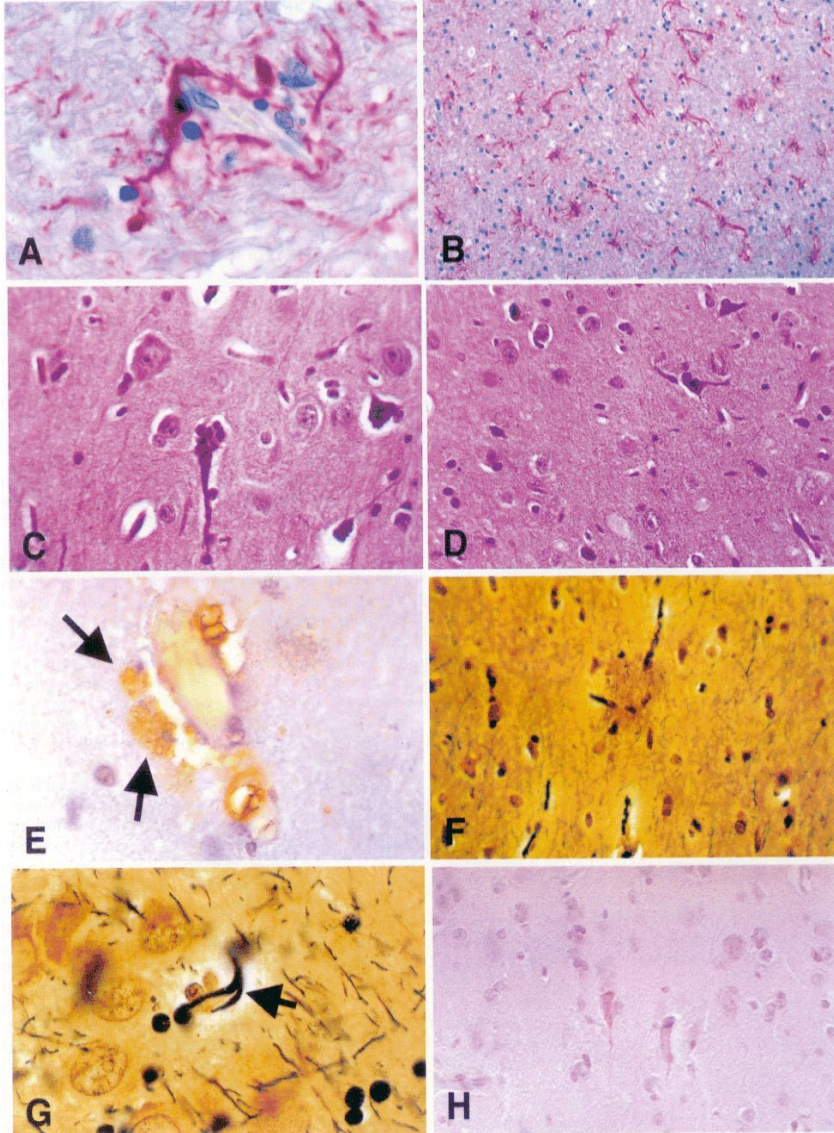# Air Pollution and the Brain
Where are we and where are we going?

Marc G. Weisskopf, PhD, ScD

Air Pollution and Neuropathology

Calderon-Garciduenas et al., Toxicol. Pathol., 2002

Dogs in Mexico City

- Reactive Astrocytes (A, B)
- Degenerating neurons (C, D)
- ApoeE (E)
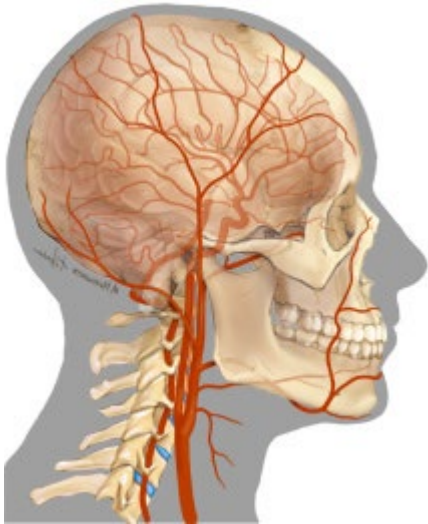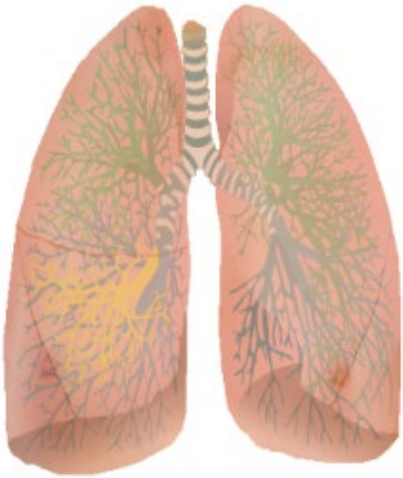- Plaques and Neurofibrillary tangles (F, G)
- Tau positive neurons (H)

→ Neurodegeneration?

Cerebrovascular Link

- Air pollution has established consequences for cardiovascular disease

    - Vascular risk factors are often associated with cognition, dementia

    - Subclinical cerebrovascular disease is implicated in dementia

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Air Pollutants and the Brain
Another Exposure Route?

