Air Pollution and Cognitive Function/Dementia

Marc G. Weisskopf, PhD, ScD

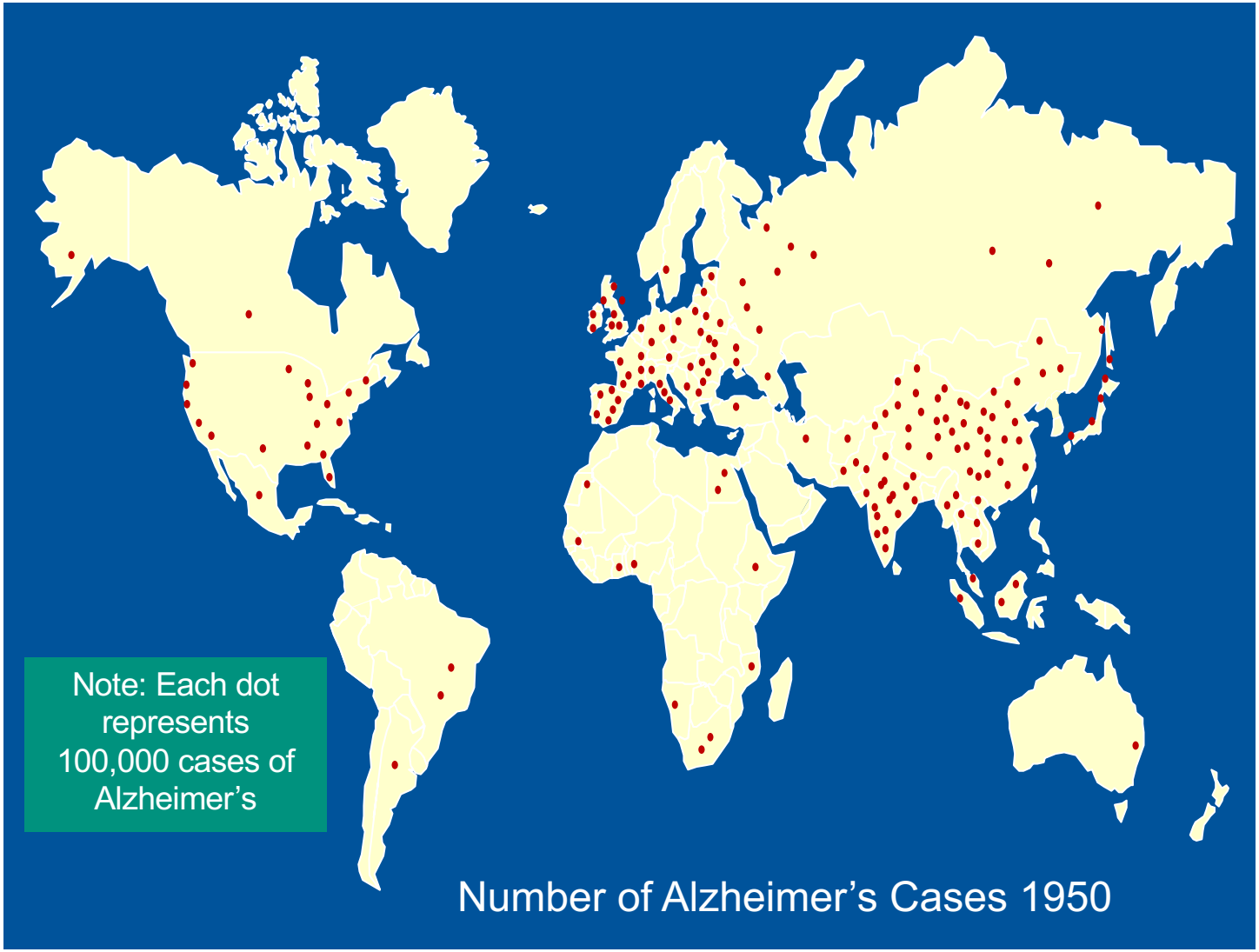
HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

What is dementia?

- Significant decline in one or more domains of cognitive function, that interferes with activities of daily living
  - Cannot be better explained by another disorder
  - Does not occur exclusively within a period of delirium

