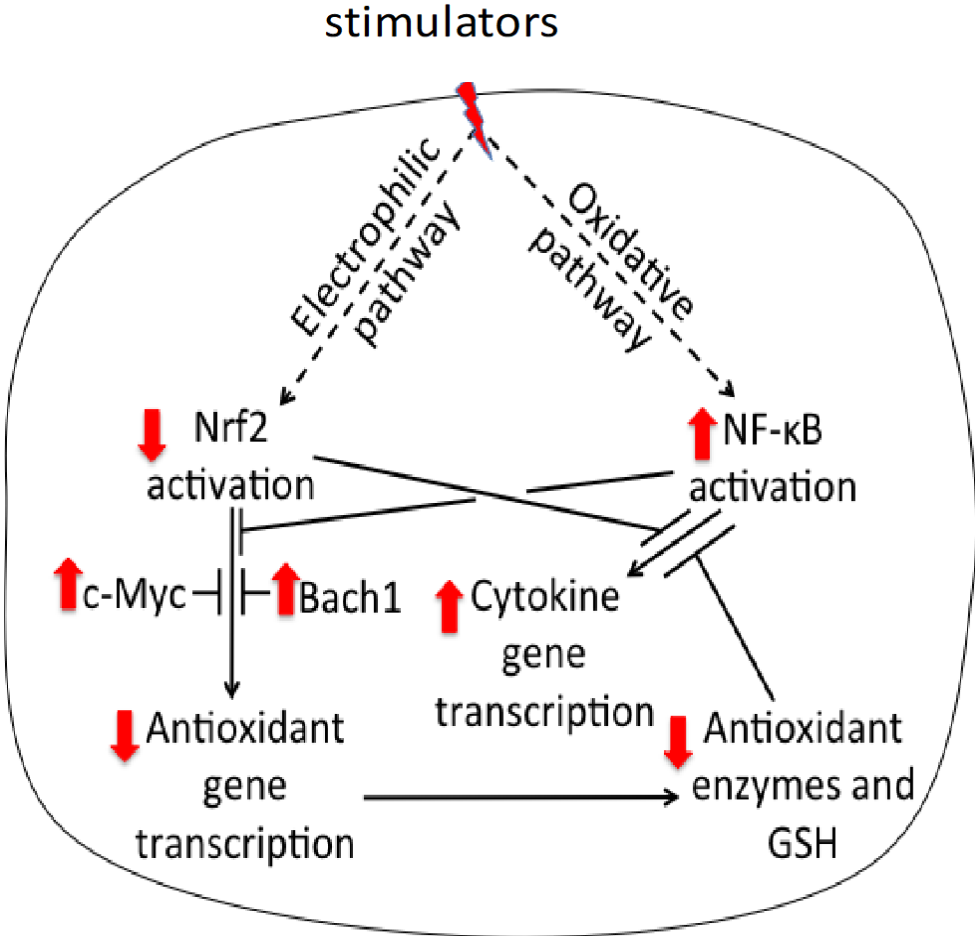

technology developed by Constantinous Sioutas, USC

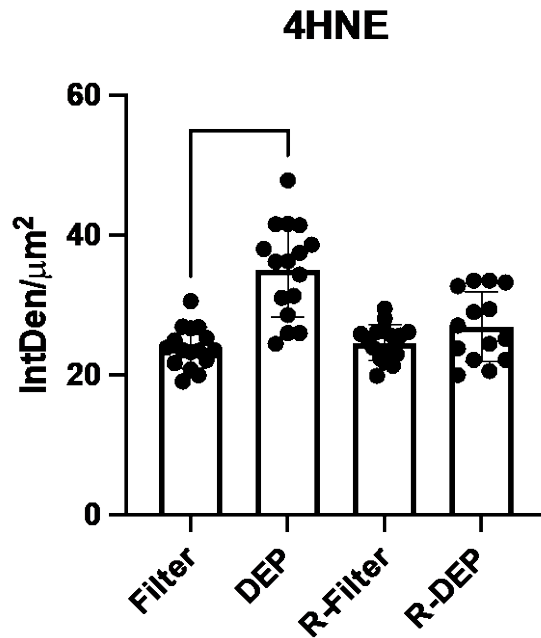# AirPoll-nPM increased brain amyloid more in E4FAD mice

Cacciottolo et al 2017, *Transl Psych*

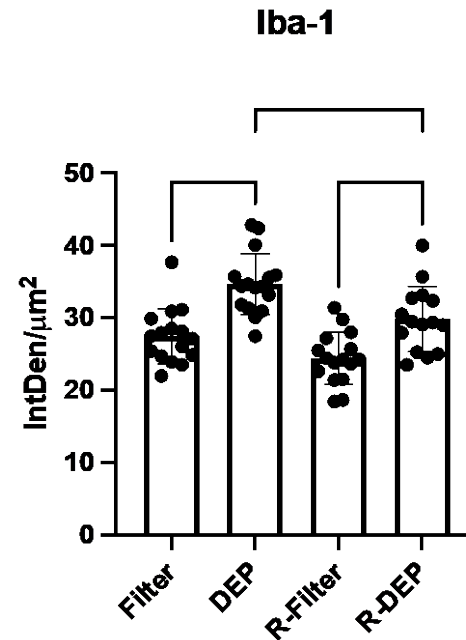# Molecular pathways in air pollution

How permanent is AirPoll damage to brain?