http://med.uc.edu/neurosurgery/divisions/
cerebrovascular.aspx
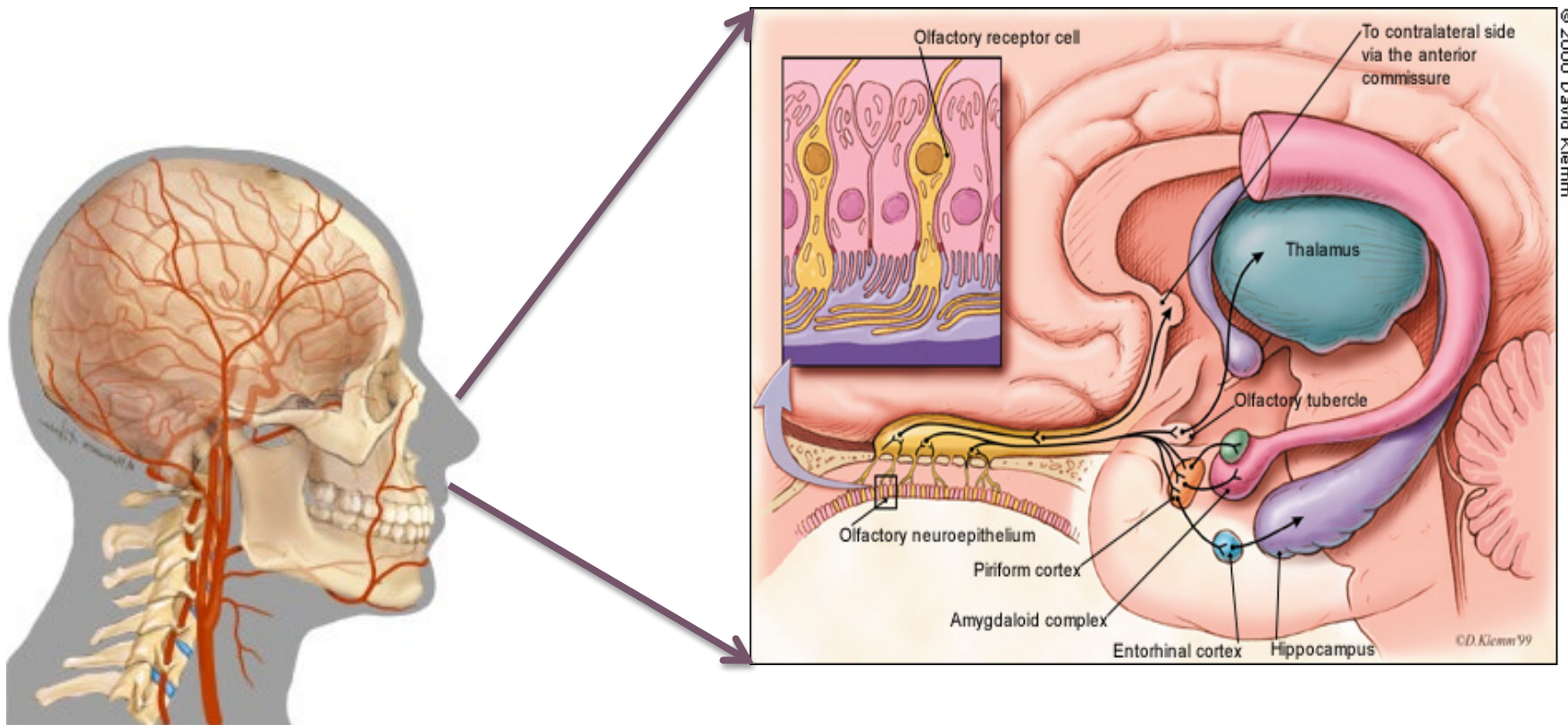
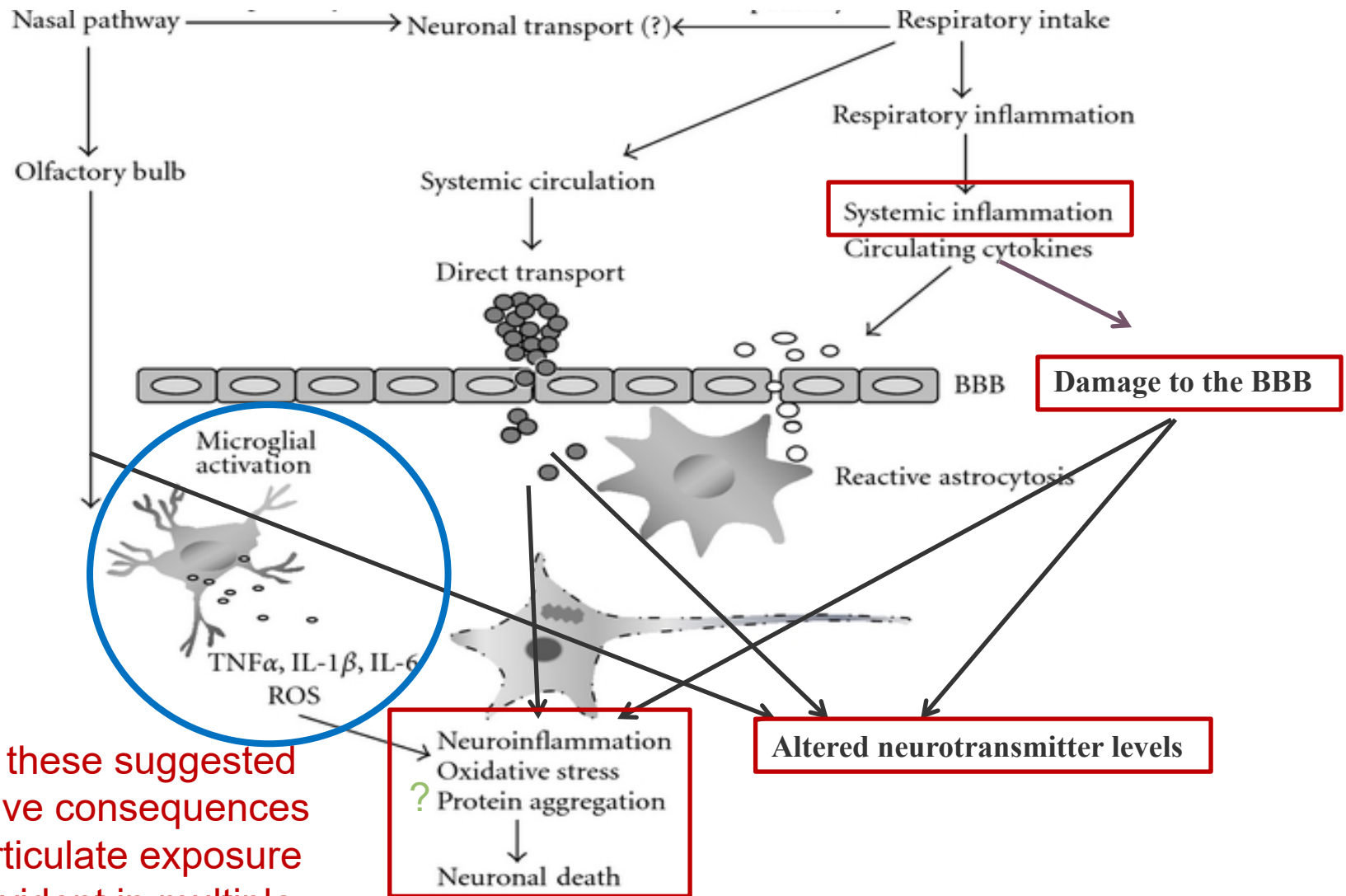Animals: *Oberdorster et al., Inhal Toxicol, 2004*