DSM-V, American Psychological Association

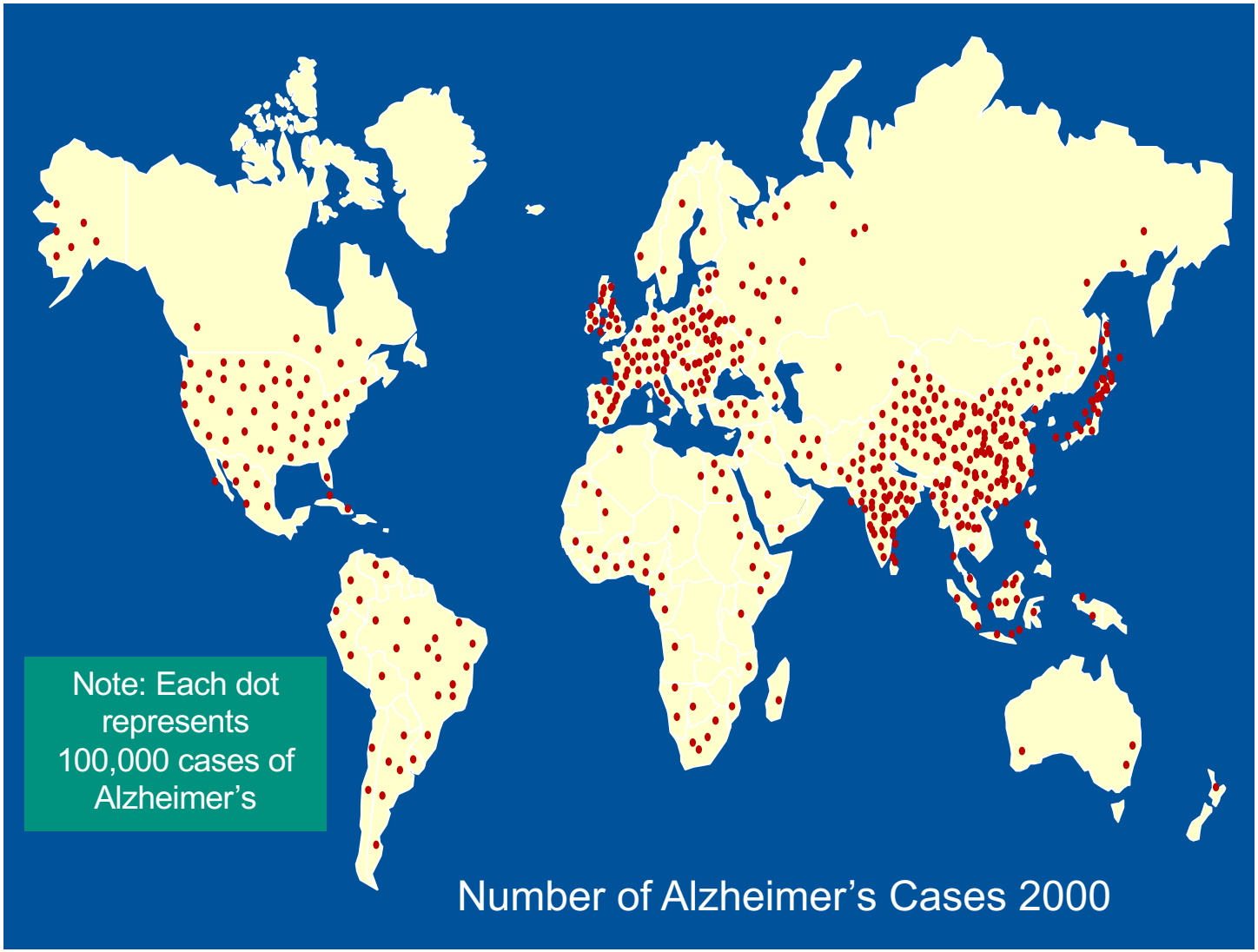
Dementia is a global problem



Source: United National Population Database and Age Wave calculation
Courtesy of Melinda Power via Steven DeKosky

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

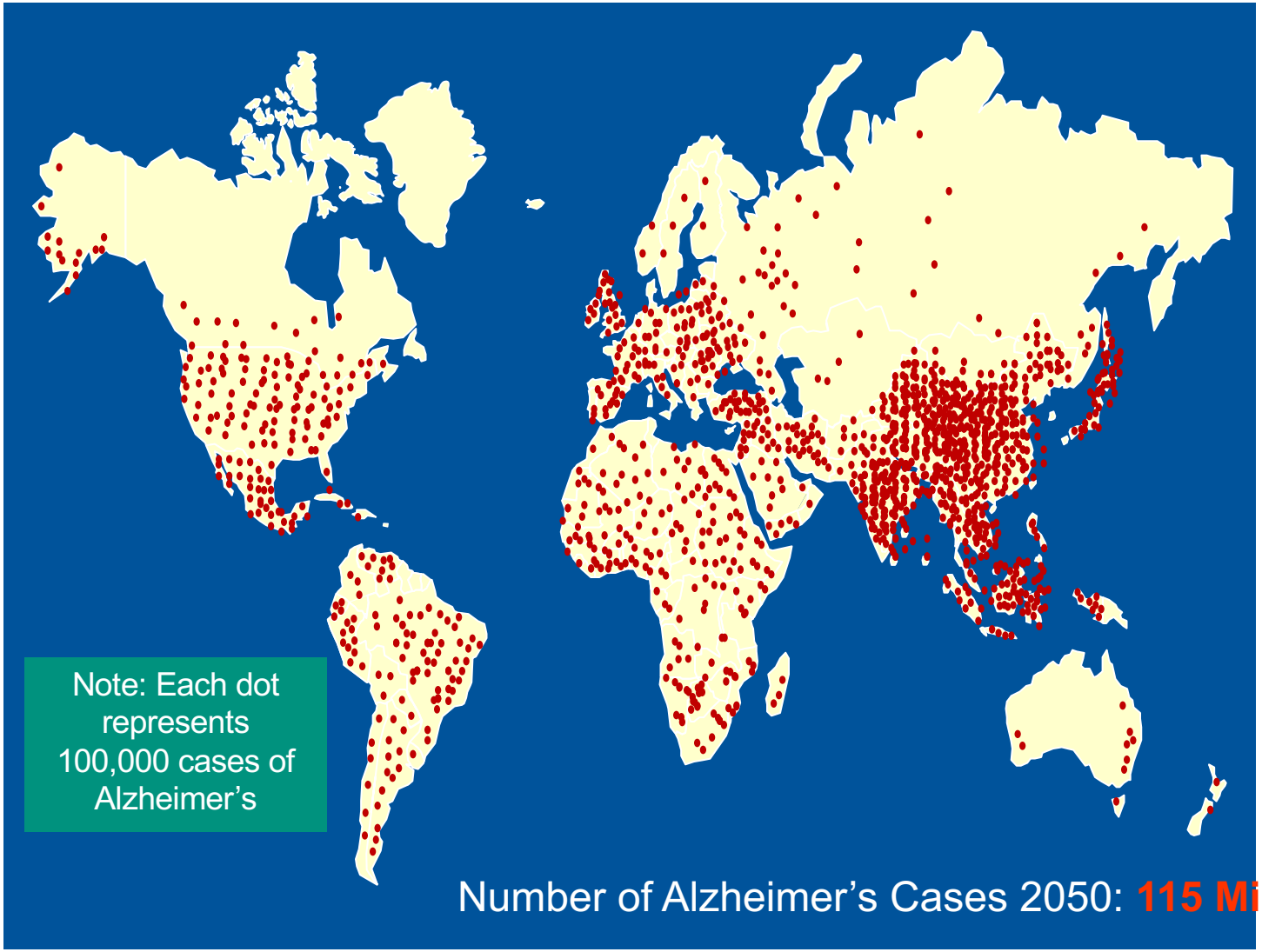
Dementia is a global problem



Source: United National Population Database and Age Wave calculation
Courtesy of Melinda Power via Steven DeKosky

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Dementia is a global problem

