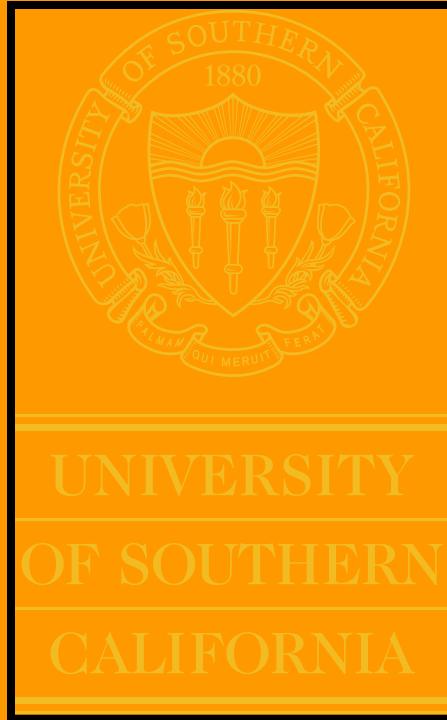


Caleb Finch, PhD



Davis School of
Gerontology,
Dornsife College

NBER Cohort Studies Meeting, UCLA

April 15, 2016

Air Pollution in Brain Development & Aging

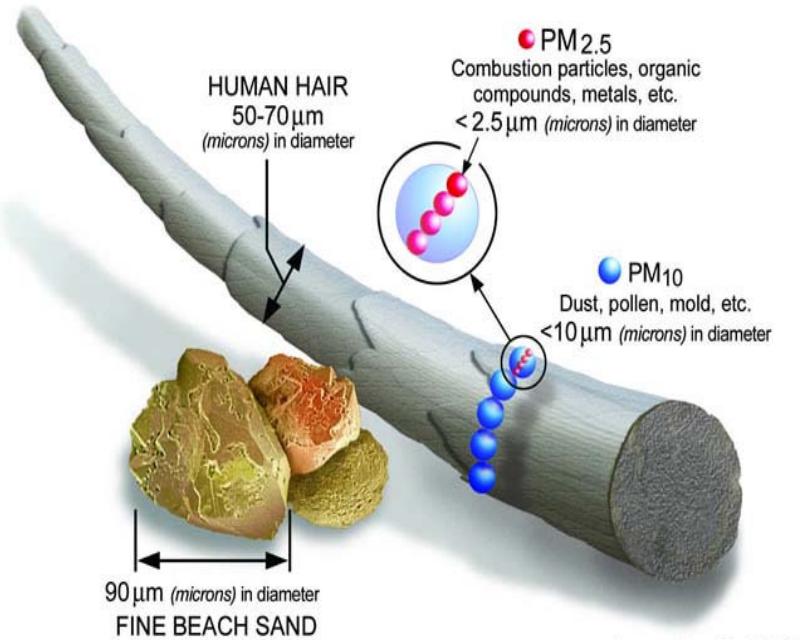


Urban Air Pollution

- **Vapor phase:** ozone; NOx & SOx; organics
- **Particulate matter (PM):**
fossil fuel combustion from engines & power plants;
biomass combustion: burning brush & garbage;
earth crust oxides of aluminum, iron, and silicon

primary emissions vs secondary aerosols
(sun-temperature driven chemistry)

Air pollution particulate matter (PM) size classes

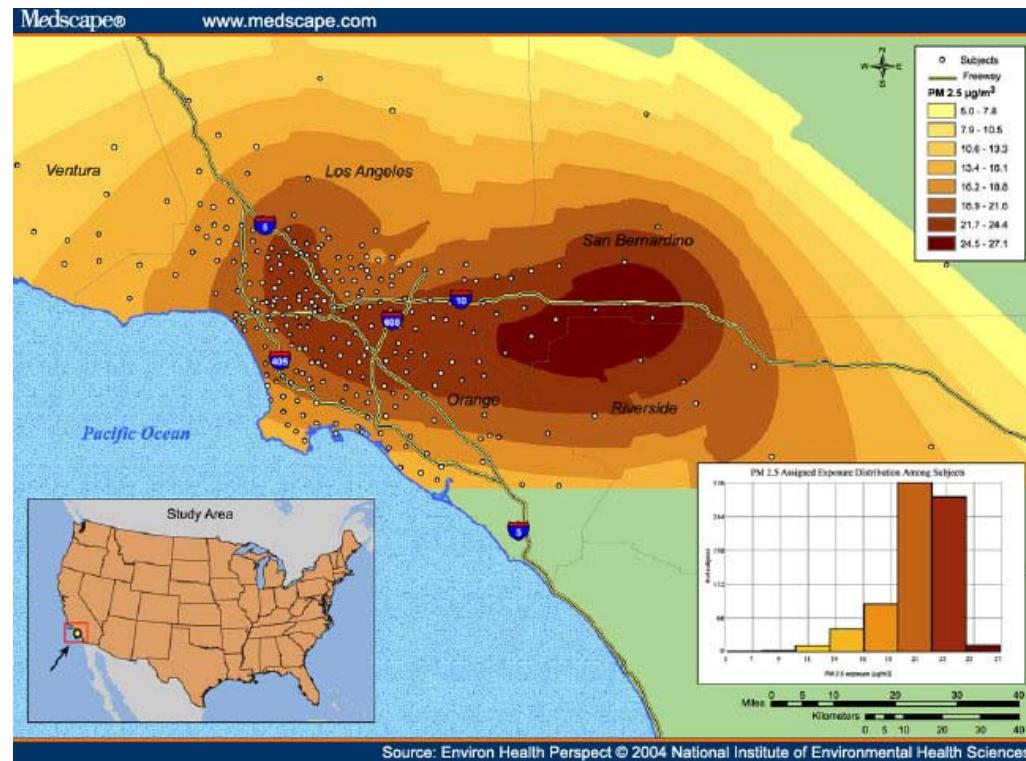


- Coarse PM: 2.5 - 10 μm
- Fine PM: $\leq 2.5 \mu\text{m}$
- Ultrafine PM: $\leq 0.25 \mu\text{m}$
- EPA regulates PM2.5
USA standard 12.5 $\mu\text{g}/\text{m}^3$
- Adult breathing volume
10 m^3 per day

Los Angeles Basin

7 year follow-up on airborne PM_{2.5} μ

carotid thickness increased 4%/10 ug/m³

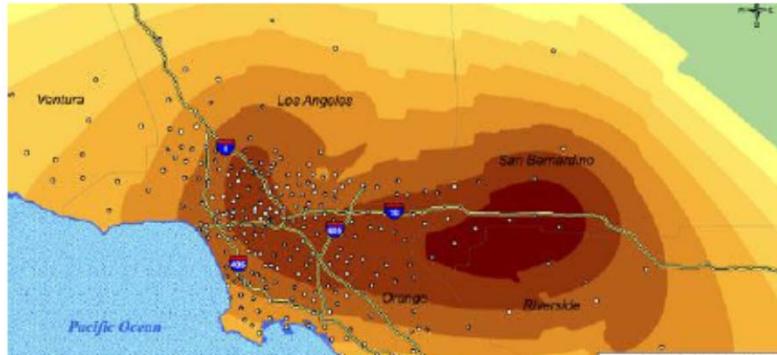


Kunzli et al, PLoS 2005, Environ Health Perspect, 2010

Shared inflammatory mechanisms in atherosclerosis and Alzheimer disease?

	atheroma	senile plaque
<i>cells</i>		
macrophages (CD68)	+++ (foam cells)	++ (microglia)
T helper (Th1)-cells	++	0
mast cells, platelets	++	0
neovascularization	++	+
<i>proteins</i>		
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

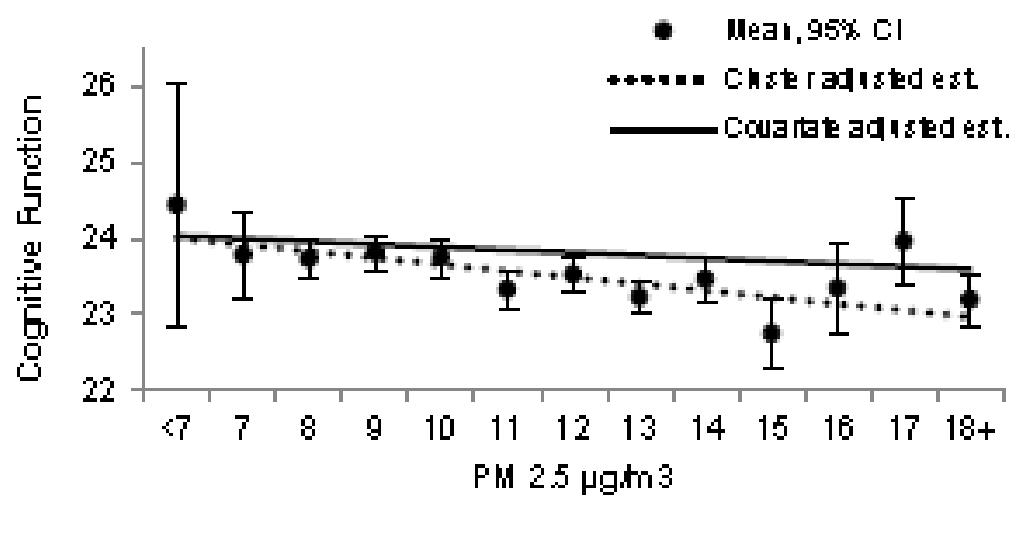


- PM_{2.5} & with lower verbal learning ($\beta=-0.32$ per $10 \mu\text{g}/\text{m}^3$ PM_{2.5}).
- NO₂ >20 ppb, lower logical memory.
- O₃ >49 ppb, lower executive function

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

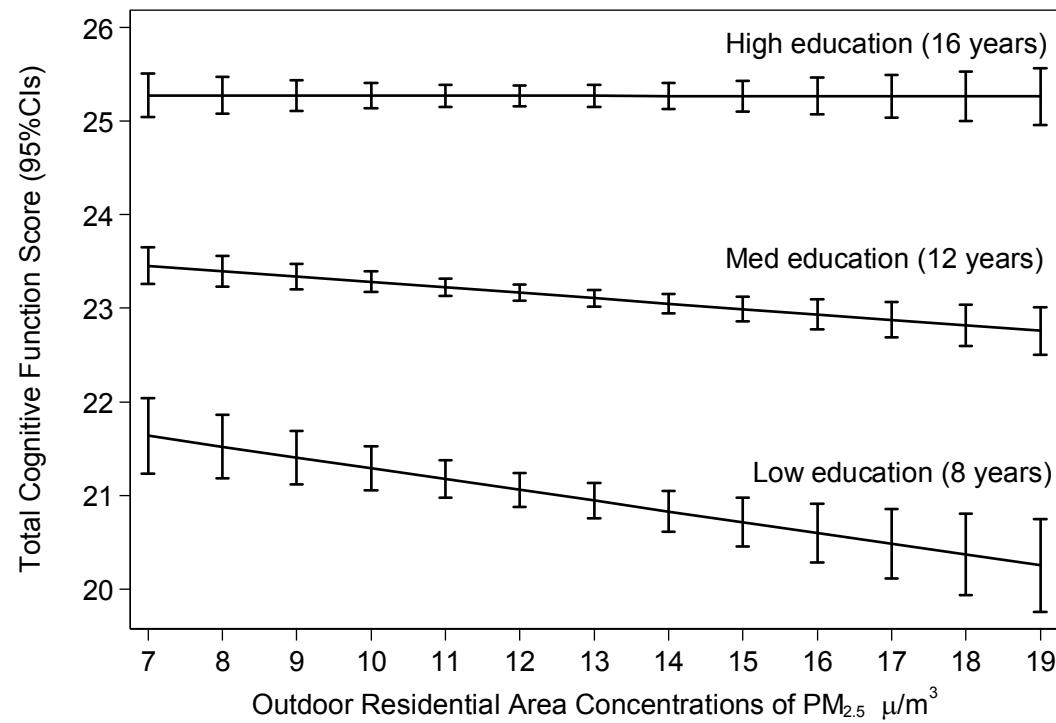
Health Retirement Survey (US Sample)