Air Pollutants and olfaction
Ajmani et al., Environ Health Perspect., 2016

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Particulate matter exposure appears to lead to…

Nasal pathway ——————→ Neuronal transport (?)←———————— Respiratory intake

Olfactory bulb

Respiratory inflammation

Systemic circulation

Systemic inflammation
Circulating cytokines

Direct transport

BBB

Damage to the BBB

Microglial activation

Reactive astrocytosis

TNFα, IL-1β, IL-6
ROS

Neuroinflammation
Oxidative stress
? Protein aggregation

Neuronal death

Altered neurotransmitter levels

All of these suggested negative consequences of particulate exposure are evident in multiple neurodegenerative and psychiatric diseases

Adapted from: Genc et al. 2012 J Toxicol
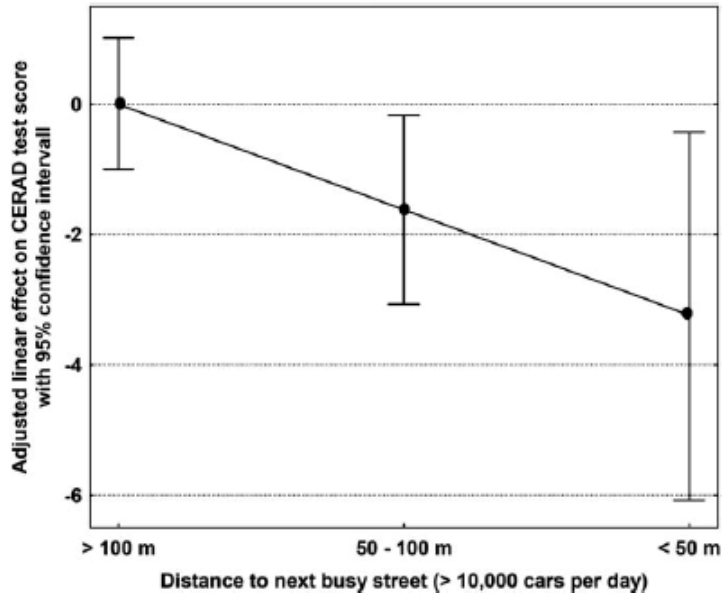
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Where are we with the Epidemiology?

Air Pollution-Cognitive Function

Adjusted linear effect on CERAD test score with 95% confidence interval

Distance to next busy street (> 10,000 cars per day): > 100 m, 50 - 100 m, < 50 m

Ranft et al., Env Research, 2009
Women, 68-79, in Germany

→Lower CERAD score with less residential distance to road

Chen and Schwartz, Neurotoxicology, 2009
US adults, 20-59

→ Worse executive function/short-term memory with higher county annual average ozone

Crude and adjusted difference in neurobehavioral test performance associated with 1-year average ozone exposure.

	Neurobehavioral test performance			
	SRTT	SDST	SDLT-trials to criterion	SDLT-total score
	Regression coefficient β^a (95% confidence interval)			
Crude	1.15 (−3.69, 5.99)	0.15 (0.04, 0.26)	0.27 (0.07, 0.47)	0.59 (0.14, 1.05)
Model-I[b]	0.45 (−4.20, 5.10)	0.16 (0.06, 0.25)	0.32 (0.14, 0.51)	0.73 (0.31, 1.15)
Model-II[c]	−0.01 (−4.74, 4.73)	0.14 (0.05, 0.23)	0.23 (0.05, 0.41)	0.53 (0.13, 0.93)
Model-III[d]	−0.92 (−6.45, 4.61)	0.11 (0.00, 0.22)	0.26 (0.03, 0.48)	0.52 (0.03, 1.01)
Model-IV[e]	–	0.12 (0.01, 0.23)	0.28 (0.06, 0.51)	0.57 (0.08, 1.06)

Per 10ppb ozone: ~3.5-5.3 years of age
No association with PM_{10}
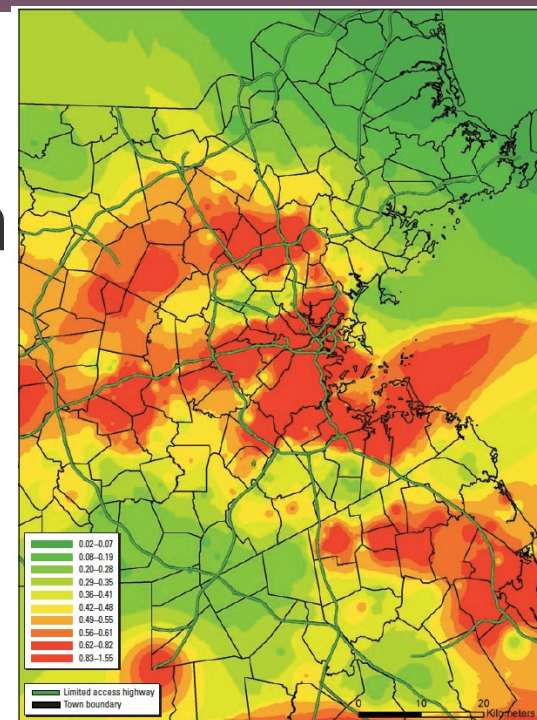
Black Carbon and Cognitive Function
Power et al., Environ. Health Perspect., 2011

- Cognitive testing among Normative Aging Study participants

→ Worse MMSE/global cognition with higher residential black carbon

Figure 1. Predicted 1-year average BC exposures (µg/m³) for the greater Boston area in 1995.