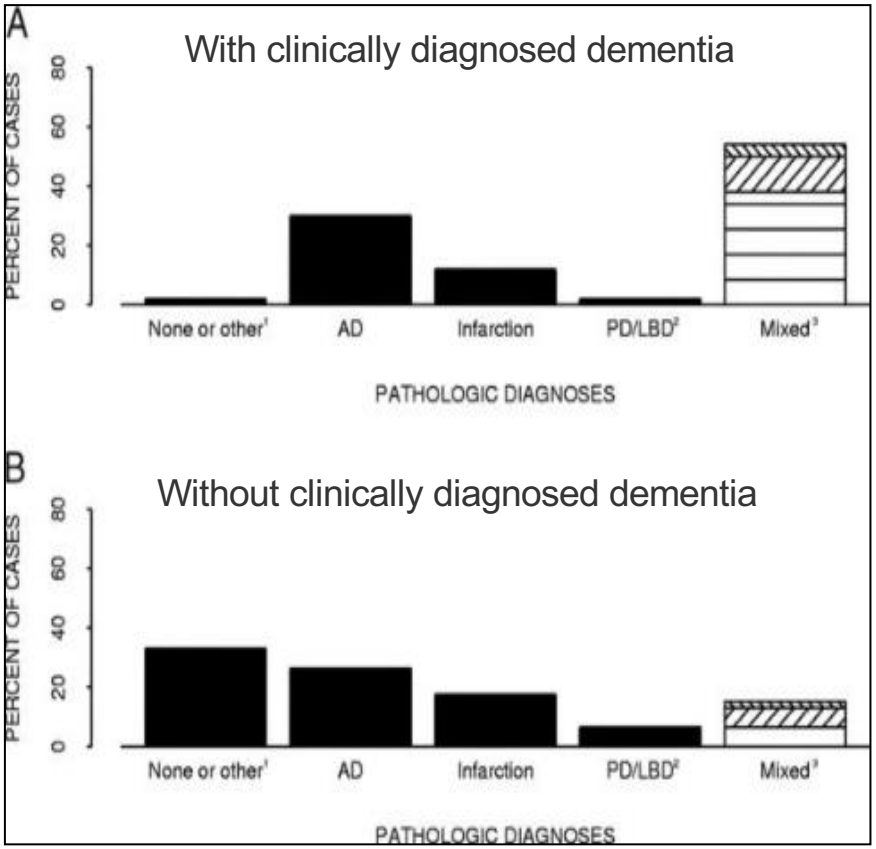


Source: United National Population Database and Age Wave calculation
Courtesy of Melinda Power via Steven DeKosky

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Dementia is clinically & pathologically heterogeneous

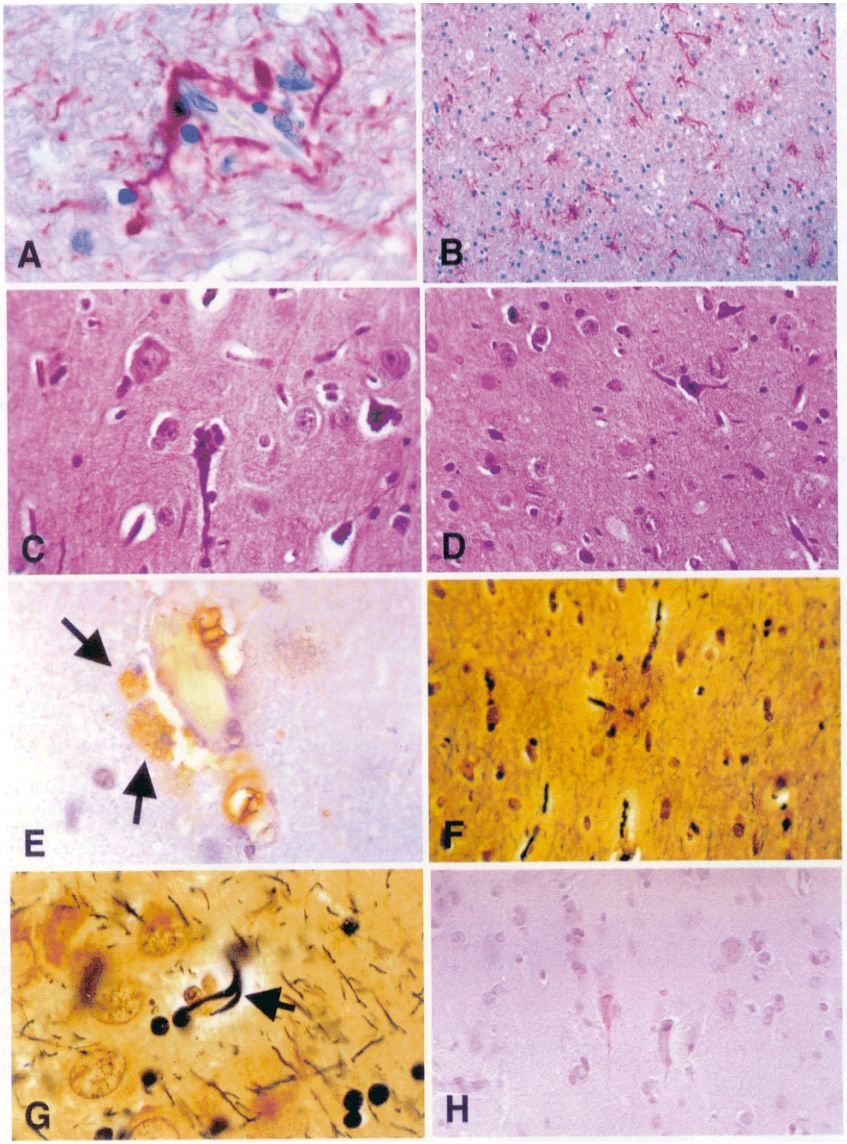
- Clinical symptoms may be diagnosed as:
  - Alzheimer's disease
  - Vascular disease
  - Frontotemporal lobar degeneration
  - Lewy body disease
  - Traumatic brain injury
  - HIV infection
  - Prion disease
  - Substance/medication use
  - Etc.



DSM-V, American Psychological Association

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Air Pollution and Neuropathology



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

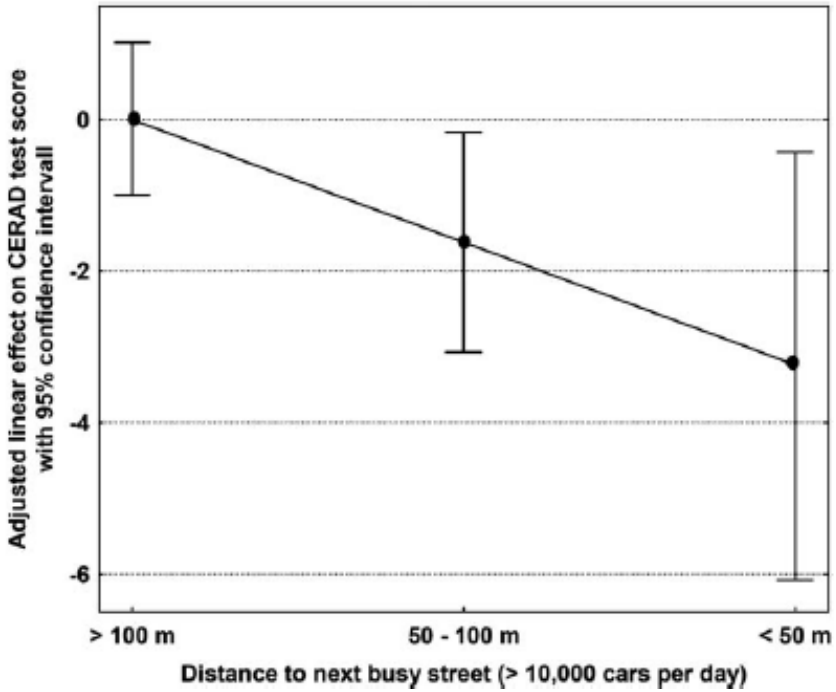
Dogs in Mexico City

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

- Activated microglia in cortex and white matter
- Vascular abnormalities (including Blood-Brain Barrier damage)

→ Neurodegeneration?