Wildtype B6 mice exposed to DEP for 8 hrs
corpus callosum 1d and 14 d post exposure

4HNE
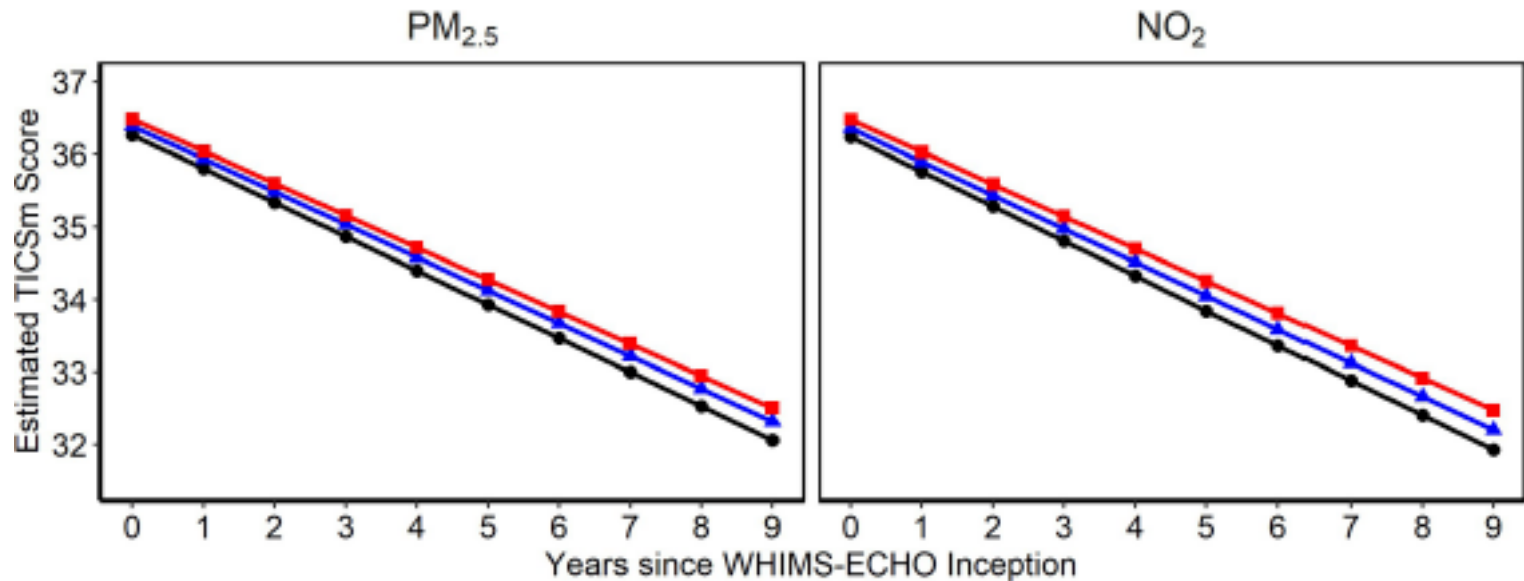
Oxidative damage
recovered

Iba-1

Microglial activation
persisted

Demetriou A, Finch CE, Pike CJ, Mack W, in prep.

Association of improved air quality with lower dementia risk in older women. Longitudinal cohort study
Younan D et al *PNAS* 2022

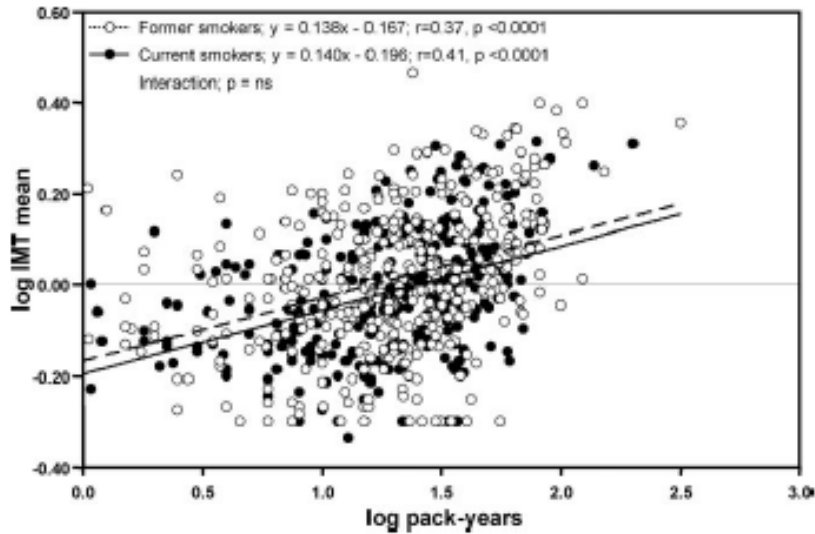(A) Associations on general cognitive ability decline (N=2232)

Carotid atherosclerosis: CIMT

tobacco

PM2.5: 4% thicker/10 ug/m^3

Baldassarre 2009 *Stroke*

Kunzli 2010 *PLoS*

Longevity genes

?

e.g. *FOXO3*
      mTOR
      APOE?

Lifespan

Healthspan,
Stress resistance

e.g.

ADCY2	GNG4	*MRAS*	PPP2R5E
ADCY8	*GRM7*	*MYLK*	PRKAG2
ADCY9	HLA-DQB1	*OSMR*	*RAP1A*
APBB1IP	HLA-DRB1	*PAK1*	*RASA1*
BMPR2	IL7	PAK2	RFX5
CACNA1C	*ITGA1*	PARVB	*RGS7*
CD19	ITGA4	PDE1B	*RORC*
COL5A3	ITPR2	PDGFC	RXRA
CRHR1	*JAK1*	PIK3C2G	*SMAD3*
DOCK1	LAMA1	PLA2G4C	*SOS2*
DSCAM	LEF1	*PLCG1*	STAT1
EPHA3	*LPAR1*	PLCG2	STAT4
ETS1	LYZ	PLG	TEK
FGFR1	MC1R	POU2F2	