1995 average BC; Gryparis et al., 2007

Table 2. Adjusted associations for a doubling in BC concentration on the natural scale and cognitive test score(s).

	Effect per doubling in BC concentration (95% CI)		
Analysis	Model 1: age adjusted	Model 2: age and education adjusted	Model 3: multivariable adjusted[a]
Low MMSE score OR	1.4 (1.1 to 1.6)	1.3 (1.0 to 1.5)	1.3 (1.1 to 1.6)
Global analysis estimate	−0.073 (−0.122 to −0.023)	−0.052 (−0.100 to −0.004)	−0.054 (−0.103 to −0.006)

[a]Adjusted for age, education, first language, computer experience, physical activity, alcohol consumption, diabetes, dark fish consumption, percentage of residential census tract that is nonwhite, percentage of residential census tract adults with a college degree, indicator for first cognitive assessment, and indicator for part-time resident.
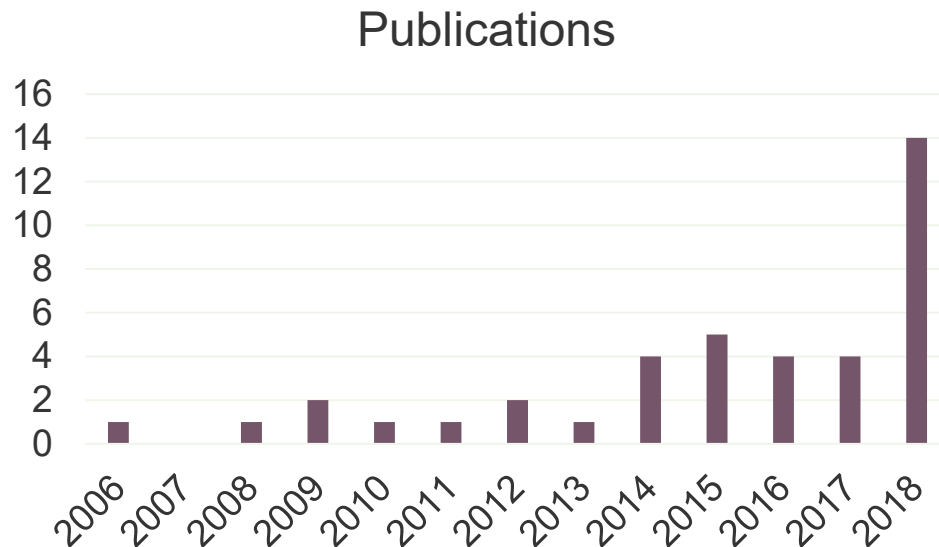
Where are we with the Epidemiology?
Air Pollution-Cognitive Function/Dementia
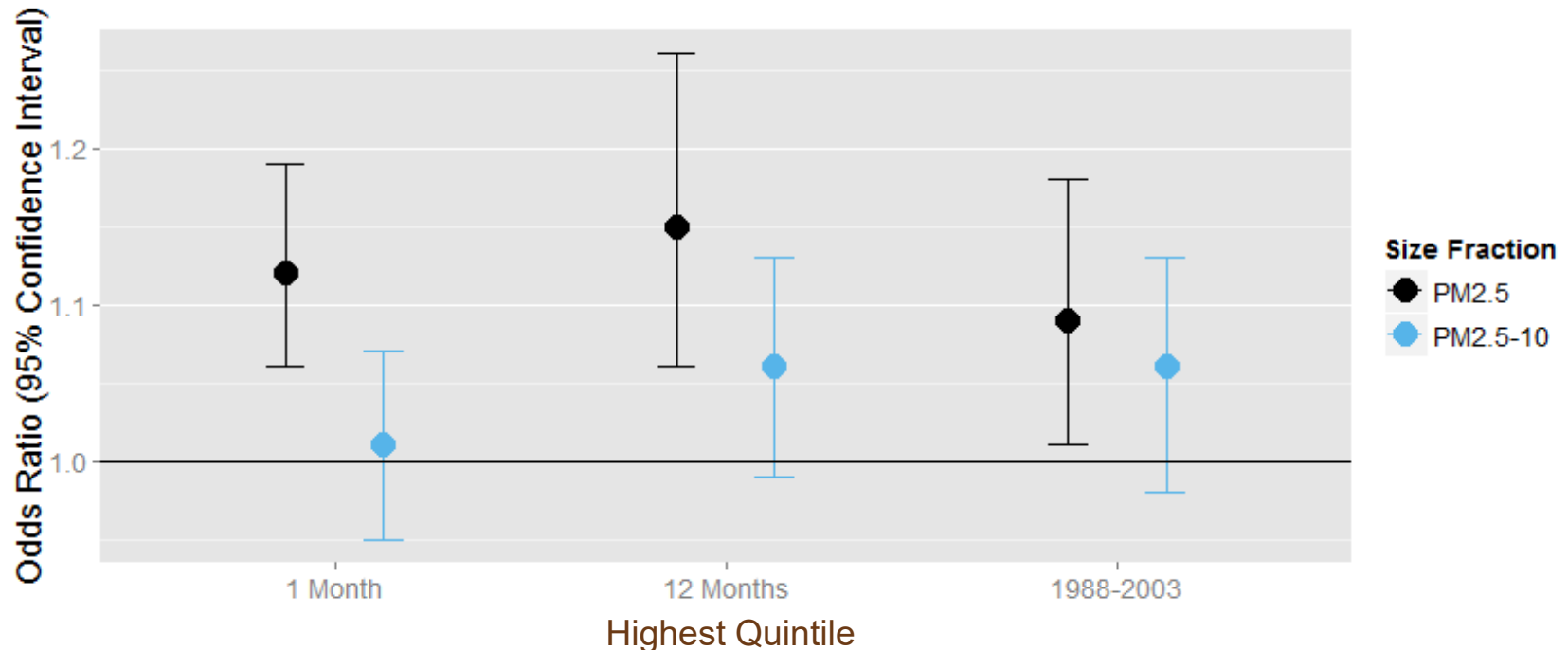
Several reviews