Air Pollution-Cognitive Function



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

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

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Black Carbon and Cognitive Function

Power et al., Environ. Health Perspect., 2011

- Cognitive testing among Normative Aging Study participants

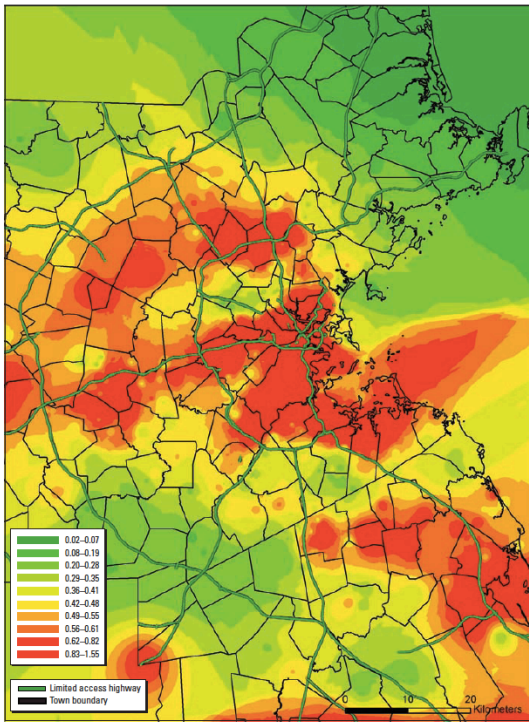


Figure 1. Predicted 1-year average BC exposures (μg/m³) for the greater Boston area in 1995.

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).

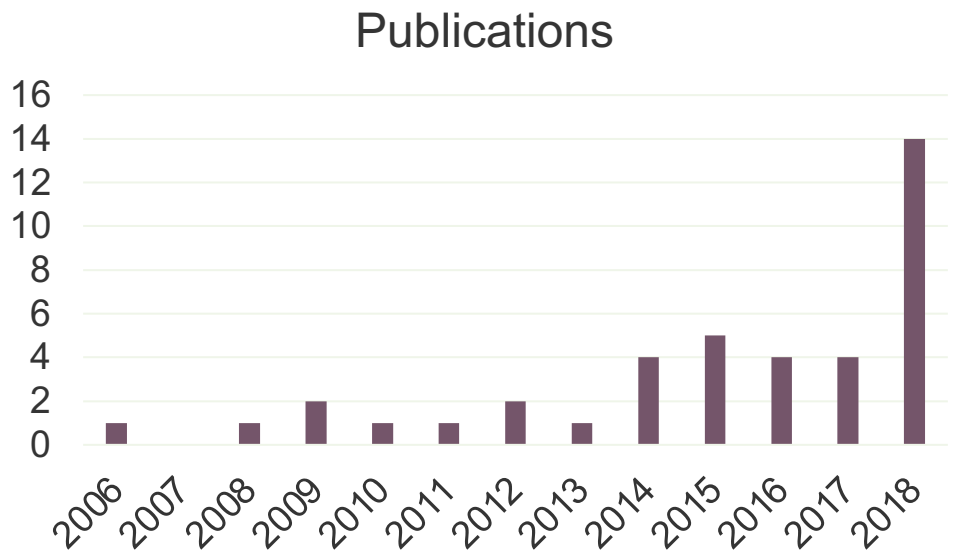
	Effect per doubling in BC concentration (95% CI)		
Analysis	Model 1: age adjusted	Model 2: age and education adjusted	Model 3: multivariable adjusted[a]
Low MMSE score OR	1.4 (1.1 to 1.6)	1.3 (1.0 to 1.5)	1.3 (1.1 to 1.6)
Global analysis estimate	–0.073 (–0.122 to –0.023)	–0.052 (–0.100 to –0.004)	–0.054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