SNPs of inflammatory genes in
cigarette survivors

* ***Bolding*** shows genes in
mouse brain responding to
air pollution
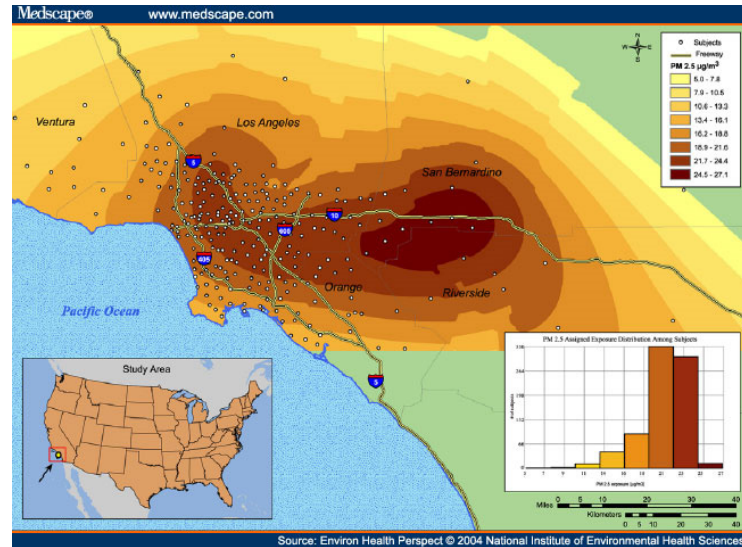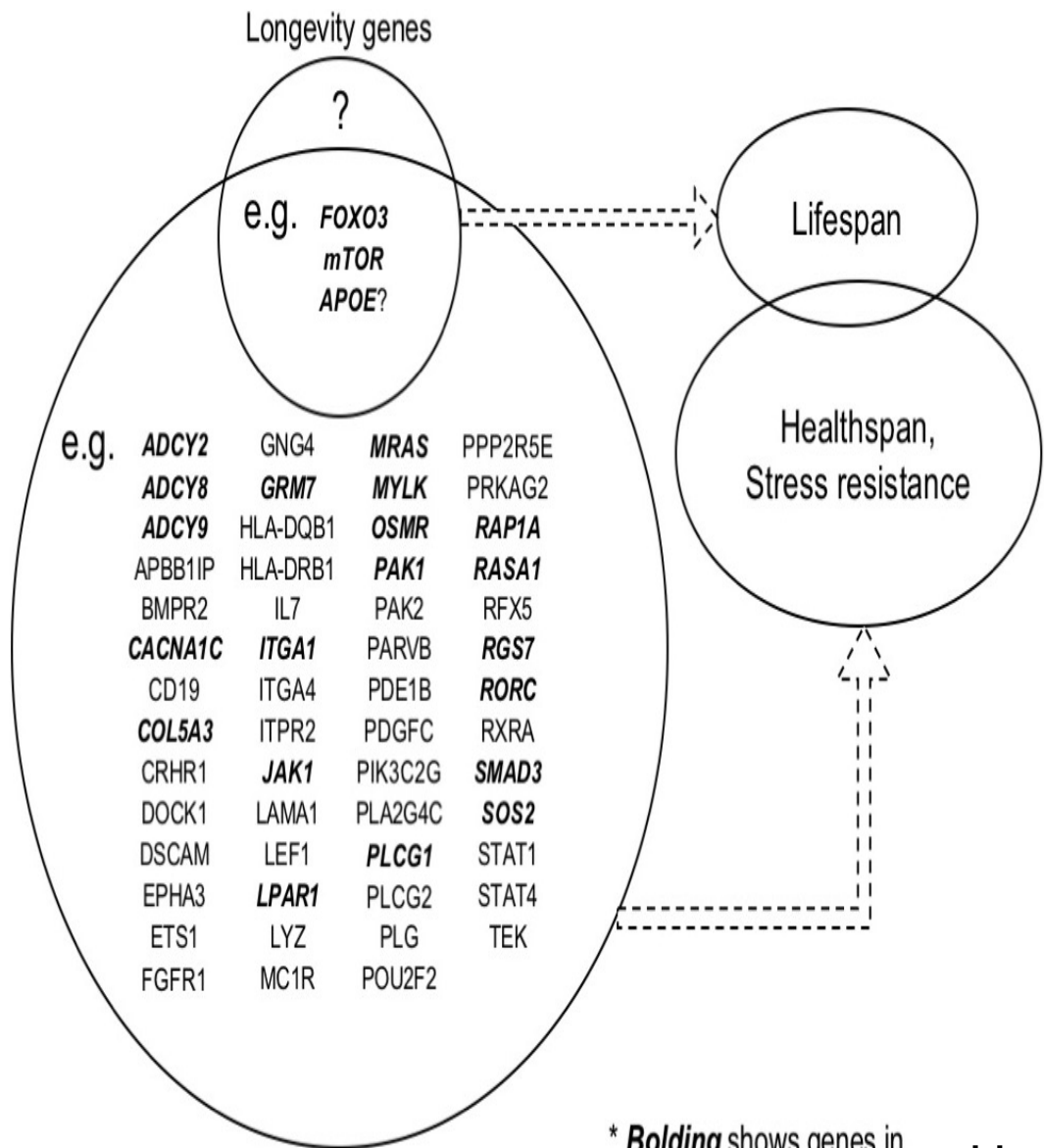
Cig-Poll shared risk genes

Haghani, Levine, Finch
J Gerontol 2021.