- Power et al., Neurotoxicology, 2016
- Kilian and Kitazawa, Biomedical Journal, 2018
- Bejot et al., Int J Stroke, 2018
- Dimakakou et al., Int J Environ Res Public Health, 2018
- Russ et al., Curr Opin Psychiatry, 2019

Publications

Air Pollution and Anxiety
Power et al., BMJ, 2015

- Study Sample: Up to 71,271 Nurses Health Study participants residing across the continental U.S.

- Elevated anxiety symptoms (Crown Crisp Index)

Where are we with the Epidemiology?
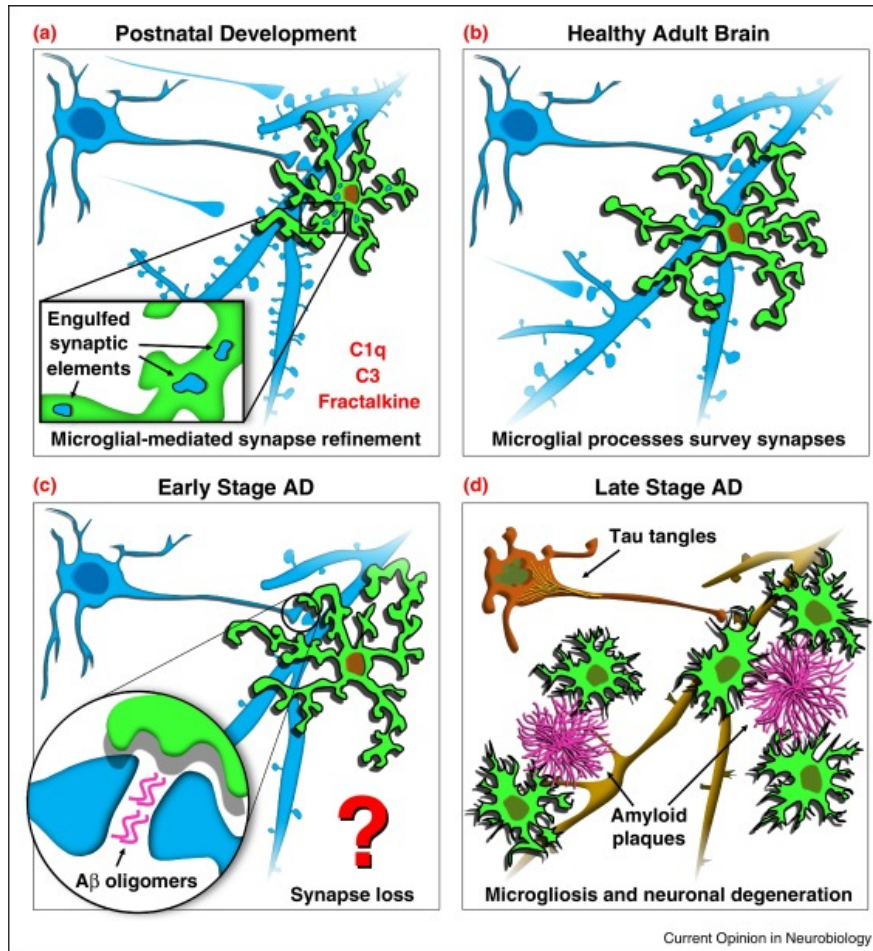## Air Pollution-Depression/Anxiety studies

Several reviews
- Gladka et al., Int J Occup Med Environ Health, 2018
- Zhao et al., Environ Res, 2018
- Buoli et al., Environ Int, 2018
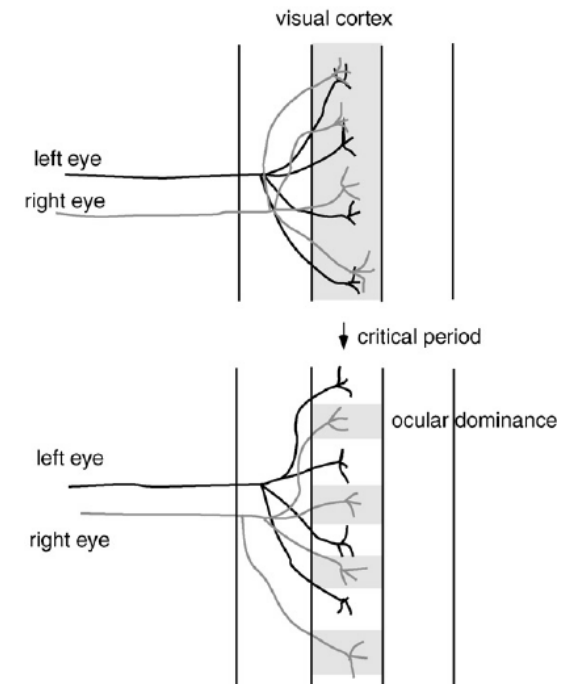- Dickerson et al., Curr Env Health Rpts, in press

Publications

Microglia and the Brain

Hong et al., Curr Opinion Neurobiol., 2016
(Beth Stevens, Harvard)

Immune molecules play critical role in brain development
(Lenz et al., Front Immunol., 2018)