Air Pollution-Cognitive Function/Dementia

Several reviews

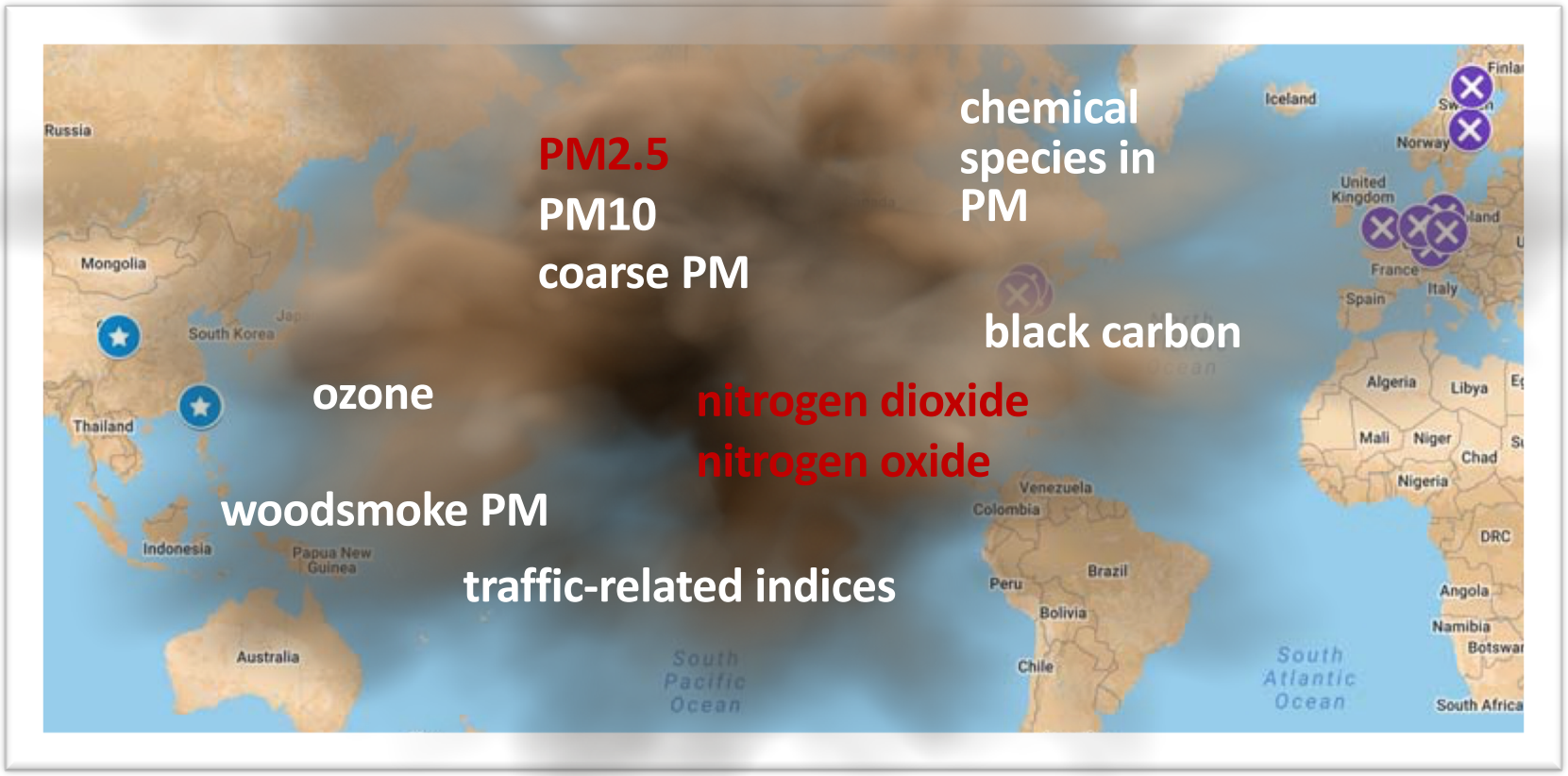
- Power et al., Neurotoxicology, 2016
- Kilian and Kitazawa, Biomedical Journal, 2018
- Dimakakou et al., Int J Environ Res Public Health, 2018
- Russ et al., Curr Opin Psychiatry, 2019
- Tham & Schikowski, J Alz Dis, 2020
- Schikowski & Altug, Neurochem Int, 2020