Shared inflammatory mechanisms in atherosclerosis and Alzheimer disease?

|	atheroma	senile plaque
cells		
macrophages (CD68)	**+++** (foam cells)	**++** (microglia)
T helper (Th1)-cells	++	0
mast cells, platelets	++	0
neovascularization	++	+
proteins		
amyloids	**++**	**++**
Abeta	**?** (platelet APP)	**+++**
C-reactive protein (CRP)	**++**	**+**
serum amyloid P (SAP)	**++**	**++**
clotting factors	++	0
complement: C3, C5b-9	**++**	**++**
cytokines: IL-1, IL-6	**++**	**++**

CE Finch, Neurobiol Aging, 2005

Shared inflammatory processes in normal aging and diseases
active macrophages/monocytes
local oxidative damage from free radicals

arterial atheroma

Alzheimer senile plaque

J-O Daguchi Circ 2006

CJ Pike, pers comm
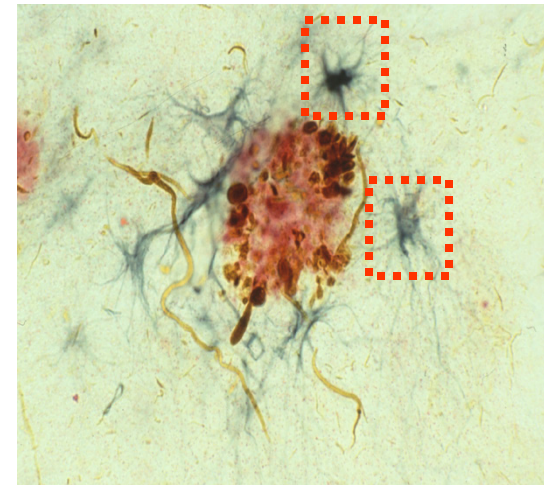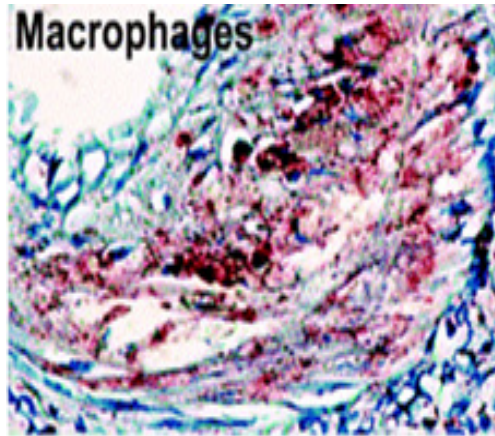
Mal-convergent Smokes:
Air pollution (AAP) & Cigarettes (CS)

|	AAP	CS	AAP-CS interactions
Atherosclerosis **carotid** **coronary**	Aguilera 2016; Liu 2015 Hartiala 2016; Kaufman 2016	Hansen 2016, Huang 2016 Benziger 2016, Nicoll 2016	 Burnett 2014
Cancer lung	Hamra 2014; Cui 2015	Doll 2004; Chen 2015	Burnett 2014, Turner 2014
Metabolism **insulin sensitivity,** **BMI, children**	Wolf 2016, Thiering 2016 McConnell 2015	weak or no association	 McConnell 2015
Brain aging **grey matter** **atrophy** **myelin atrophy** **cognitive decline**	Chen 2015 Casanova 2016 Ailshire 2014 Cacciottolo 2017;	Karama 2015; Prom-Wormley 2015	 Ailshire 2014
Alzheimer disease	Cacciottolo 2016; Oudin 2016; Jung 2015	Barnes 2011; Durazzo 2014; Deochand 2016	
Stroke	Sheers 2015; Wang 2014	O'Donnell 2011;	

Finch CE & Forman HJ, *Free Rad Biol Med* 2018

Childhood obesity: superadditive effects of
secondhand tobacco smoke (STS) & near roadway air pollution (NRP)

McConnell R et al, *Environ Health Perspect.* 2015
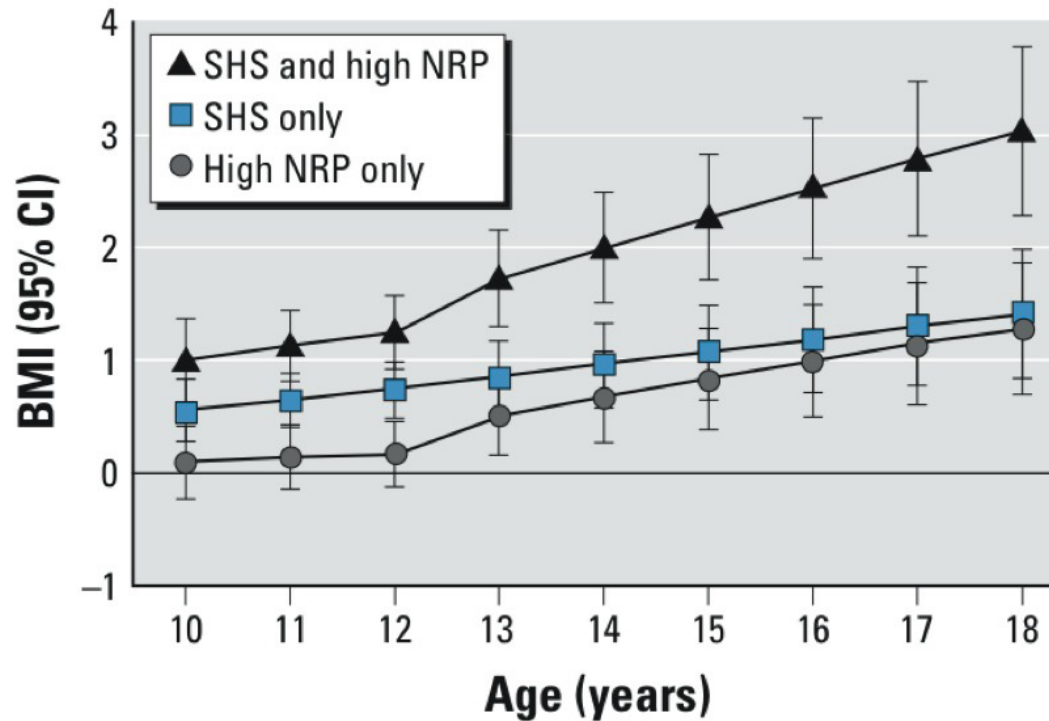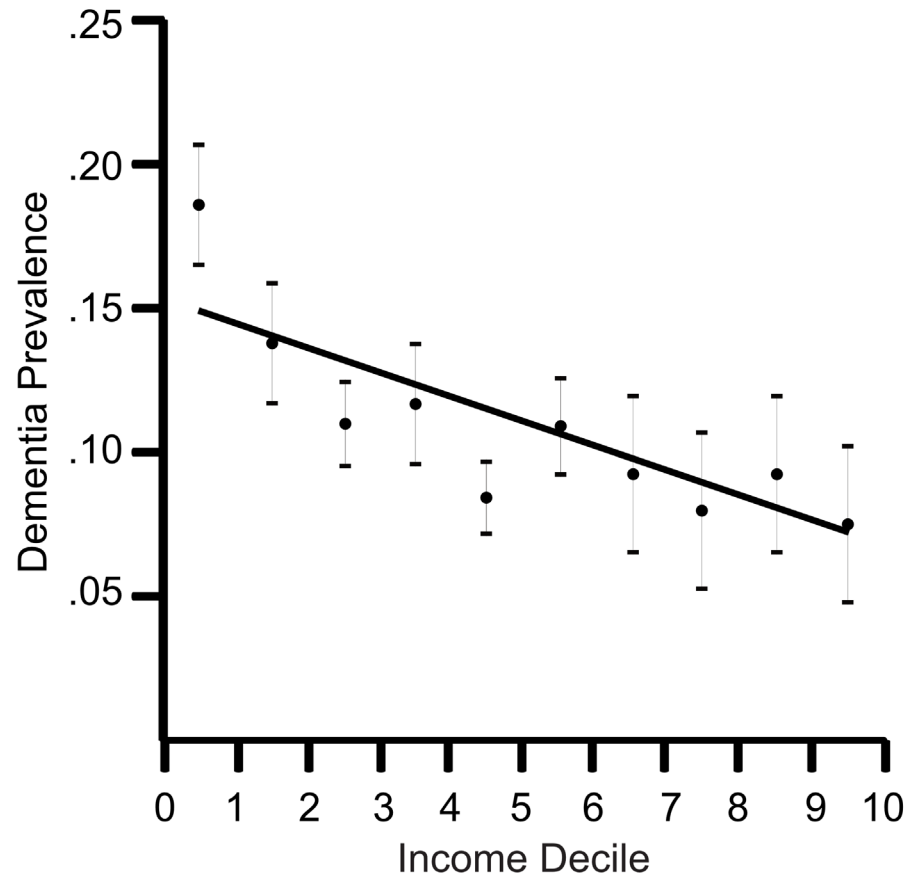
Low Education-SES 15 yr shorter lifespan ?GxE?
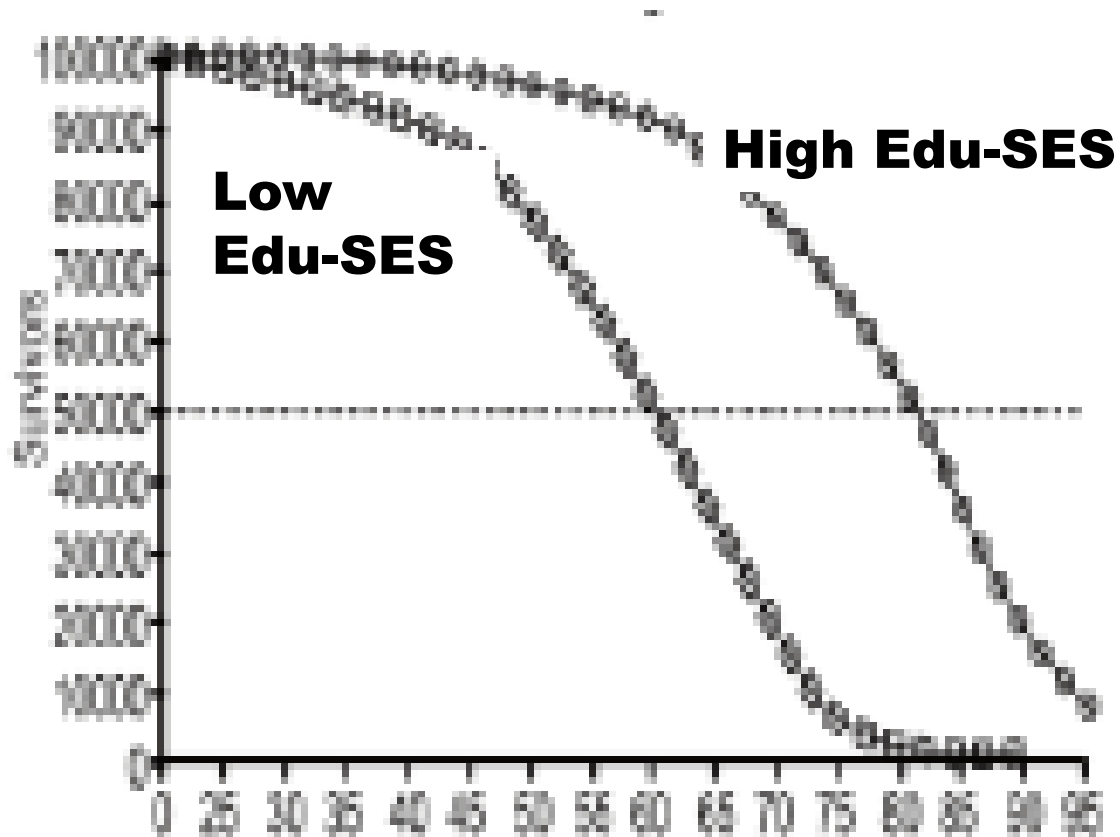
Adapted from Crimmins, *J Gerontol*, 2009

low SES: doubles dementia risk

Arakapis, *BMJ Open* 2021

Children from low SES families are born biologically disadvantaged

- Low SES: smaller cerebral cortex & hippocampus (McDermot 2019)

- Low SES: worse executive function (Ferguson 2021)

- Low SES: childhood obesity, 2-fold more

- Low SES: more adult smokers and higher air pollution

- Maternal smoking increased DNAme (Joubert 2016)

Life-course exposure to early socioeconomic environment in relation to late-life cognitive function in the Sacramento Area Latino Study on Aging.
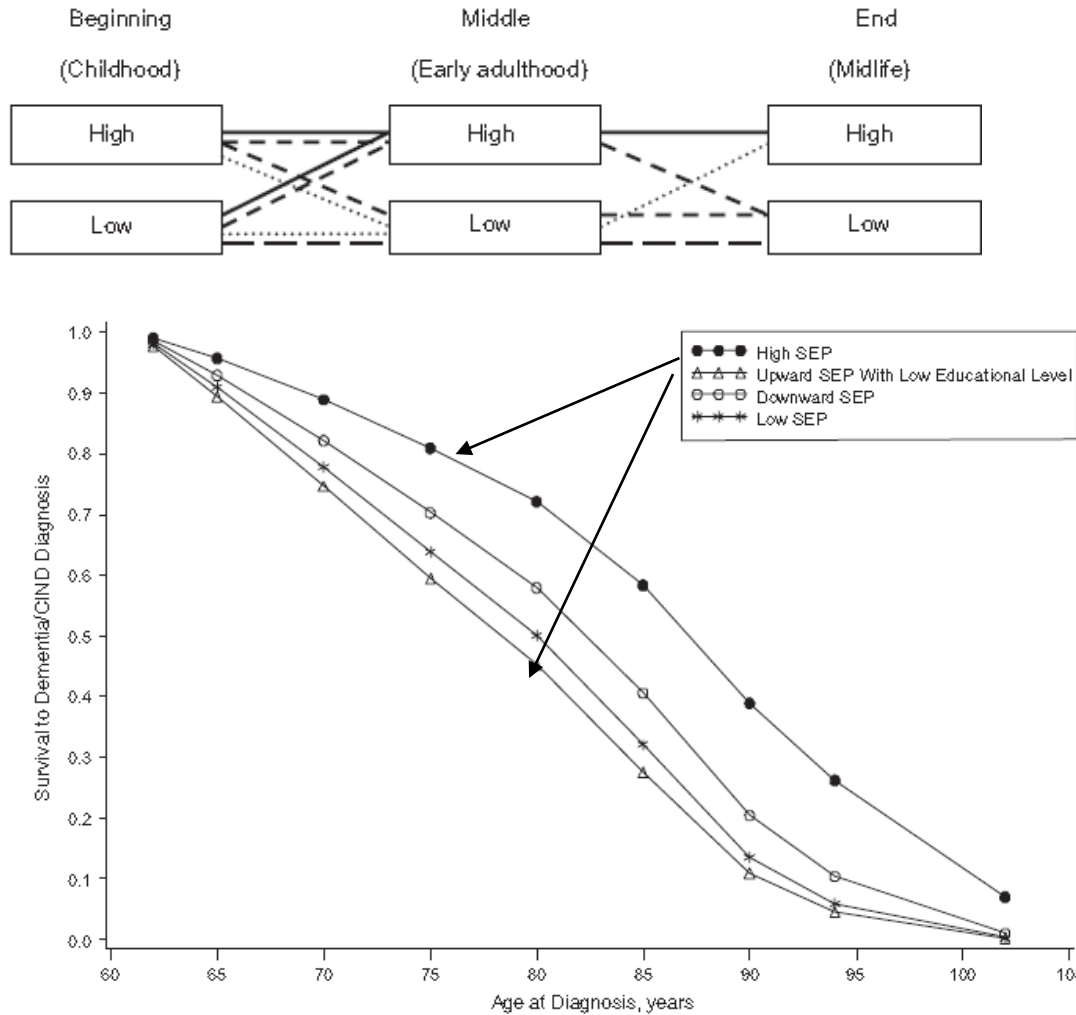
Zeki Al Hazzouri et al.
J Aging Health 2011

ure 2. Survival to dementia/cognitive impairment but not dementia (CIND) by socioeconomic position (SEP) trajectory group in the Sacramento a Latino Study on Aging, 1998–2008. Results were adjusted for age at enrollment, alcohol consumption, type 2 diabetes, and stroke.
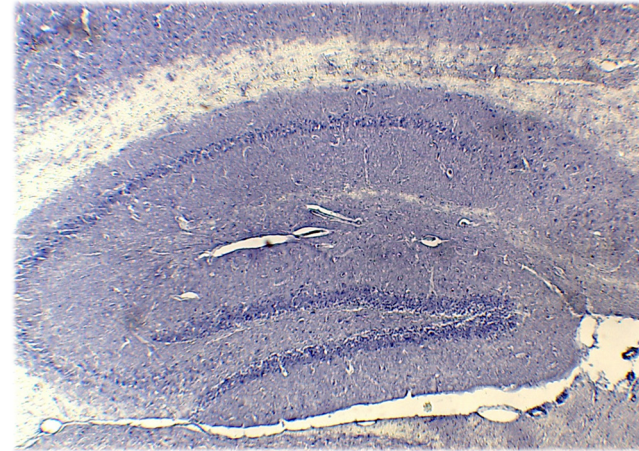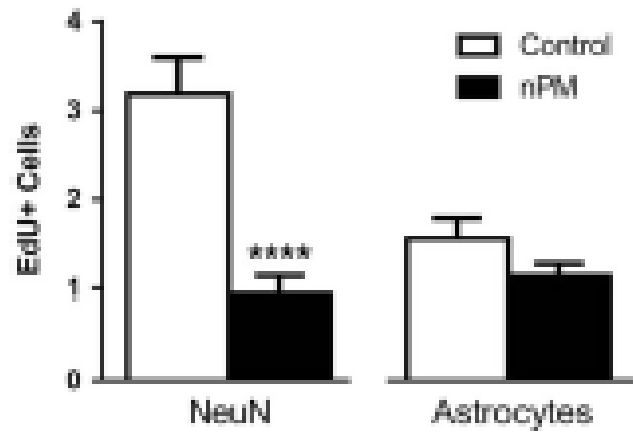
Prenatal AirPoll exposure of wildtype mice enhances Alzheimer neurodegeneration

- Impaired adult neurogenesis
- Obesity & glucose intolerance
- Lower hypothalamic peptides
- Brain microbleeds

Woodward *Trans Psych, 2018; Sci Reports 2019*

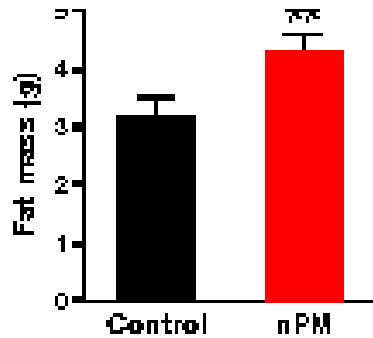# Mouse gestational AirPoll exposure (nPM) impairs adult neurogenesis in hippocampus
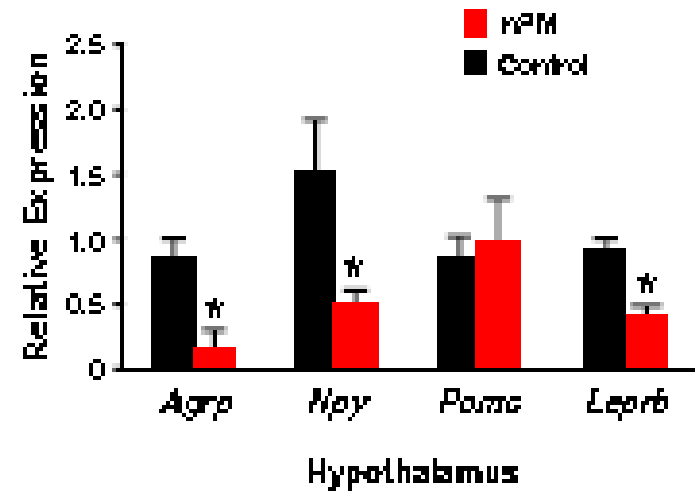

dentate gyrus

Woodward 2019, *Trans Psych*
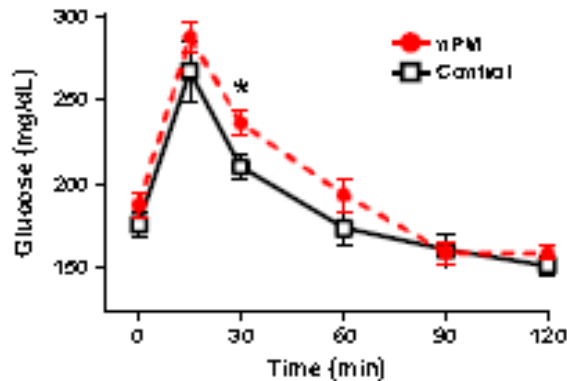
Gestational AirPoll nPM exposure

adult fat

glucose tolerance

Hypothalamic peptides

Woodward *2019*
Nature Sci Reports

Gene-Environment in SES transitions?
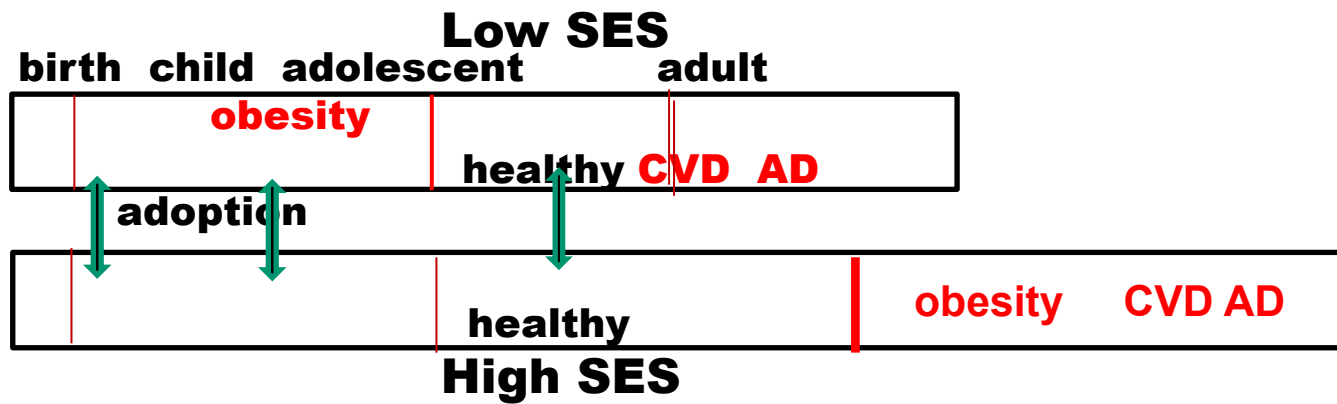
Low SES

birth child adolescent   adult

obesity

healthy CVD AD

adoption

healthy

obesity   CVD AD

High SES

The Gero-Exposome: developmental framework for GxE & gerogens of aging
Gestation thru old age

EXOGENOUS
air pollution
SES
diet
exercise
infections
toxins
TBI

ENDOGENOUS
biomes
fat deposits
hypertension
blood-lymph
nutrients lipids proteins
cells

G x E x T
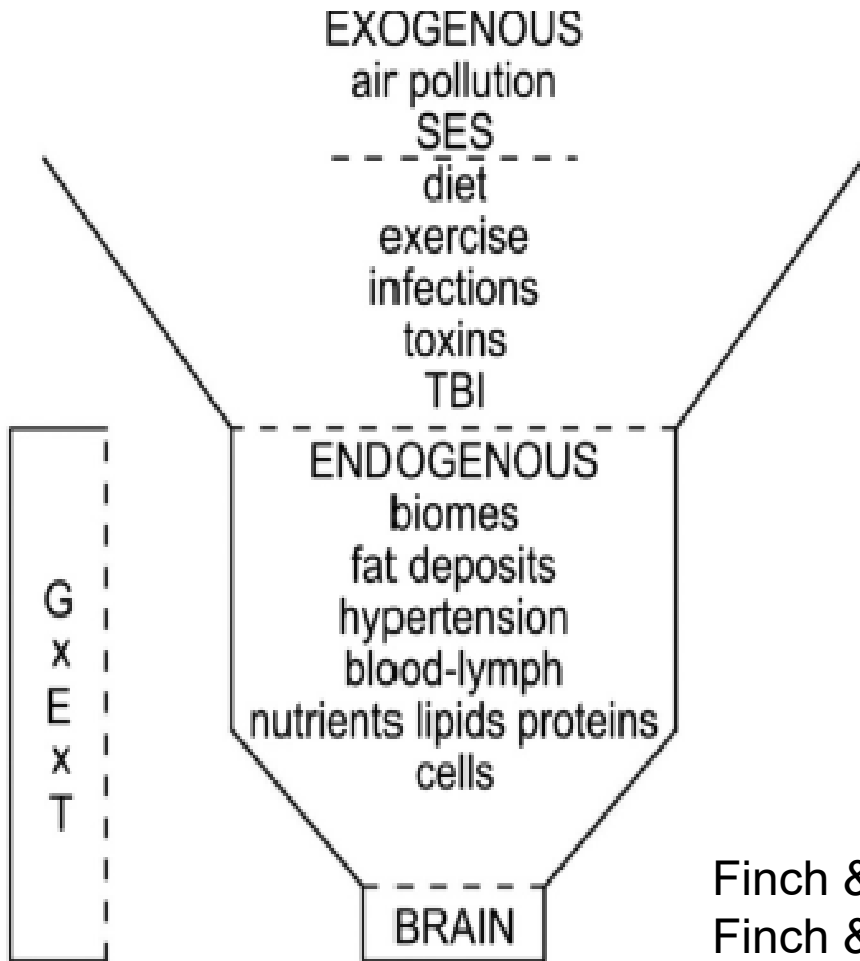
BRAIN

- **Exo**genous macrolevel

- **Exo**genous individual

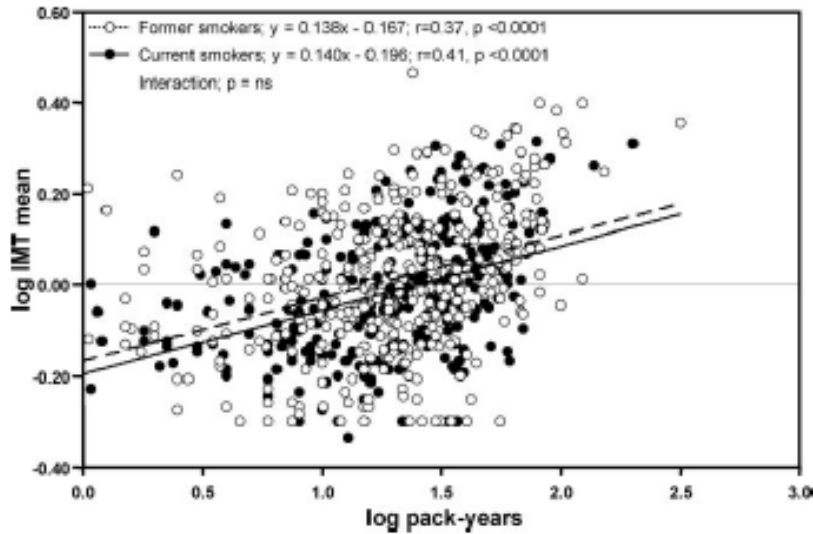
- **Endo**genous individual

Finch & Kulminski, *Alz Dement* 2019
Finch & Haghani, *J Gerontol* 2021

AirPoll from fossil fuels and tobacco accelerate aging of heart and brain

- Shorter lifespan

    atherosclerosis

     lung cancers and COPD

    Brain atrophy and Alzheimer

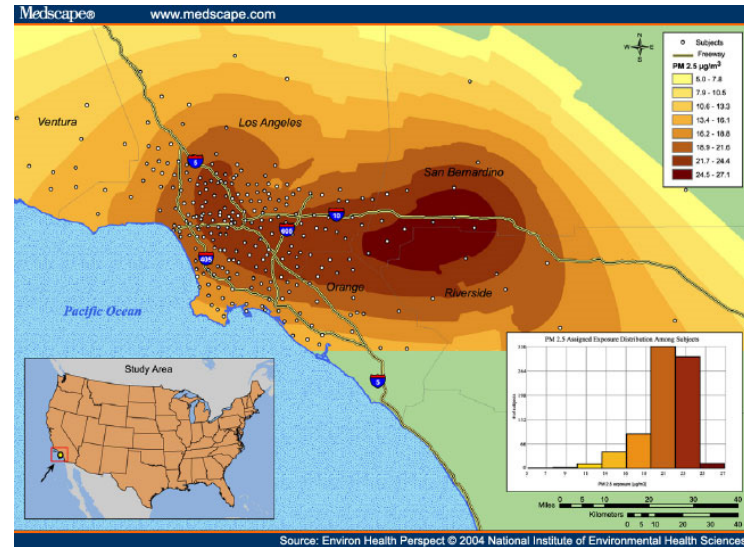- Shared mechanisms: activated monocytes, inflammation, & oxidative stress

Carotid atherosclerosis: CIMT

tobacco

PM2.5: 4% thicker/10 ug/m^3

Baldassarre 2009 *Stroke*

Kunzli 2010 *PLoS*

The future of healthy brain aging

minimize gerogens to optomize GxE

development thru aging

Gustav Vigeland, Oslo