Microglia are central to synaptic pruning

Adjusted OR of ASD by IQR NO$_2$
Mutually Adjusted Models

Raz et al., Am J Epidemiol, 2018a

Live birth bias?
Raz et al., Am J Epidemiol., 2018b
Leung et al., submitted
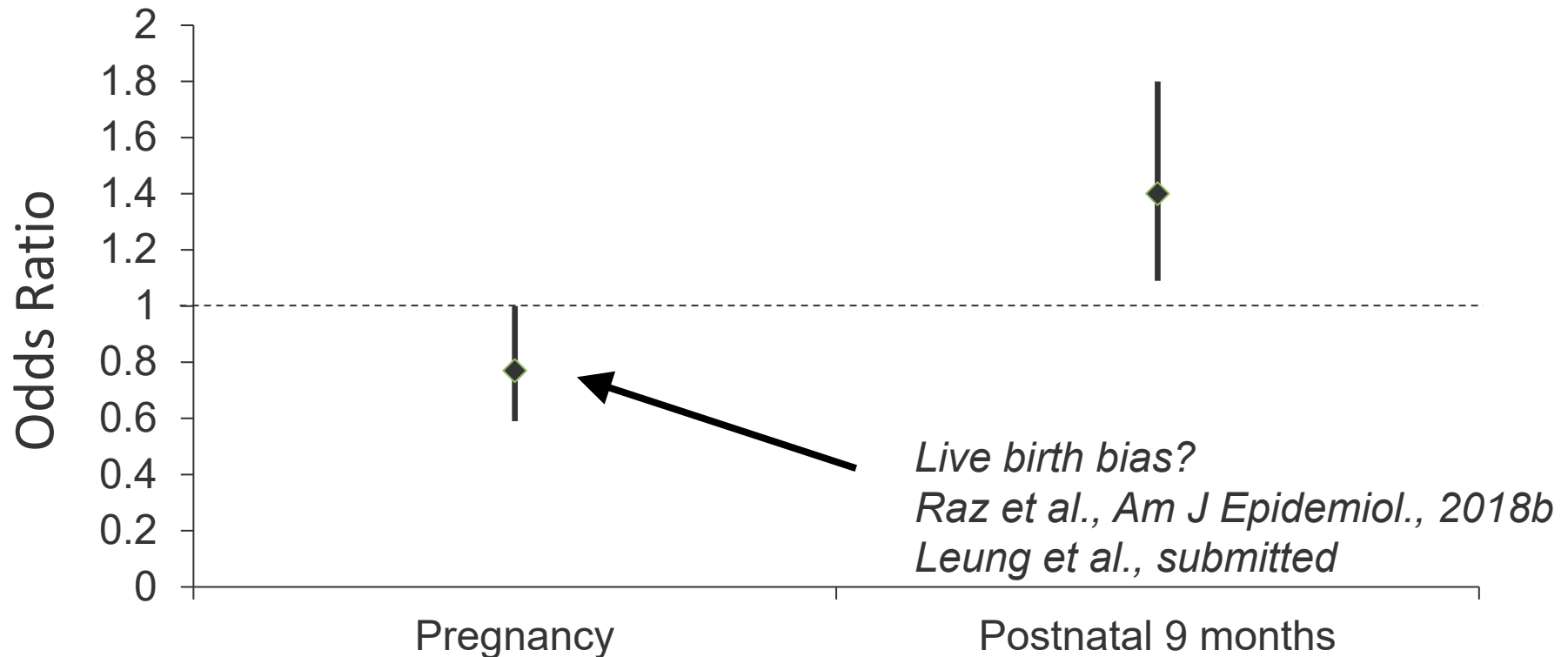
Tel Aviv area, Israel
2,098 ASD cases, 54,191 controls
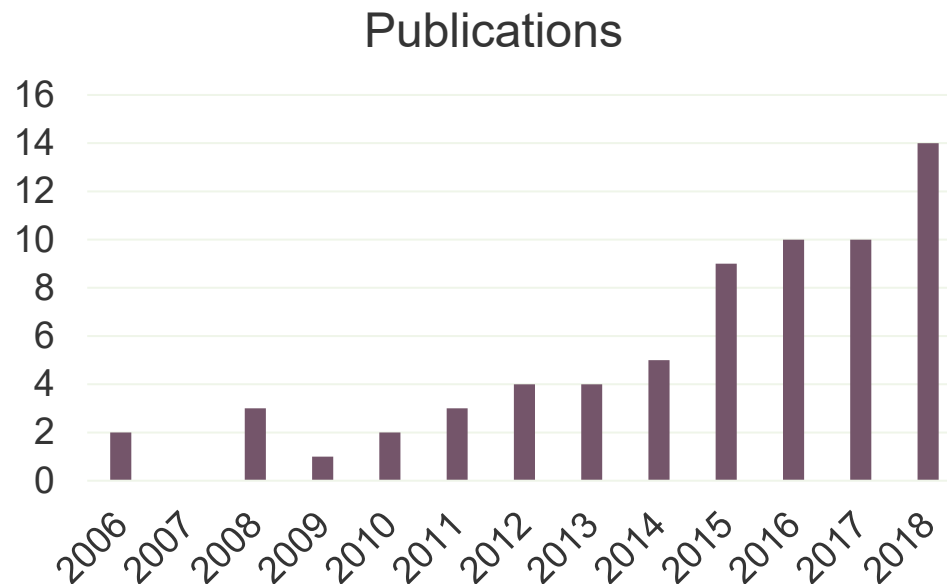
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Where are we with the Epidemiology?
Air Pollution-Neurodevelopment

Several reviews

- Weisskopf et al., Curr Environ Health Rpts, 2015
- Suadez-Gonzalez et al., Endocrinology, 2015
- Xu et al., Front Pub Health, 2016
- Lam et al., Plos ONE, 2016

Publications

Where are we Going?
Epidemiology

Issues

- Potential confounding, esp. SES
  - Negative control exposures *(Lipsitch et al., Epidemiology, 2010; Weisskopf et al., Epidemiology, 2016)*
  - Cognition: decline less susceptible than cross sectional state
  - Exposure metric choice *(Weisskopf and Webster, Epidemiology, 2017)*

- Selection biases
  - When the exposure of interest affects who is in your study, bias can result—can get paradoxical results! *(Weisskopf et al., Environ Health Perspect, 2015; Raz et al., Am J Epidemiol, 2018b)*

- Dose-response relations
  - Mostly linear assumption

- Dementia is a common outcome!