The Lancet Commission
2020 Report on Dementia

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

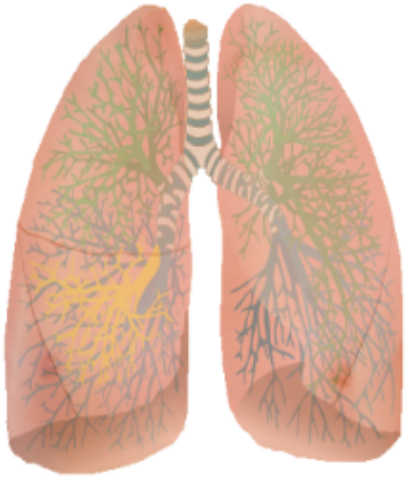
Pollutants investigated

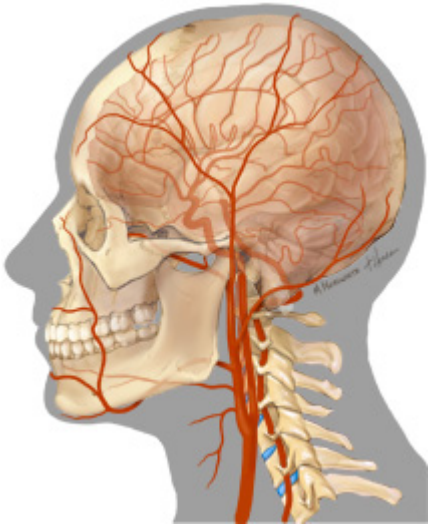


But … can be important limitations of

- 1-time cognitive testing
- Claims/medical record data

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH



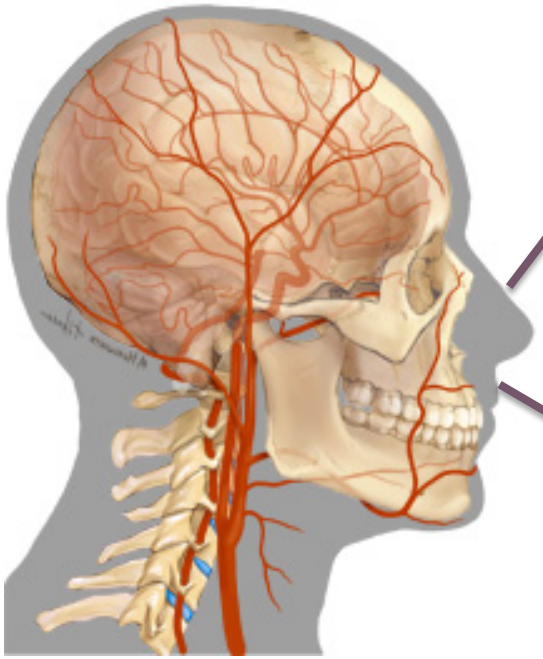


http://med.uc.edu/neurosurgery/divisions/cerebrovascular.aspx

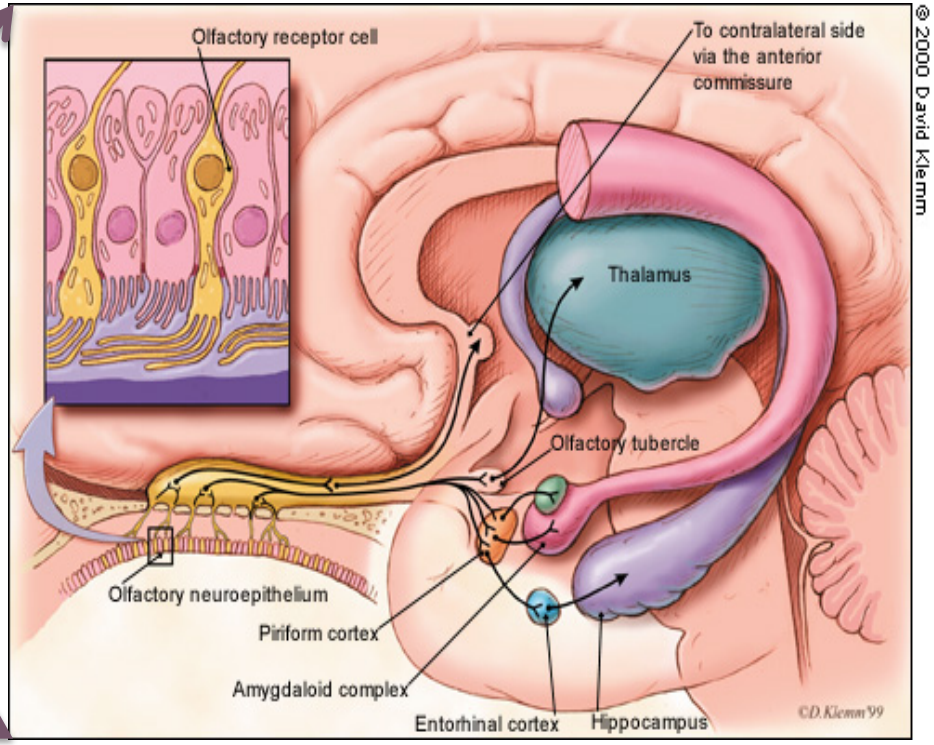
Cerebrovascular Link

- Air pollution has established consequences for cardiovascular disease
  - Vascular risk factors are often associated with cognition, dementia
  - Subclinical cerebrovascular disease is implicated in dementia