extremes of PM2.5 differ by 2 y cognitive aging



Jennifer Ailshire, Eileen Crimmins, *Am J Epidemiol*, 2014

SES and brain sensitivity to air pollution



J Ailshire & A Karraker, submitted

Chen JC et al 2015. Ambient air pollution and neurotoxicity on brain structure: Evidence from Women's Health Initiative Memory Study (WHIMS). Ann Neurol. In press. doi: 10.1002/ana.24460.



“JC” Jiu-Chiuan Chen,
Assoc Prof Preventive Medicine, USC

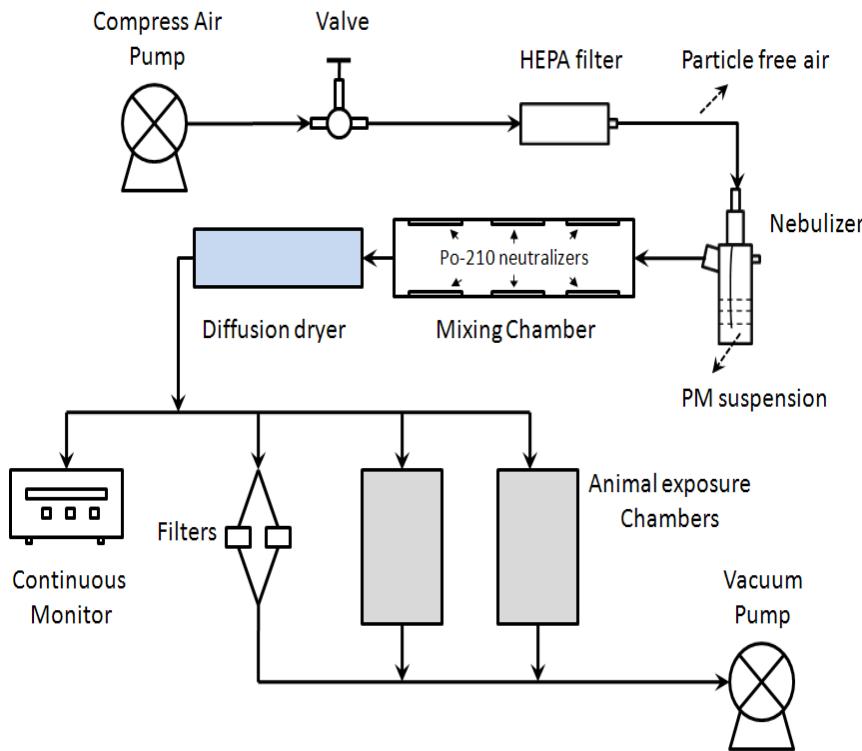
1. **Brain white matter volume loss 5 cm³ per 3.5 µg/m³ PM_{2.5}**
2. **Frontal & temporal lobes and corpus callosum.**
3. **Equivalent to 1 to 2 years of brain aging in high PM2.5.**

Ultrafine PM <0.25 μ

- ufPM have the highest activity in stimulating cell production of free radicals
- 110 Freeway corridor air is fractionated collect PM0.25
- PM0.25 is trapped on filters and eluted into water suspensions for re-aerosolization. This elution depletes black carbon and water insoluble organics
- Designated as **nPM (nano-sized PM)**

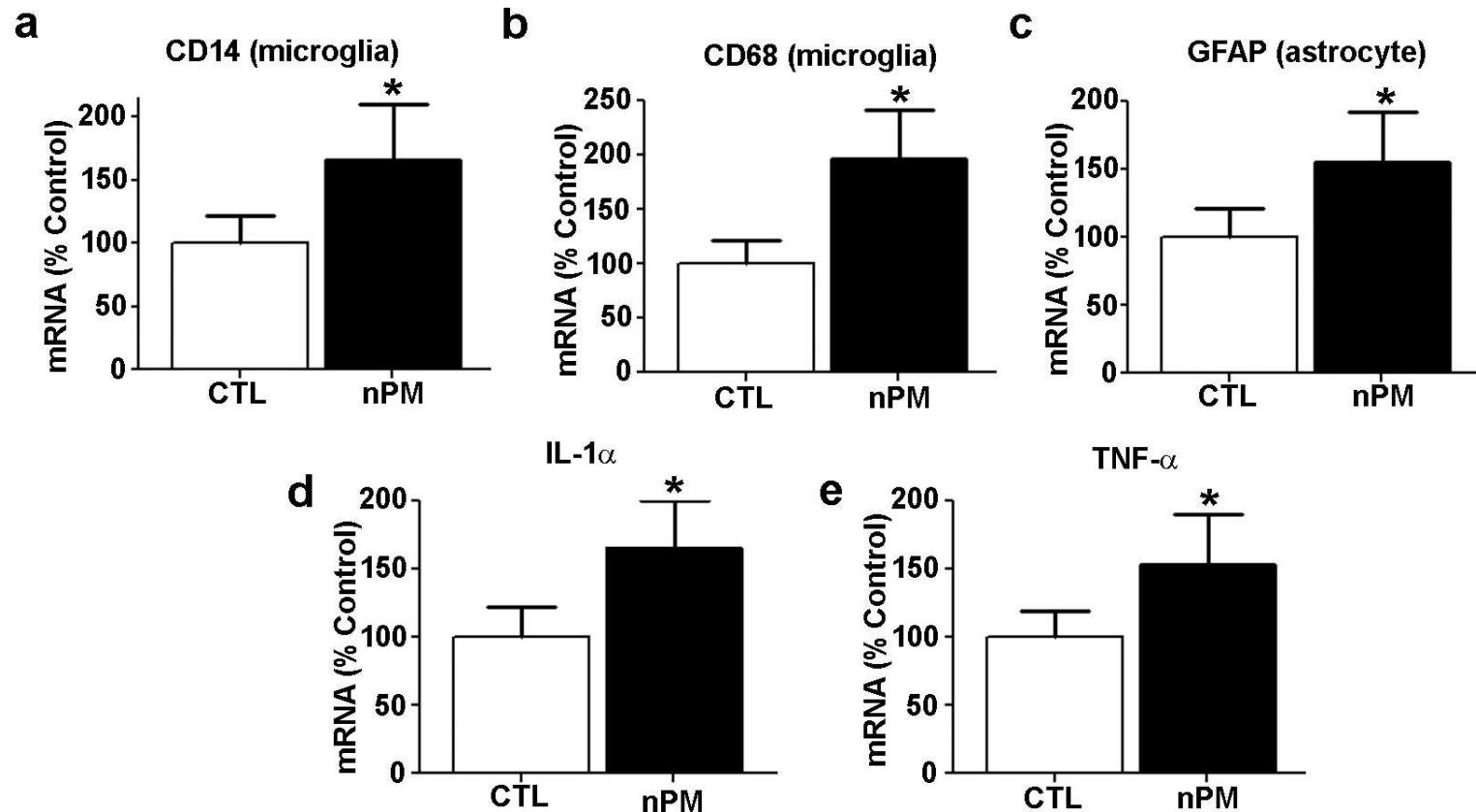
Re-aerosolized nPM for rodent exposure

150 hours during 10 weeks



(technology developed by Costas Sioutas, USC)

nPM 150 h activates brain inflammation Mouse (B6 male)

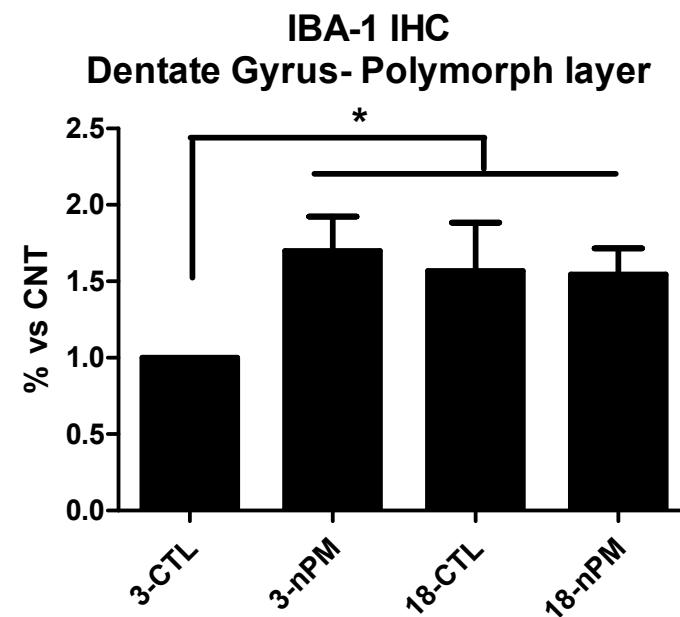
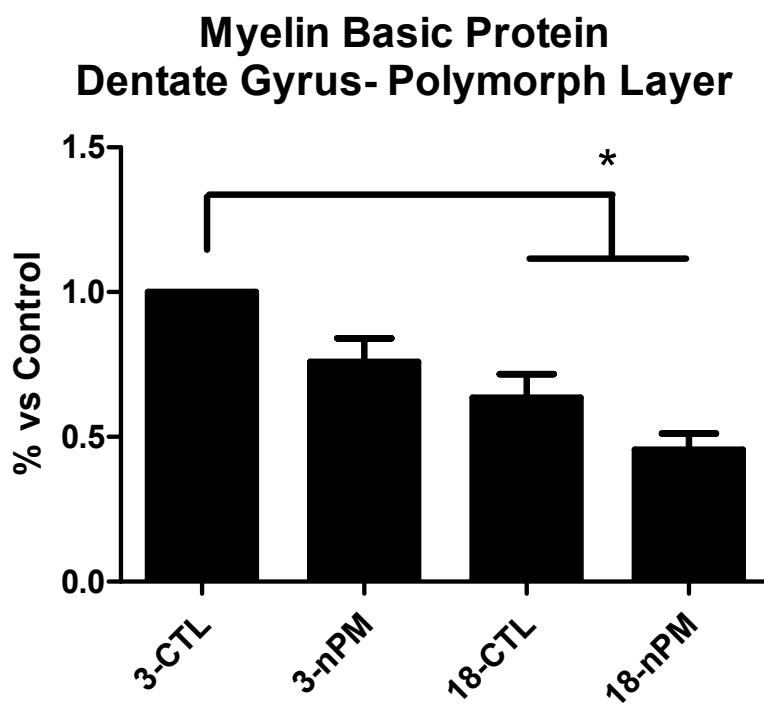


Morgan et al. *Env Health Pers* 2011

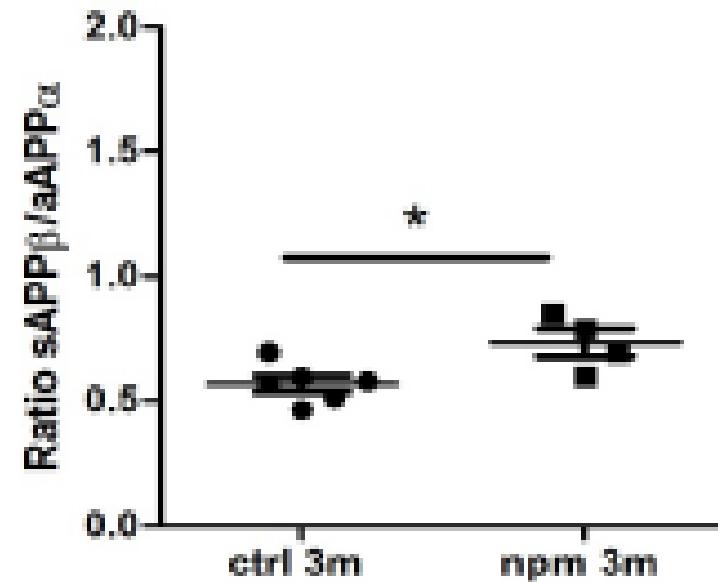
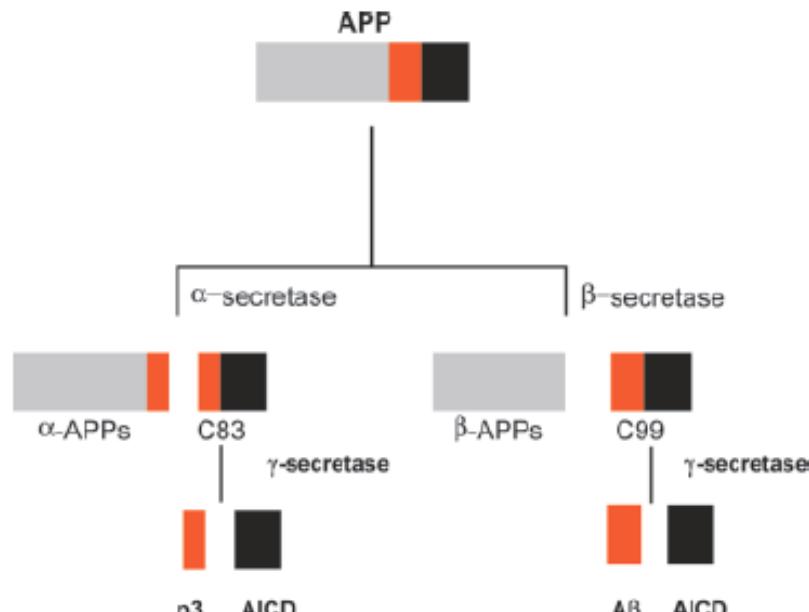
white matter loss

oligodendroglia

microglia

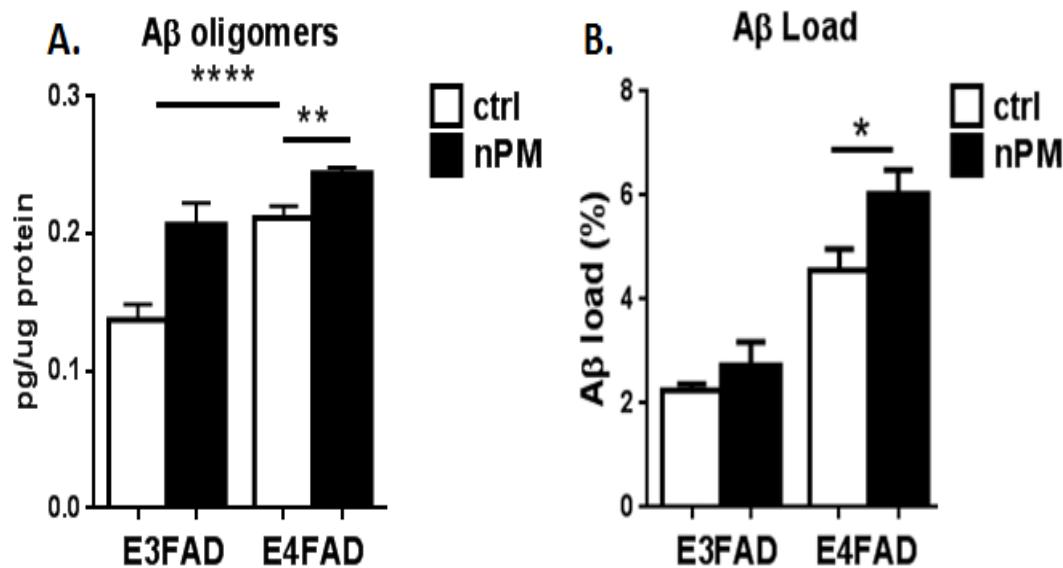


increased amyloidogenic APP processing higher β APPs: aAPPs



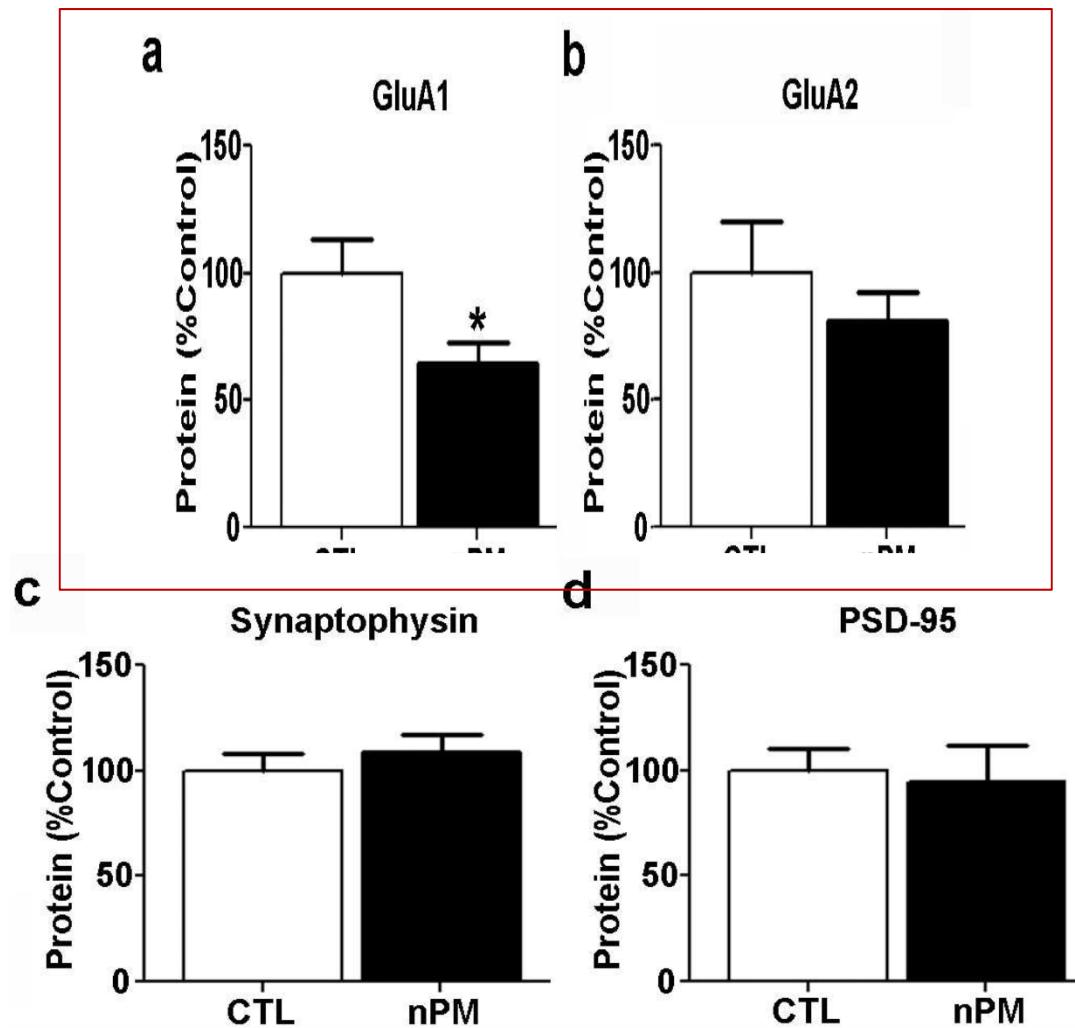
Cacciotolo M and Finch CE (unpubl)

Increased brain amyloid EFAD mice with human APOE3 & E4 E4>E3

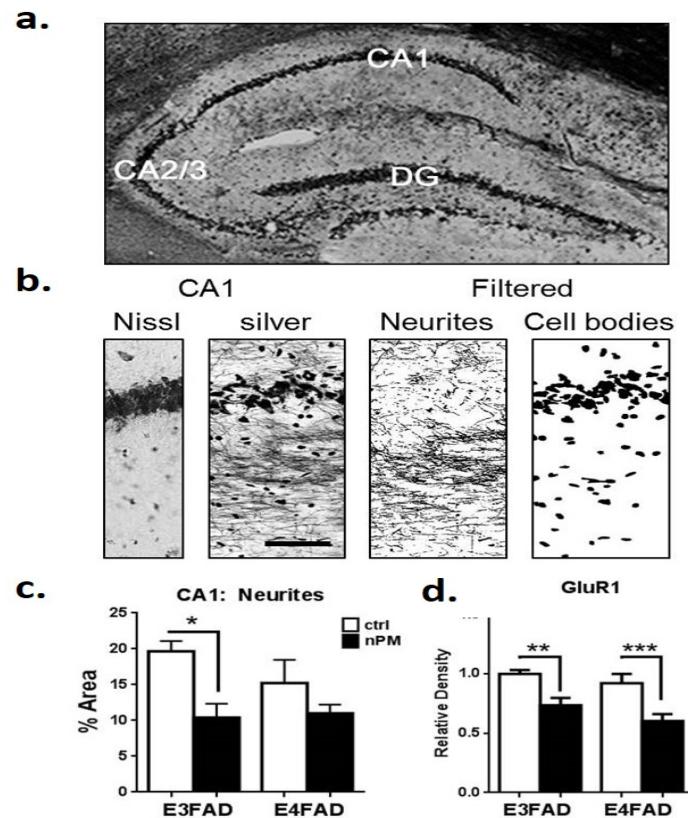


Cacciottolo et al in prep.

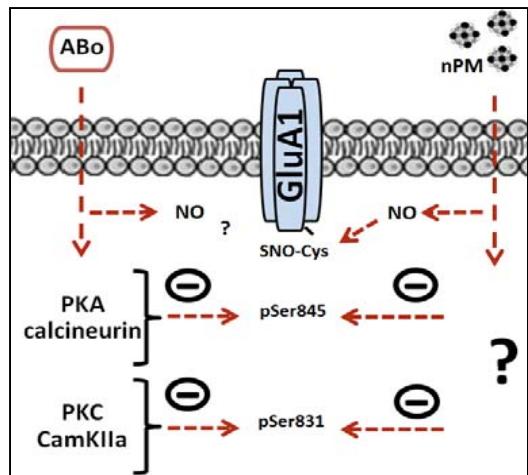
nPM 150 h alters synaptic proteins:



Decreased hippocampal neurites and glutamate receptors critical for memory



Hypothesis: GluA1 modified by synergies of Abeta-oligomers with nPM



*nPM and ABo both inhibit phosphorylation of GluA1 on **Ser831** (conductance, PKC, CamKIIa dependent) and **Ser845** (internalization, PKA, calcineurin dependent).

*nPM and ABo both induce NO;
*nPM causes S-nitrosylation

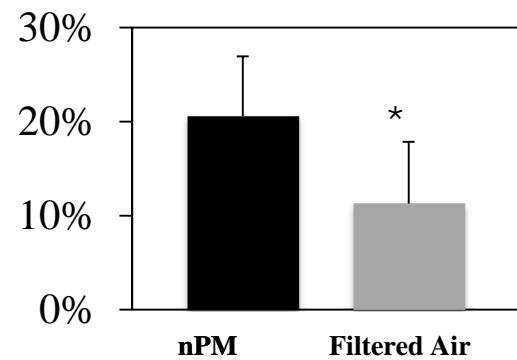
Stroke damage is exacerbated by urban air pollution in a mouse model

William Mack MD,
Assoc Prof Neurosurgery and Neuroscience
Keck School of Medicine, USC



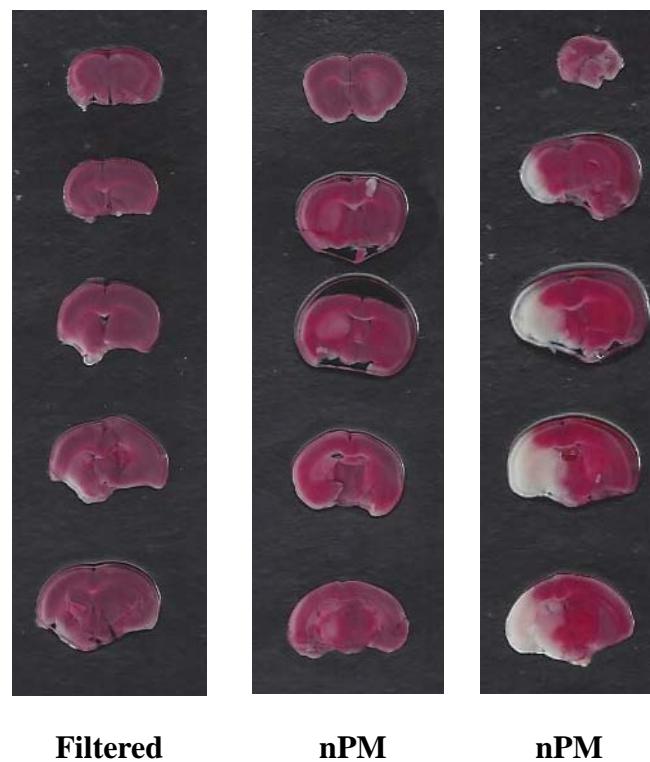
Pre-stroke exposure 3 d/week for 3 weeks (45 hr cumulative).
Ipsilateral MCA occlusion after final nPM exposure, submitted

Infarct volume

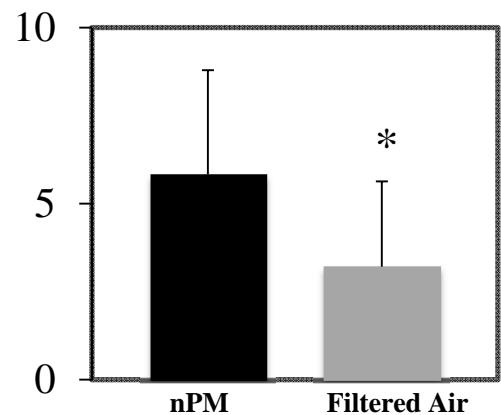


35 min

45 min



Behavioral score



developmental disorders and urban air pollution

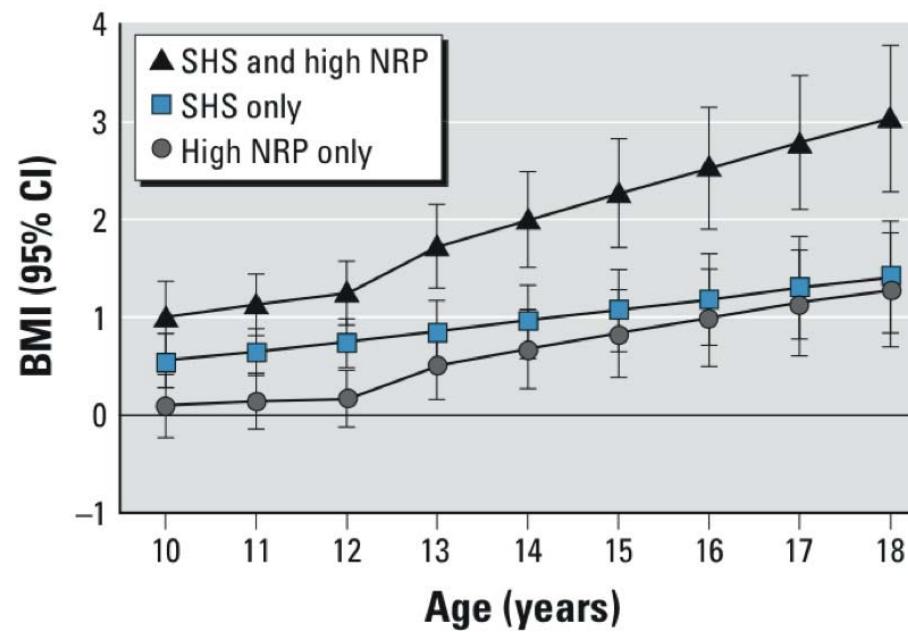
Autism spectrum disorders:
2-fold higher from
gestation-early childhood near freeway
(Heather Volk, USC)

Childhood obesity:
closeness to freeway
interacts with tobacco smoke
(Rob McConnell, USC)

Traffic-related air toxics & development in Los Angeles County

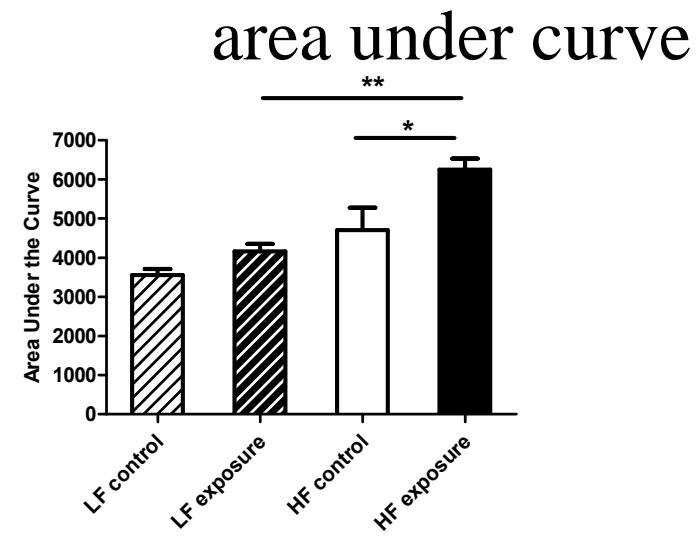
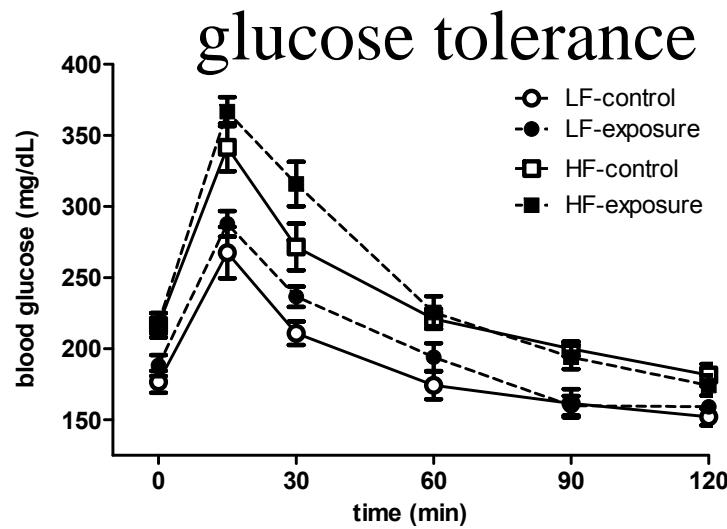
- Wilhelm et al 2012, Env Health Persp
odds of low birth weight increased 5% per quartile of PM2.5 & NOx
- Volk et al 2013, JAMA Psychiatr
autism 2-fold higher in top quartiles of PM2.5 and NOx

Body mass index (BMI) and childhood exposure to near roadway air pollution (NRP) & tobacco smoke



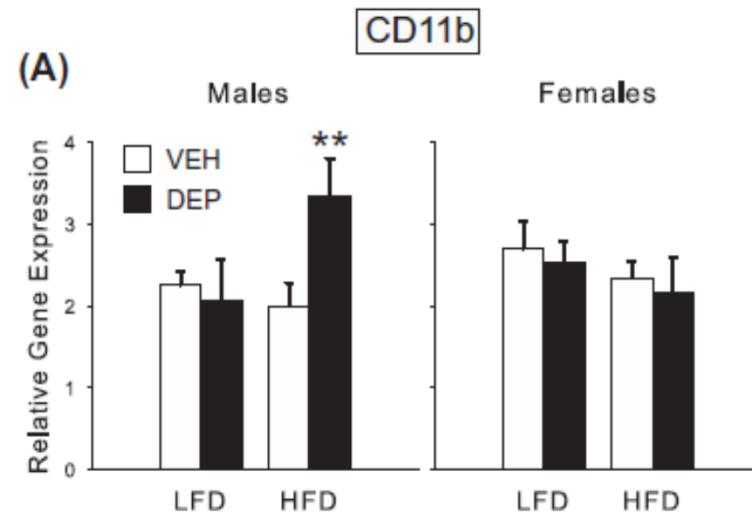
McConnell R et al, *Env Health Persp*, 2015

Prenatal exposure to nPM alters insulin sensitivity high vs low fat diet (HF vs LF)



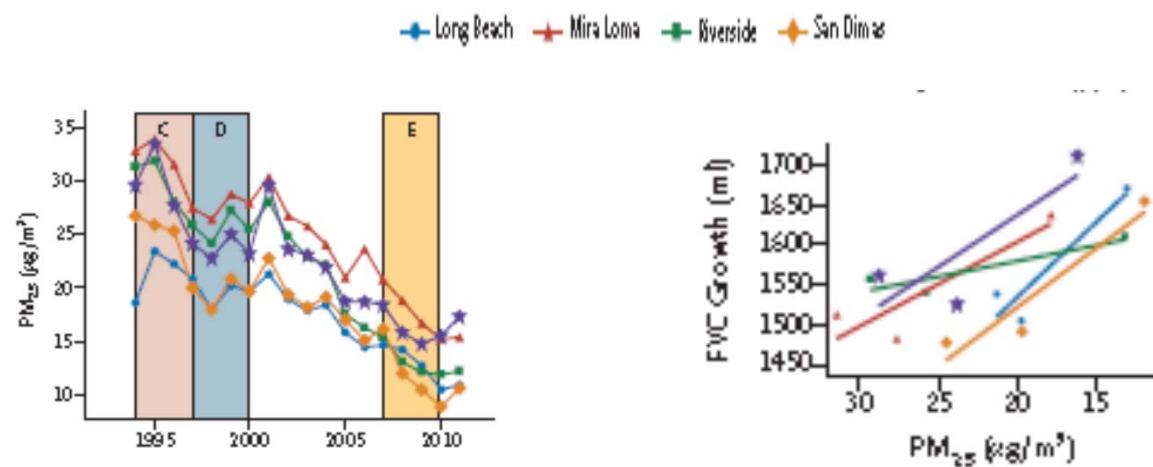
Crow, Woodward, Finch, Alleyee, in prep.

Prenatal diesel exposure alters adult brain microglia response to high fat diet with male excess



Bilbo, Duke: *Bolton Brain, Behav, Immune* 2014

Improving LA Air Quality and Lung Development in Children since 1995



USC Childrens Health Study, Gauderman J et al. *New Engl J Med*, March 2015