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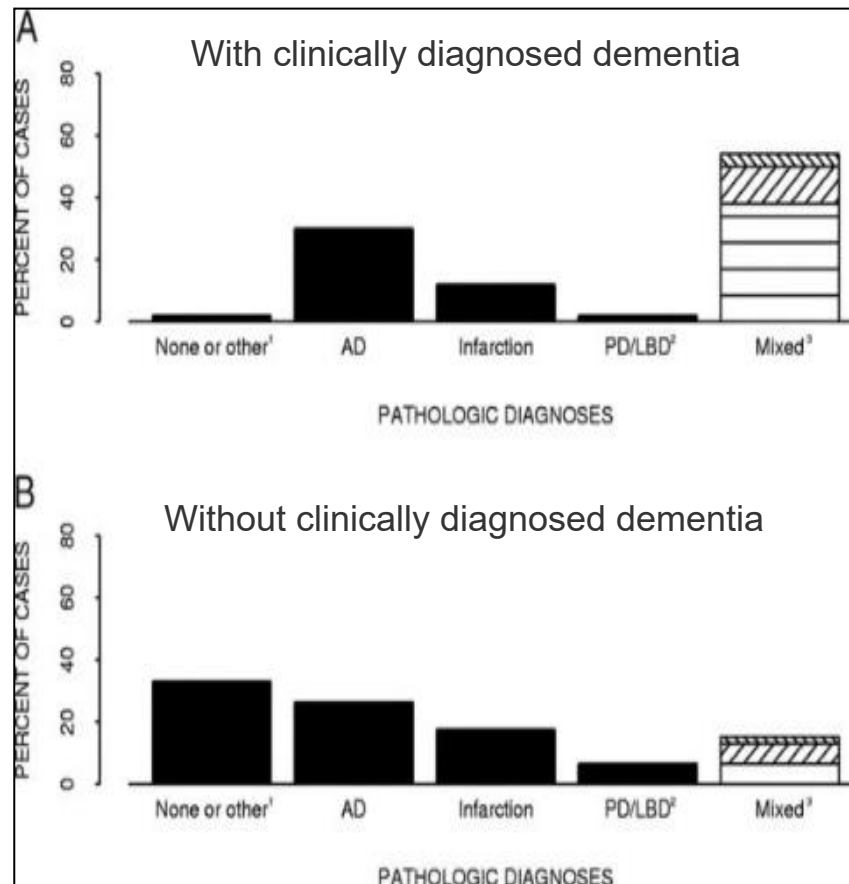
Where are we Going?
Epidemiology

Issues
- Exposure
  - What pollutant/source/mixture?
    - Particular interest in ultrafines
  - When?
    - Suggestion of critical windows for neurodevelopment
    - Most adult studies of cognition/dementia consider concurrent exposures

- Heterogeneous outcomes
  - Autism is phenotypically heterogeneous
  - Cognitive profiles varied (development and aging)
    - Are effects on specific functional domains or more global
  - How to categorize dementias
    - Pathology?

Dementia is Pathologically Heterogeneous

What is behavior-pathology relation?

Where are we Going?
Brain Imaging

- Gets at target tissue in living humans
- Can assess many variables
  - Volume; Activity (blood flow, glucose,...); Specific targets (flortaucipir, microglia?...)

Casanova et al., Front Human Neurosci., 2016

But also consider…
- Cost; Access
  - Lower tech?: ASR, fNIRS
  - Extracellular vesicles
- Brain is built to respond to the environment -- what's abnormal?
  - Parallels with known/clinical dysfunction?
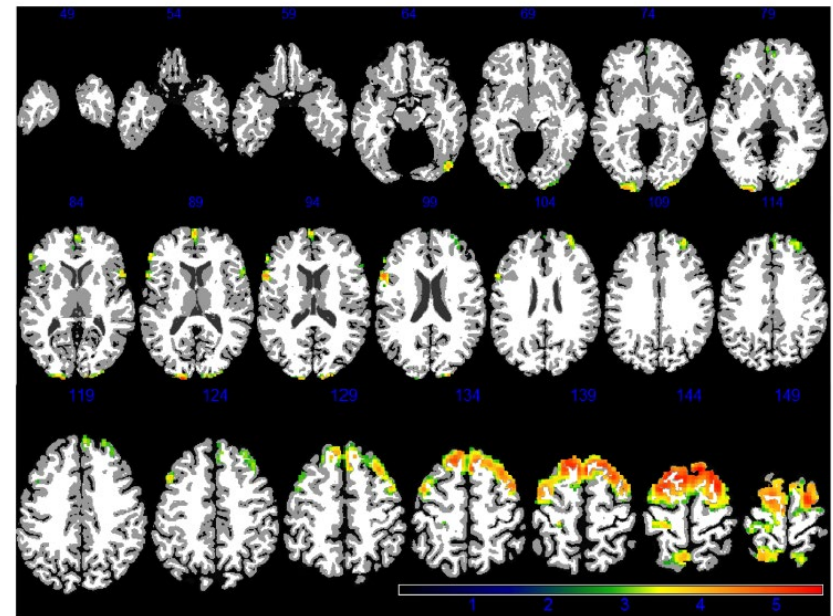 - Biomarkers are not necessarily causal
  - Pathology ≠ behavior

FIGURE 1 | GM areas negatively associated to PM$_{2.5}$ exposure (q < 0.05 FDR corrected) in the VBM linear regression models are presented in color. Images are oriented according to the neurological convention.
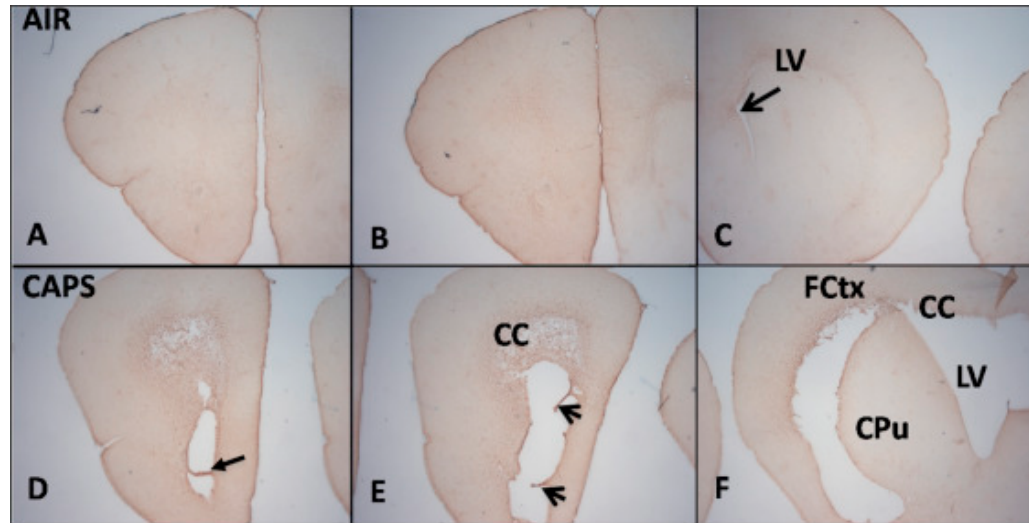
Where are we Going?
Animal Studies

Neuropathology of Inhaled Ultrafine Particles
→ parallels with autism neuropathology

Allen et al., Neurotoxicology, 2015

- Can do true experiments

But consider…
- Correct animal model?
- Animal to human translation?
  - Parallels with human neuropathology?
- Are exposures the same?
  - Compound; Pattern; Timing?
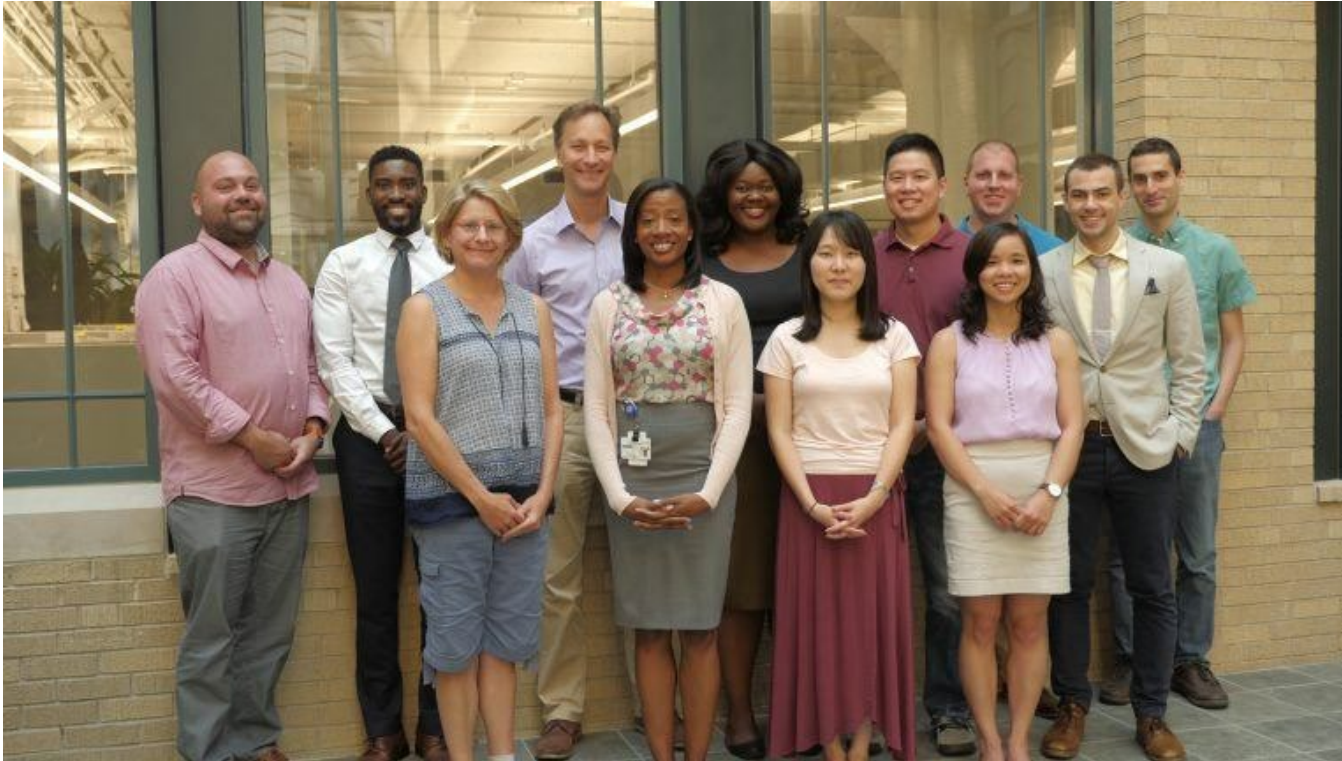
Summary

- Growing evidence for adverse effects of air pollutants on both the developing and aging brain

    - Neurodevelopment/ Autism
    - Mental Health
    - Cognitive function/Dementia
    - Parkinson's disease? Amyotrophic lateral sclerosis?

- Future is multi-pronged
    - Refining the epidemiology (exposures, timing, outcomes)
    - Imaging and other biomarker approaches
    - Animal studies

Many thanks to my collaborators

Weisskopf Environmental Neuroepidemiology Group

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