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

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Underlying Biology

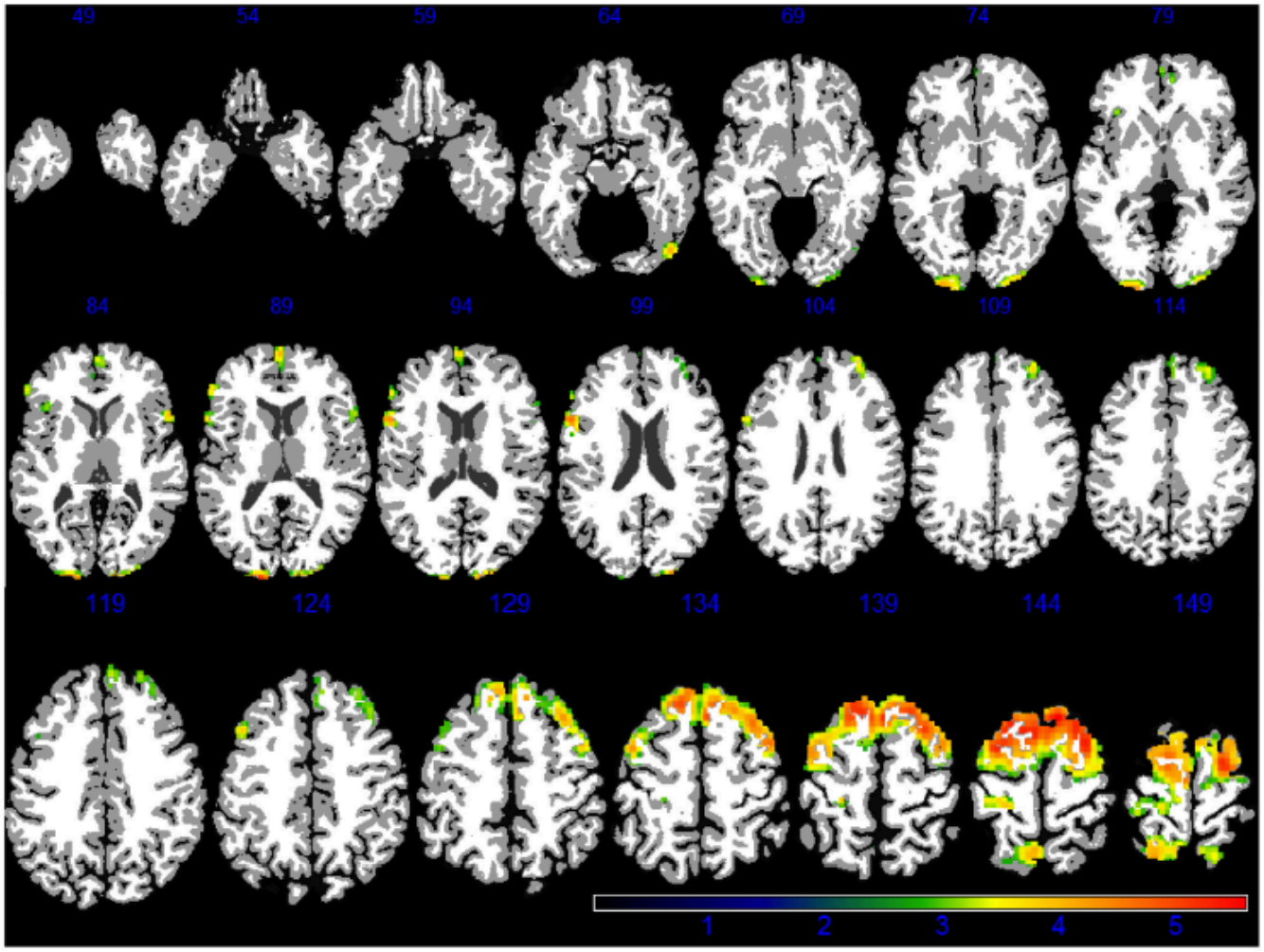


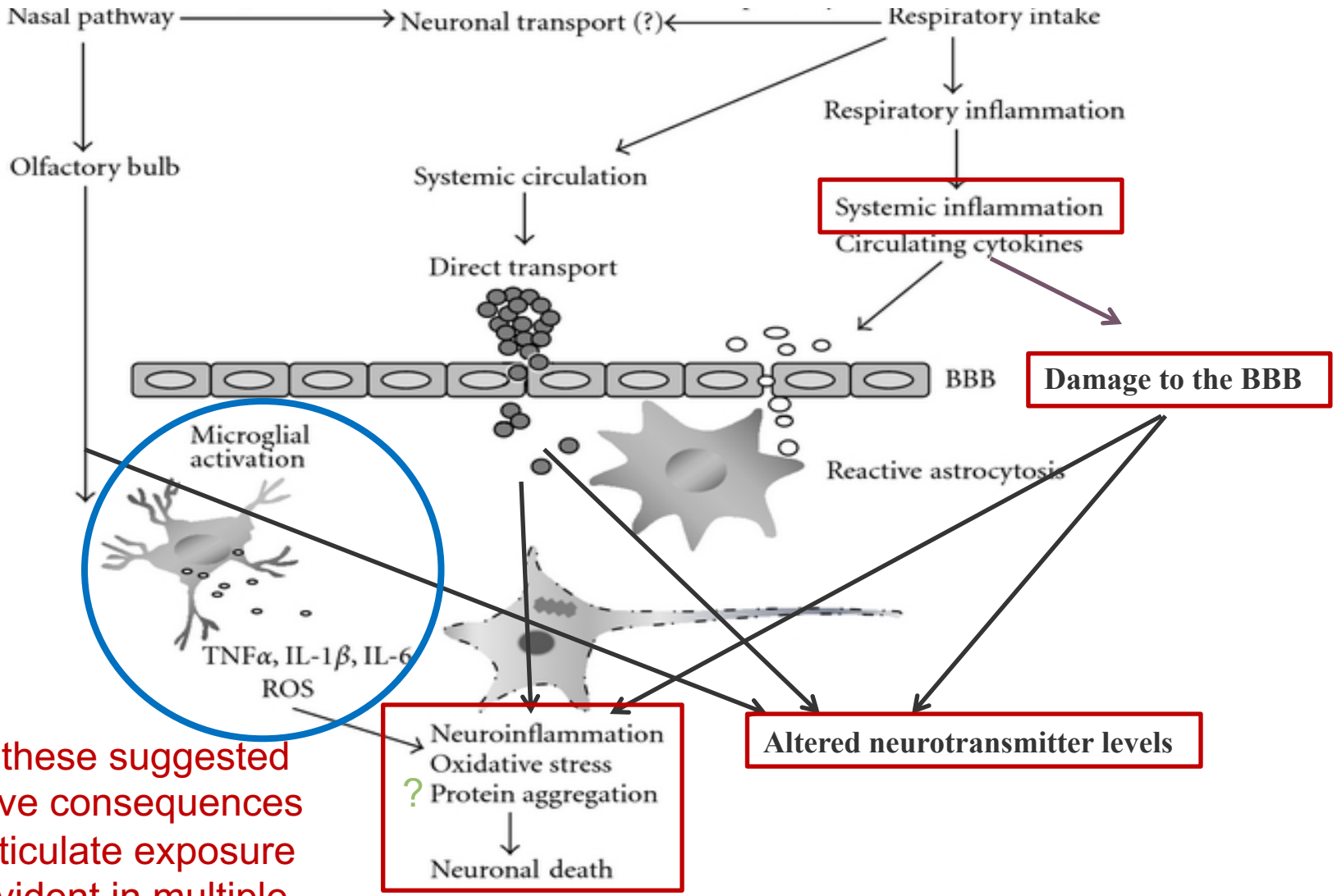
FIGURE 1 | GM areas negatively associated to $PM_{2.5}$ exposure ($q < 0.05$ FDR corrected) in the VBM linear regression models are presented in color. Images are oriented according to the neurological convention.

Casanova et al., Front Human Neurosci., 2016

Review:
De Prado Bert et al., Curr Environ Health Reports, 2018

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Particulate matter exposure appears to lead to…

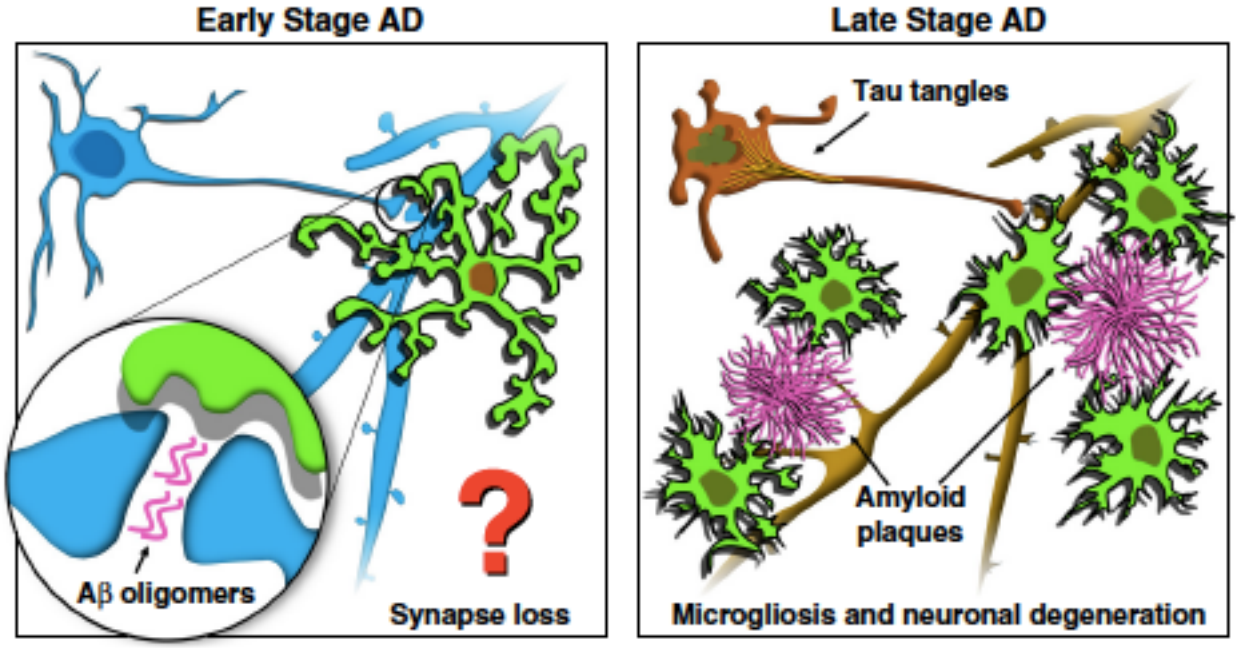


All of these suggested negative consequences of particulate exposure are evident in multiple neurodegenerative diseases

Adapted from: Genc et al. 2012 J Toxicol

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Microglia and Dementia



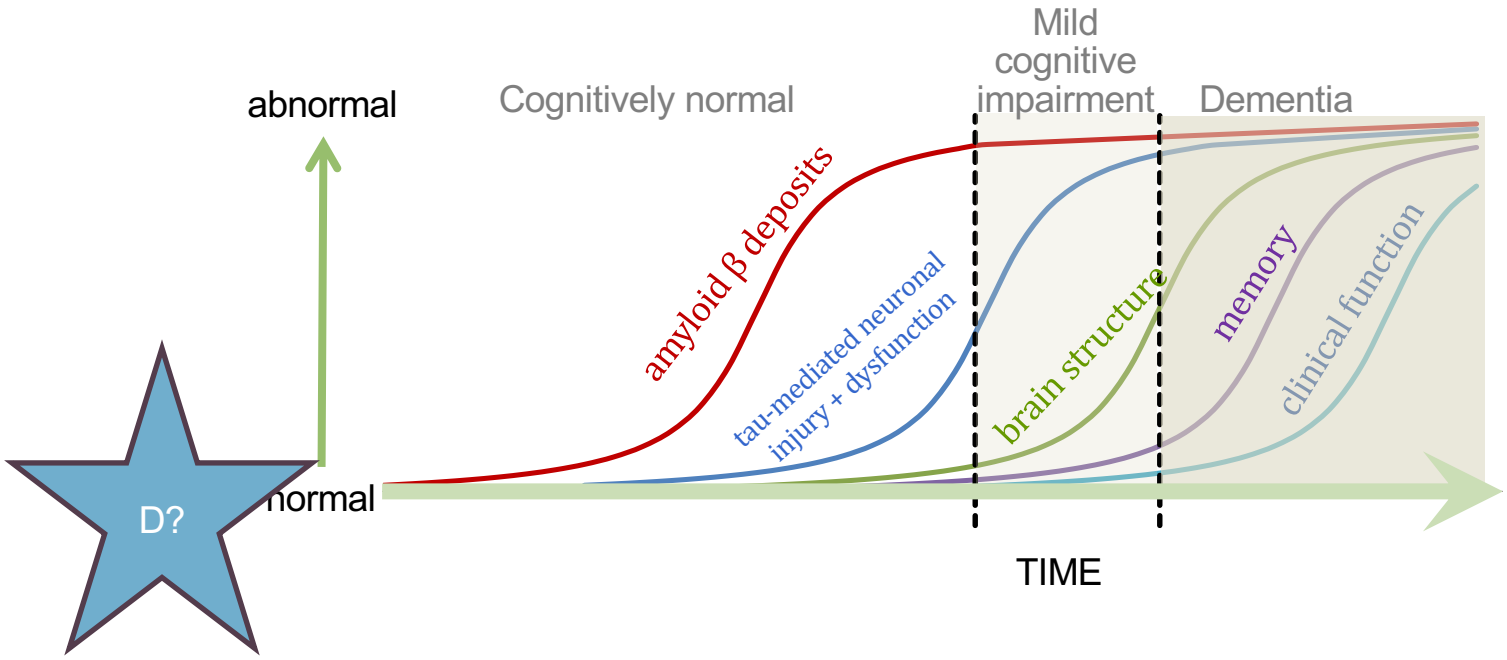
Hong et al., Curr Opinion Neurobiol., 2016
(Beth Stevens, Harvard)

Toxic activation → aberrant synapse elimination?

Air Pollution-Cognitive Function/Dementia
Where are we now?

- Much evidence for effect
  - Best is for cognitive decline; cohort dementia studies
- What pollutants?
  - Particulate matter (components?); Gases
  - Ultrafines?
    - Limited exposure data compared to particulates & gases
  - Other Hazardous Air Pollutants
- How?
  - Cardiovascular? Inflammation? Direct action on brain?
- When?
  - Most studies of recent year(s)

By the time dementia emerges, many **changes have been underway ... *for years***

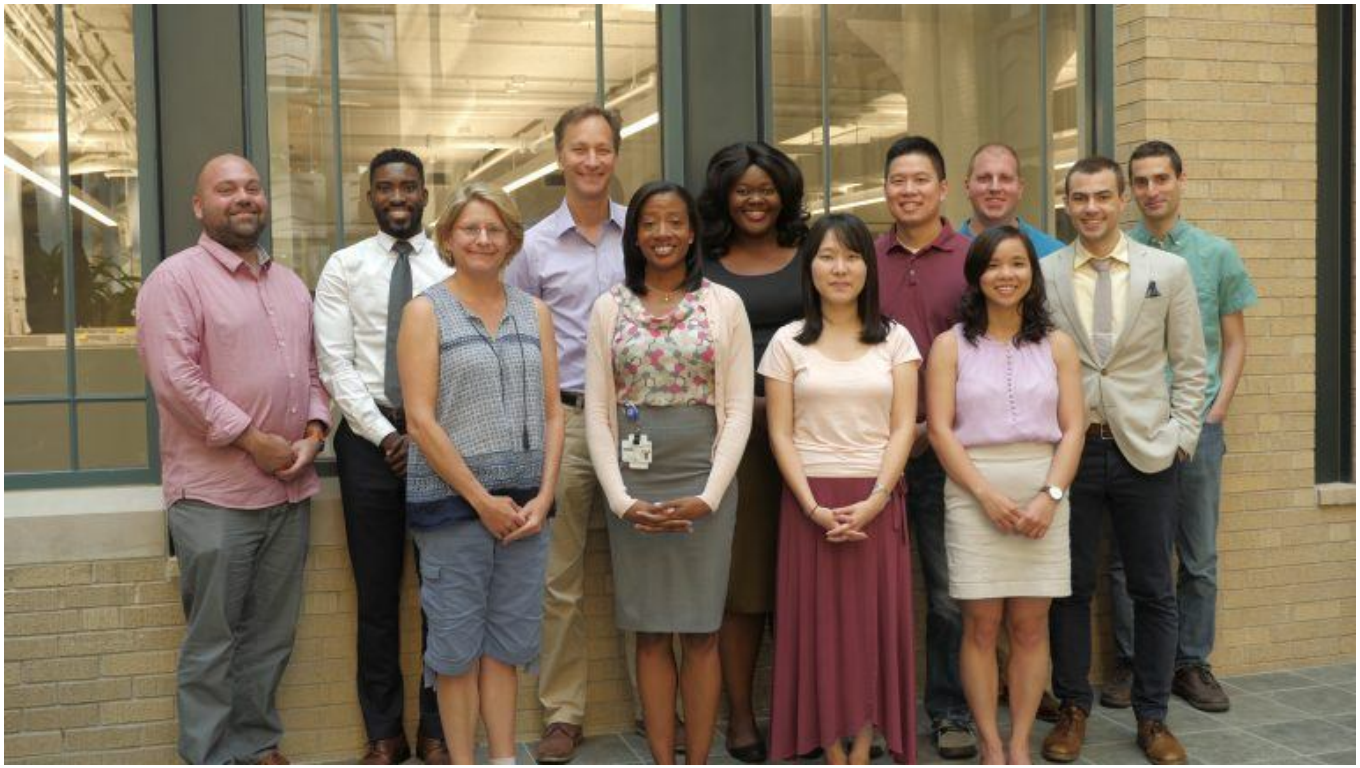


Jack CR Jr, *Lancet Neurology* 2013

Essentially all air pollution-cognitive function/dementia studies consider exposures within at most years of testing

Many thanks to my collaborators

Weisskopf Environmental Neuroepidemiology Group



HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH