Air Pollution and PD

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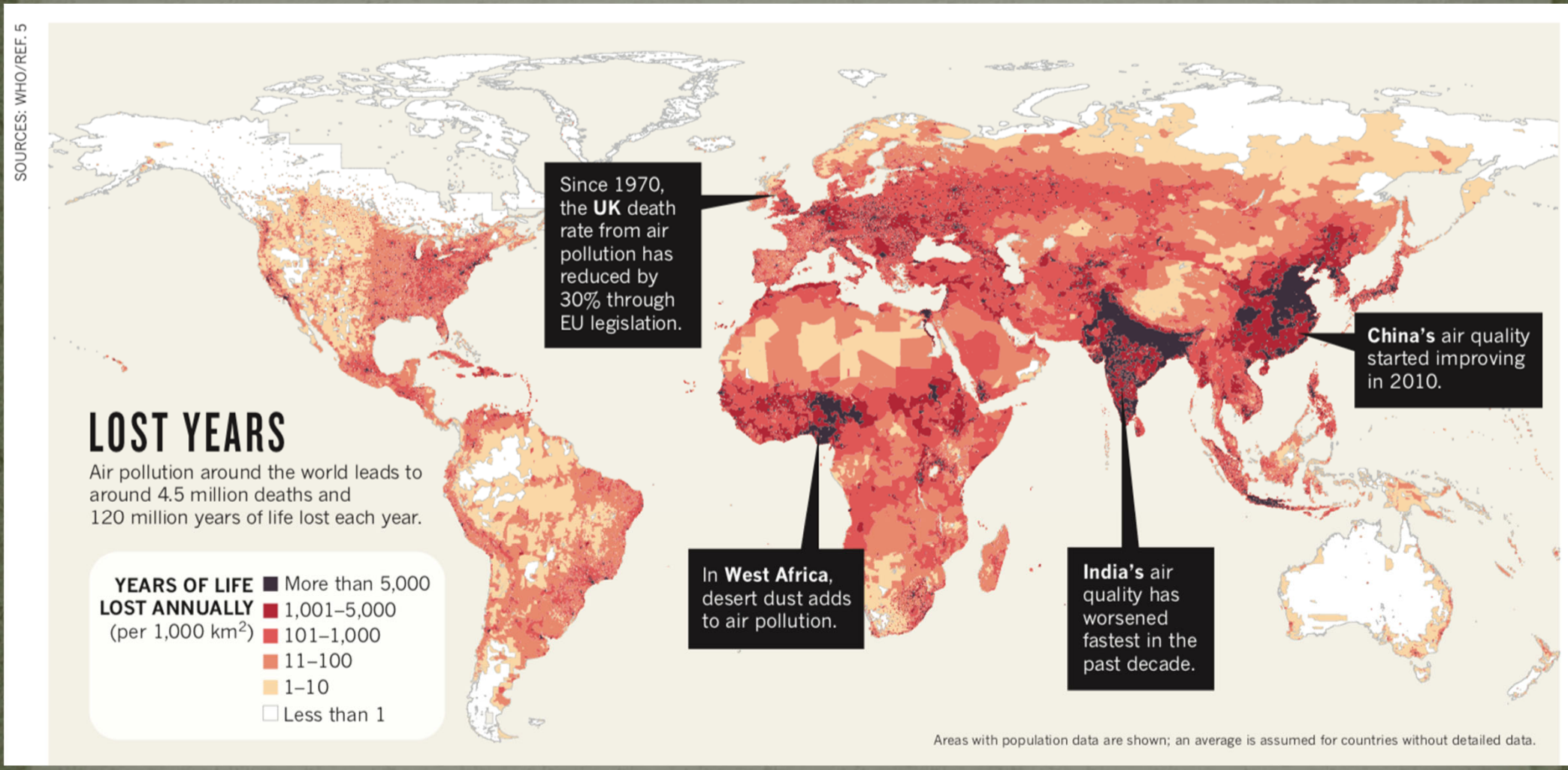
Disclosures

Nothing to disclose

Air Pollution Dramatically Increases Mortality



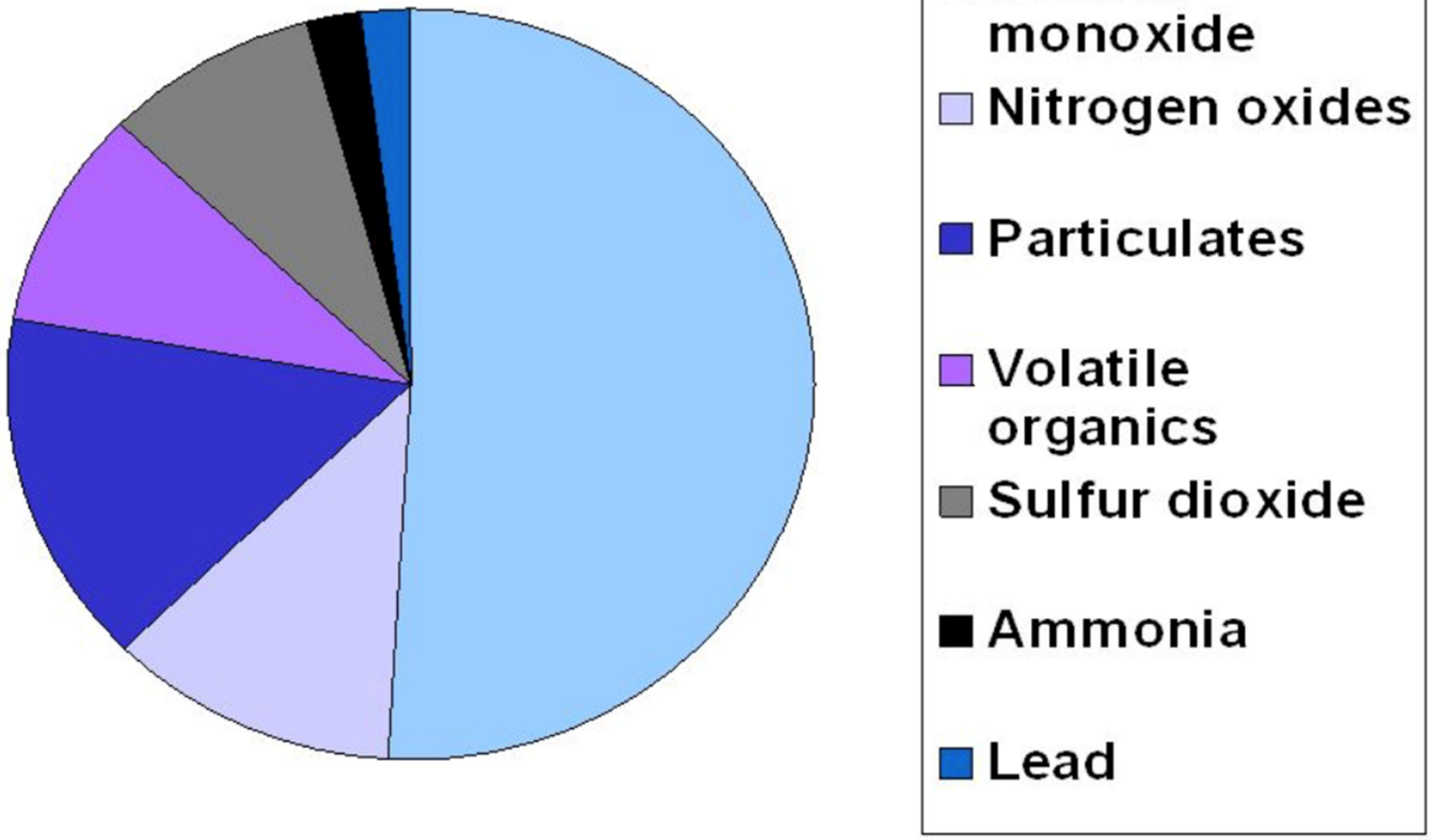
THE POLLUTED BRAIN

The microscopic particles sifting from freeways and power plants don't just harm your heart and lungs. They may also attack your brain

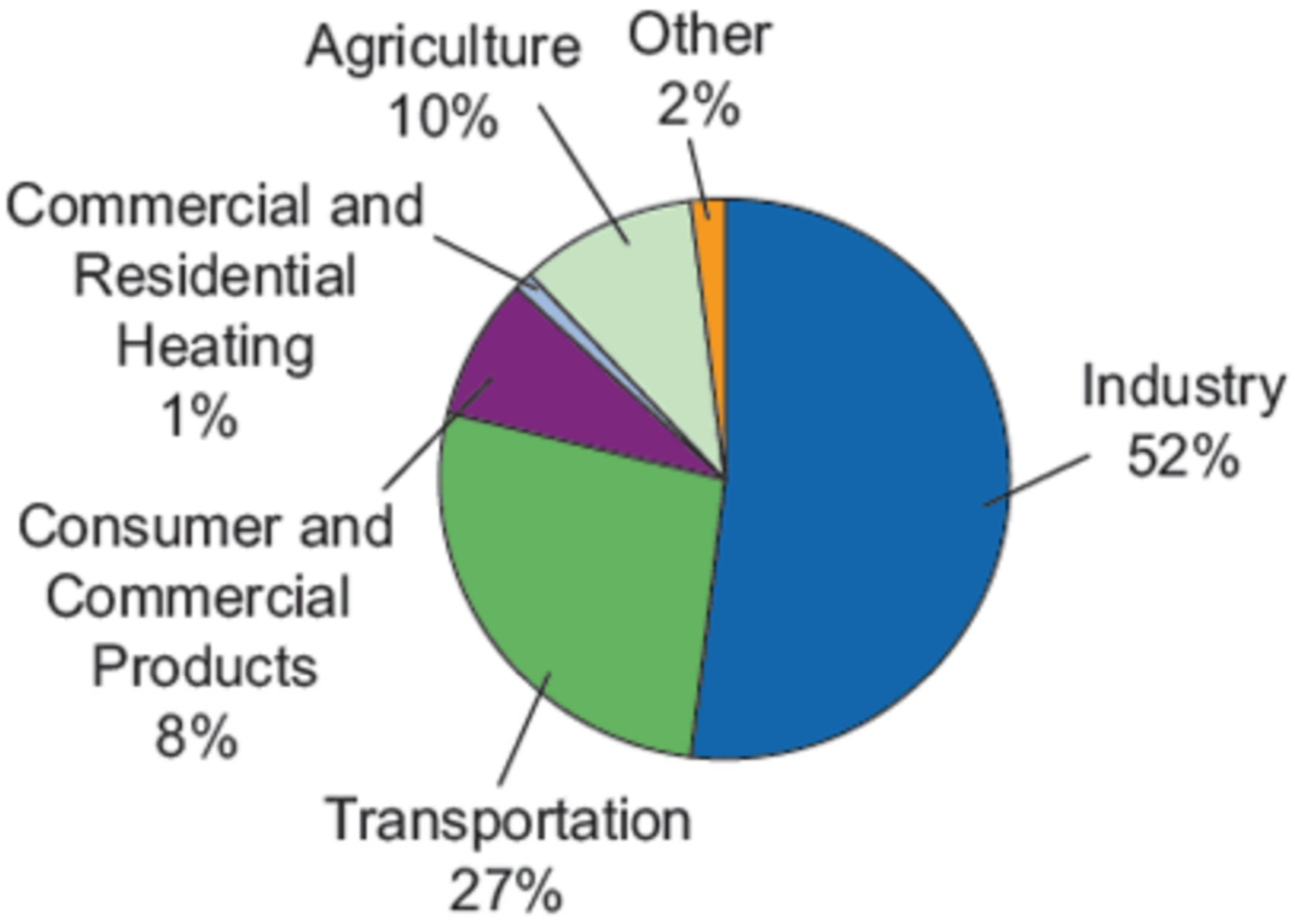
By **Emily Underwood**, *in Los Angeles, California*

Types and Sources of Air Pollution

Primary Air Pollutants



Sources of Emissions of Air Pollutants



Air Pollution and Neurological Disorders

- Stroke: Increased incidence and mortality
  - Estimated 9% of stroke disability years and 8.5% of stroke deaths could be due to PM2.5 exposure.
  - Higher living near roadway.
  - 1 study showed association with ICH
- Headaches: Increased migraines
- MS: Short-term exposure exacerbation of disease activity. Unclear if it alters incidence.
- ALS: Unclear if it alters incidence
- Dementia: Unclear if it alters incidence
- Parkinson's disease: Evidence is growing

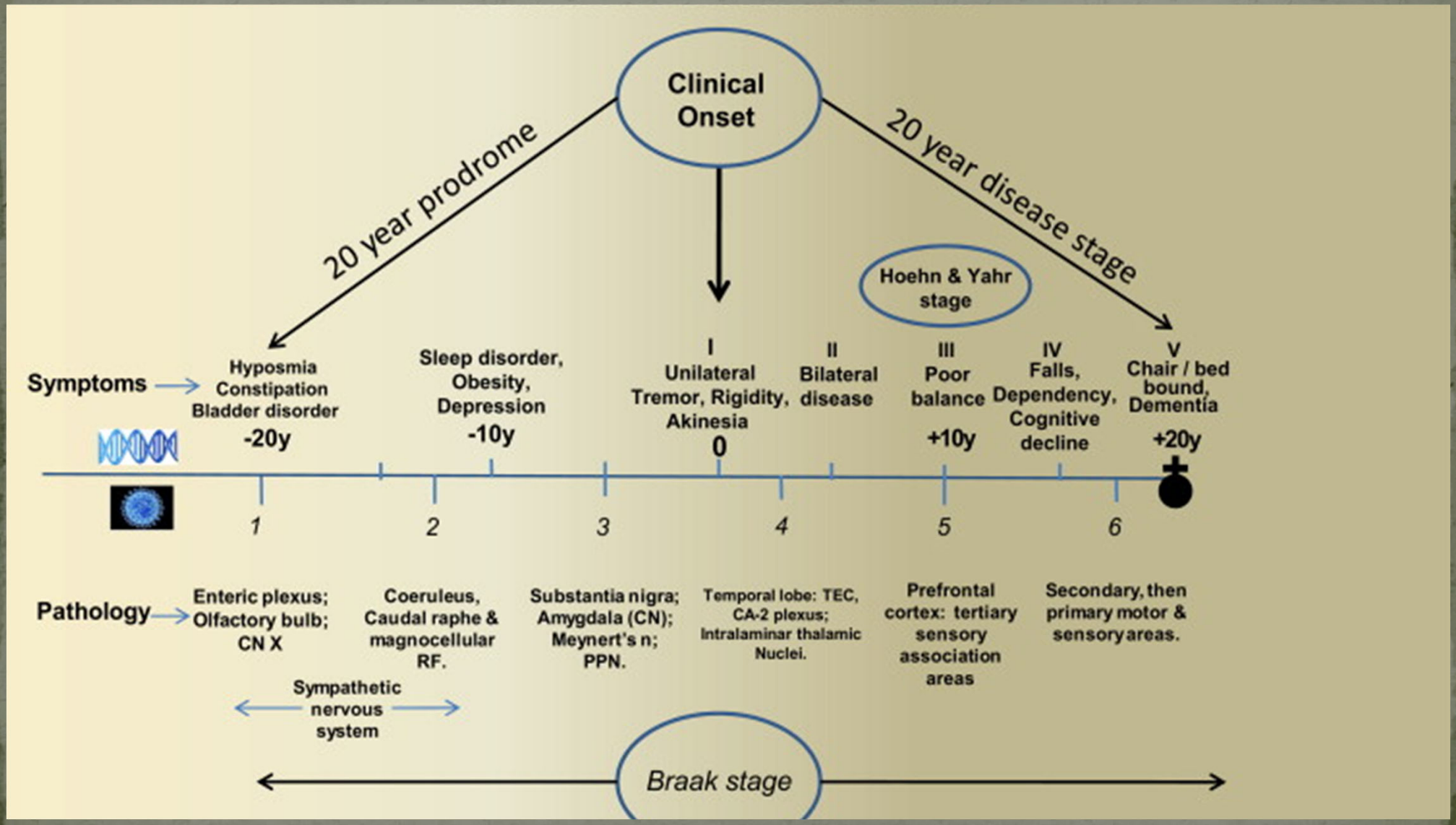
Parkinson's Disease: Why Study the Environment?

- Only approx. 30% of PD can be explained by genetics
- PD pathology starts in the gut and olfactory bulb which are entry points for environmental toxins.

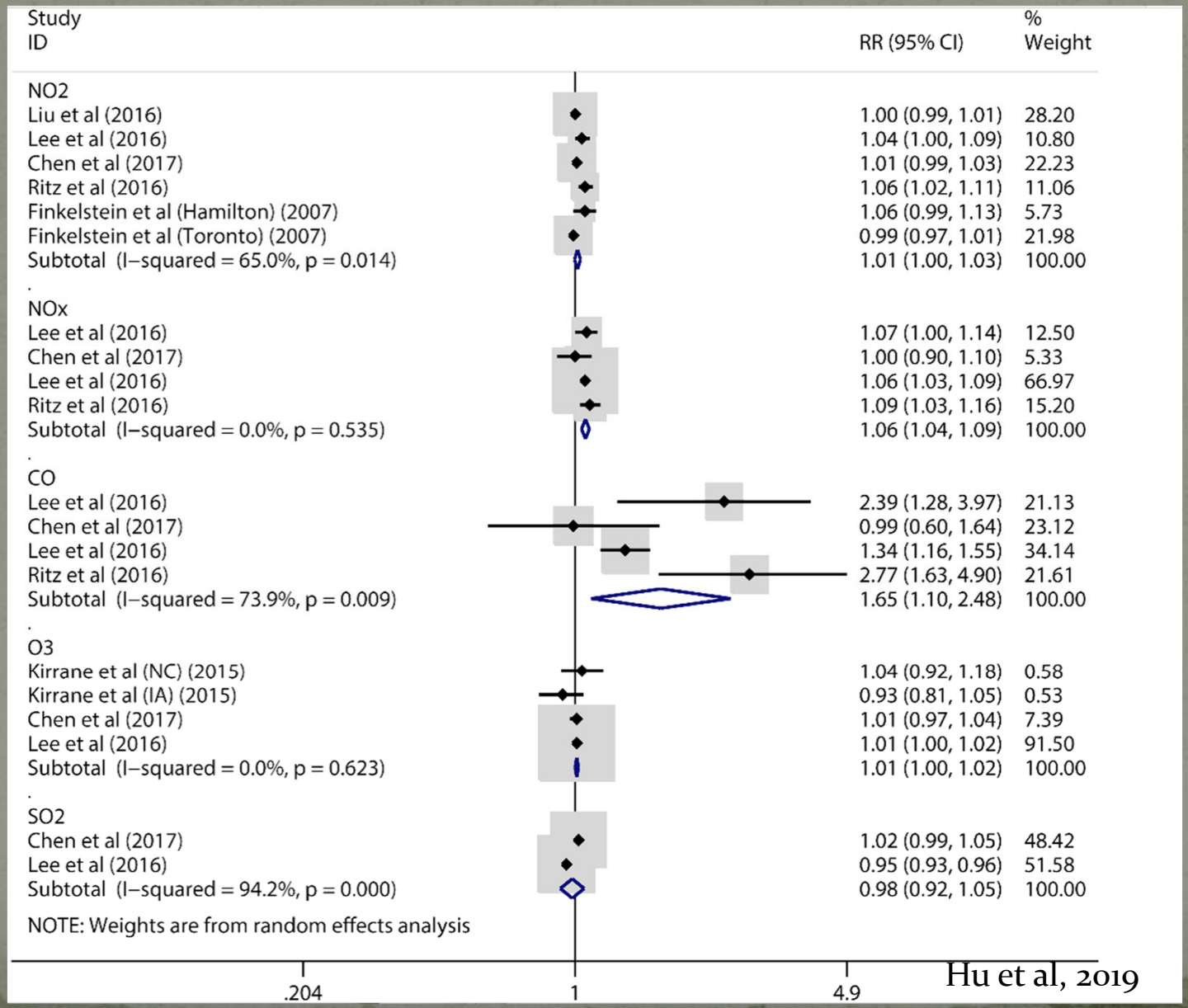
Parkinson's Disease and Air Pollution: Why is it so hard to study?

- PD is relatively rare for genetic and epidemiological studies
- Diagnosis is not always clear early in the disease and by the time you make the diagnosis, the disease process has been going on for decades.
- It is very slowly progressive so it is very difficult to model the disease in animals.

Disease Process Spans Decades



Meta-analysis of AP and PD up to 2019



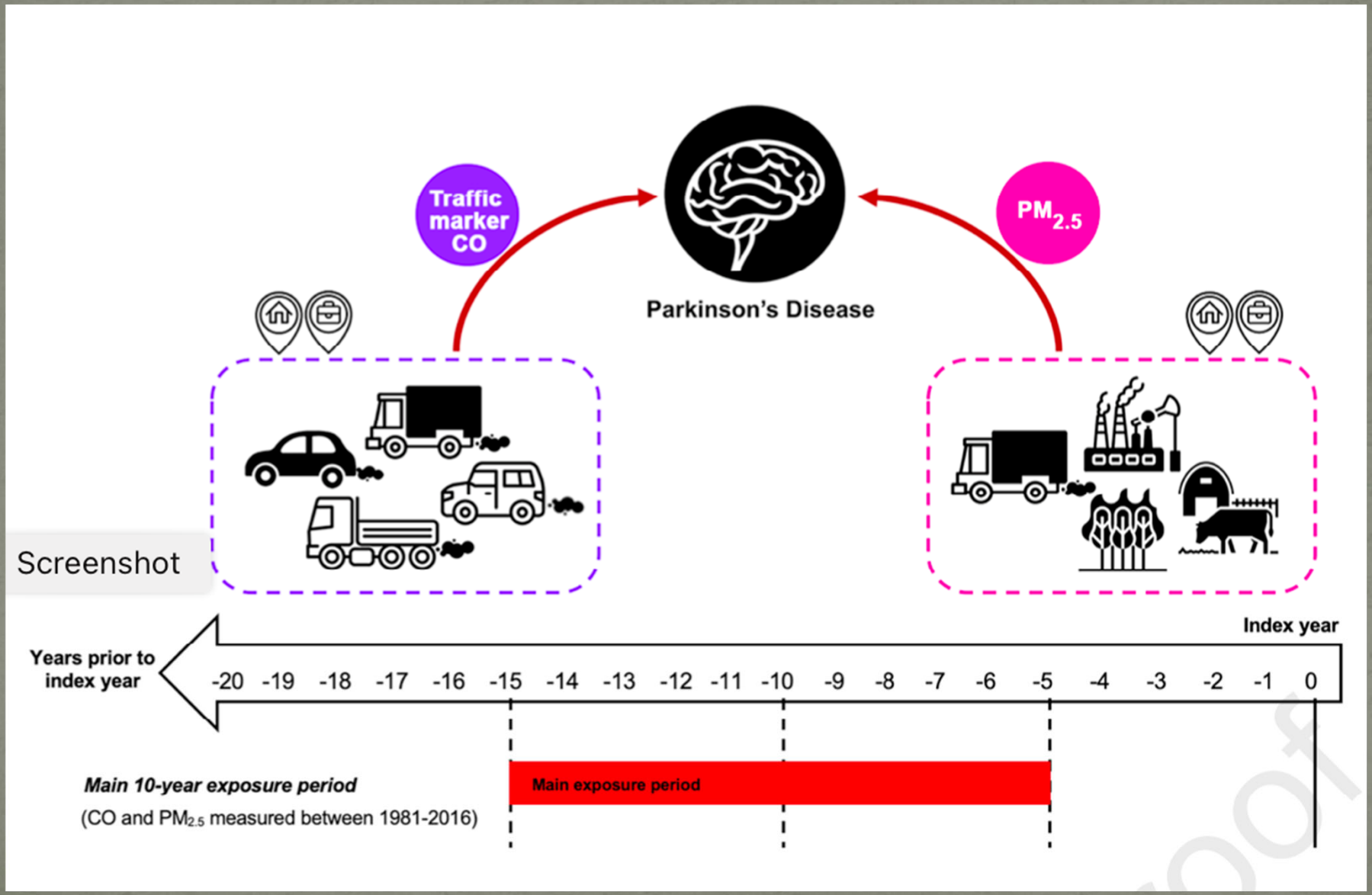
Hu et al, 2019

Some Recent Epidemiological Studies

Beate Ritz MD, PhD

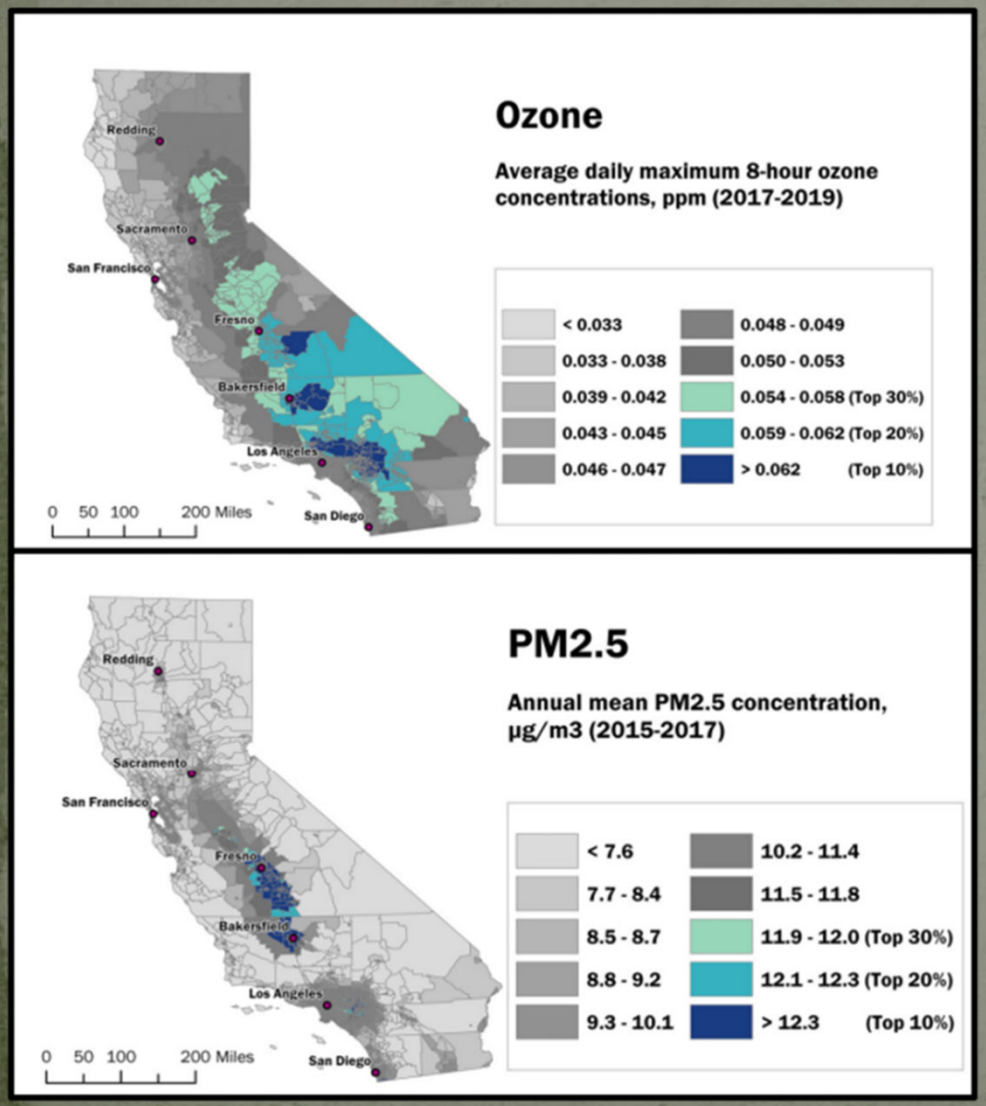
Author	Study Design	Population	Exposure Range	Length of Exposure/ Lag time to Ds	OR	Strengths	Weaknesses
Kirrane 2015 [9]	Case-Control	301 cases in US	O_3 (ppb): IA mean: 39.0, max: 41.5; NC mean 40.6 ; max 46.5. $PM_{2.5}$ (μg/m³): IA mean 8.9; max 11.5; NC mean 12.6; max 17.7	4 years	OR = 1.39 (.98-1.98) for O_3; OR = 1.34 (.93–1.93) for $PM_{2.5}$	Adjusted for multiple variables including pesticides	Short exposure time, small population
Ritz 2016 [14]	Case-Control	1696 PD cases in Denmark	NO_2: 9.8-43.26 ug/m³; NOx: 13.46-181.55 ug/ m³; CO: 0.36-2.34 mg/m³	31 years	NO2: 1.09 per 2.97 μg/m of exposure; NOx: 1.06 per 7.10 ppb of exposure; CO: 1.13 per 0.12 ppm of exposure	Large population, long exposure, adjusted for multiple variables	Low air pollution in Denmark
Lee 2016 [10]	Case-Control	11,117 incident PD cases in Taiwan	PM_{10}: 29.3-86.8 ug/m3; NO_x: 5.2-77.6 ppb; O_3: 19.0-39.2 ppb; CO: 0.2-1.5 ppm	11 years	OR = 1.37 (1.23–1.52) for CO; OR = 1.17 (1.07–1.27) in multi- pollutant models	Large population, adjusted for age, year of Dx	Short exposure time, adjusted for only a few variables
Lee 2016 [11]	Case-Control	408 incident PD cases in Denmark (subset of Ritz 2016)	NO_2: 9.8-43.26 ug/m³; NOx: 13.46-181.55 ug/ m³; CO: 0.36-2.34 mg/m³	31 years	OR=3.1 for AA allele of the interleukin-1β) gene with high NO exposure	Long exposure, adjusted for multiple variables, gene interaction with air pollution	Small population, low air pollution in Denmark,

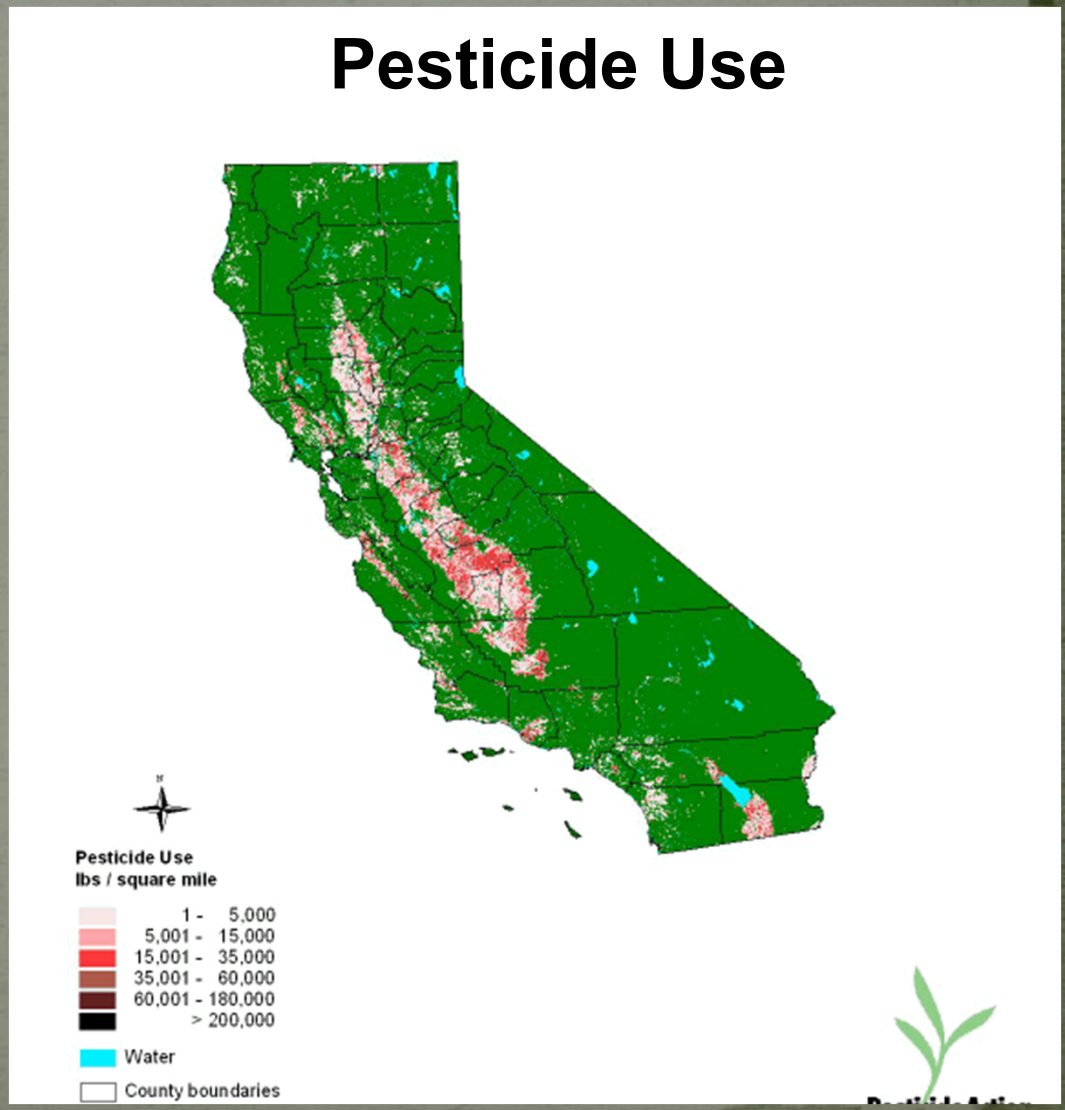
Air Pollution and PD in the Central Valley



Kwon et al, (in press)

Air Pollution in the CA Central Valley and PD





Association between 10-year average CO exposure with a 5-year lag time and Parkinson's disease

Residential	Cases/controls	Odds ratio (95% CI)		
		Unadjusted	Model1[a]	Model2[b]
Continuous CO (ppb)[c]	688/851	1.07 (1.01, 1.13)	1.08 (1.02, 1.14)	1.08 (1.02, 1.15)
T1 (0.01-2.87)	242/343	Reference	Reference	Reference
T2 (2.88-9.06)	242/292	1.17 (0.93, 1.49)	1.24 (0.97, 1.59)	1.26 (0.98, 1.61)
T3 (9.07-368.00)	204/216	1.34 (1.04, 1.72)	1.40 (1.07, 1.83)	1.47 (1.12, 1.94)
p-trend[d]		0.02	0.01	0.01
Occupational				
Continuous CO (ppb)[c]	336/309	1.02 (0.97, 1.08)	1.05 (0.99, 1.12)	1.05 (1.00, 1.12)
T1 (0.01-2.87)	70/73	Reference	Reference	Reference
T2 (2.88-9.06)	97/97	1.04 (0.68, 1.61)	1.21 (0.76, 1.91)	1.22 (0.77, 1.93)
T3 (9.07-368.00)	169/139	1.27 (0.85, 1.89)	1.72 (1.12, 2.65)	1.77 (1.15, 2.74)
p-trend[d]		0.20	0.01	0.01

[a]Adjusted for age, race, sex, education, and study wave.

[b]Adjusted as in model 1 plus smoking and pesticide exposure.

[c]Change per interquartile range (IQR) of 10.27 ppb.

[d]Based on linear model through the tertile medians.

Kwon et al 2023 *unpublished*

Association between 10-year average $PM_{2.5}$ exposure with a 5-year lag time and Parkinson's disease

Residential	Cases/controls	Odds ratio (95% CI)		
		Unadjusted	Model1[a]	Model2[b]
Continuous $PM_{2.5}$ ($\mu g/m^3$)[c]	761/910	1.29 (1.14, 1.47)	1.39 (1.21, 1.61)	1.42 (1.22, 1.64)
T1 (0.88-14.50)	245/319	Reference	Reference	Reference
T2 (14.51-17.80)	242/316	1.00 (0.79, 1.26)	1.05 (0.82, 1.34)	1.08 (0.84, 1.38)
T3 (17.81-29.40)	274/275	1.30 (1.02, 1.64)	1.39 (1.06, 1.81)	1.45 (1.10, 1.91)
p-trend[d]		0.03	0.02	0.01
Occupational				
Continuous $PM_{2.5}$ ($\mu g/m^3$)[c]	372/352	1.24 (1.03, 1.48)	1.50 (1.22, 1.86)	1.51 (1.22, 1.88)
T1 (0.88-14.50)	110/125	Reference	Reference	Reference
T2 (14.51-17.80)	133/107	1.41 (0.98, 2.03)	1.76 (1.21, 2.59)	1.79 (1.22, 2.65)
T3 (17.81-29.40)	129/120	1.22 (0.86, 1.75)	1.59 (1.06, 2.38)	1.64 (1.09, 2.47)
p-trend[d]		0.28	0.02	0.01

[a]Adjusted for age, race, sex, education, and study wave.

[b]Adjusted as in model 1 plus smoking and pesticide exposure.

Kwon et al 2023 *unpublished*

Is the Size of the Effect of AP on PD Risk Relevant?

- Since so many people are exposed to air pollution, it could account for a significant percentage of PD cases.
  - If we extrapolate the risk of PD in the Ritz study to the air pollution levels in Los Angeles CA during the 1970s and 80s (i.e. NO_2, NO_x and CO levels), air pollution could account for up to 70% of the cases

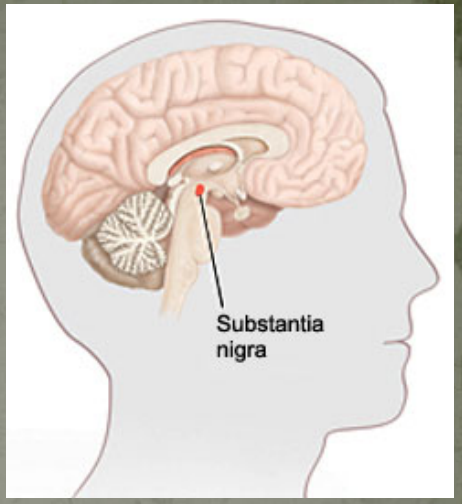
Biological Plausibility; How can AP increase risk?

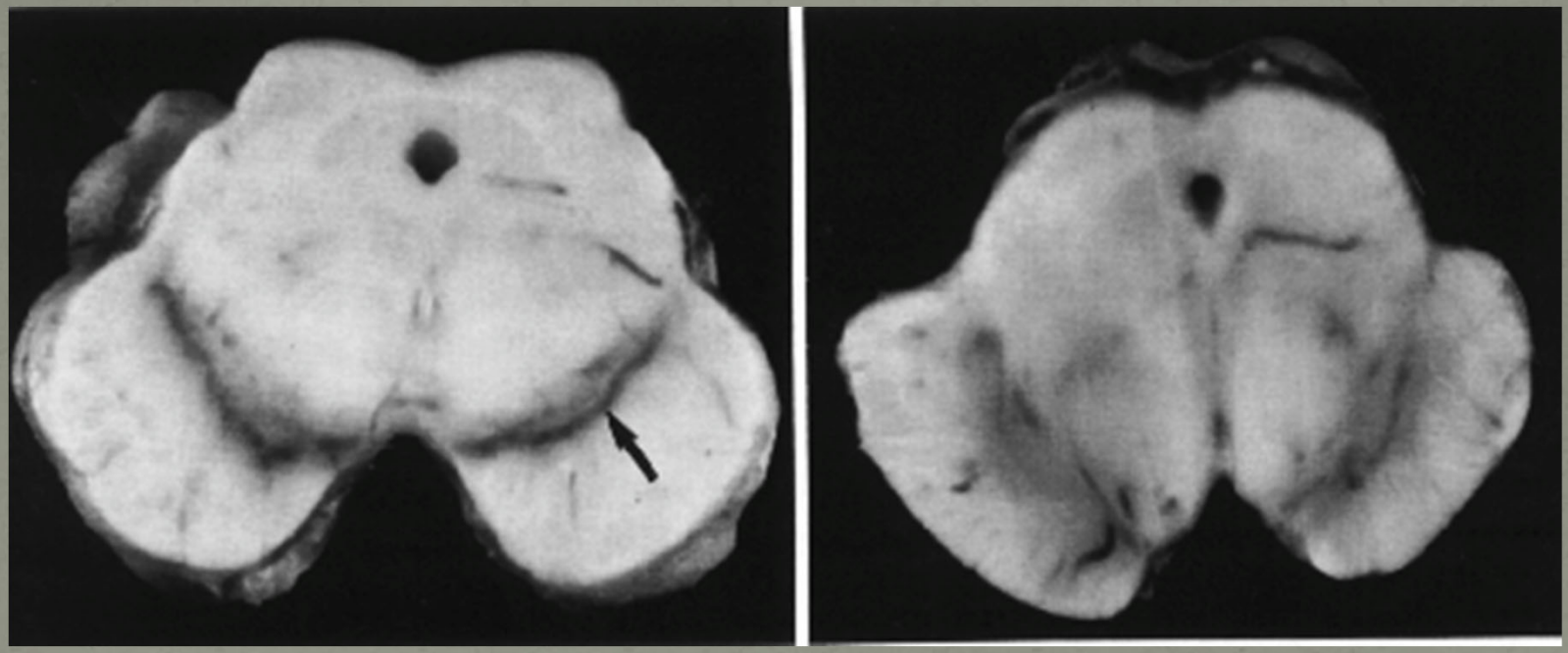
- Autopsies of people and dogs in high AP regions (Mexico City) showed increased AD/PD pathology and inflammation relative to controls.
- *In vitro*, diesel exhaust extracts cause dopaminergic cell death and inflammation.
- Subacute exposure to diesel exhaust in rodents causes CNS inflammation and increased α-synuclein but does not cause dopaminergic neuronal death.

How might Air Pollution Act?

A Brief Review on the Pathophysiology of PD

PD is Characterized by Loss of Substantia Nigra Neurons but Pathology is Widespread



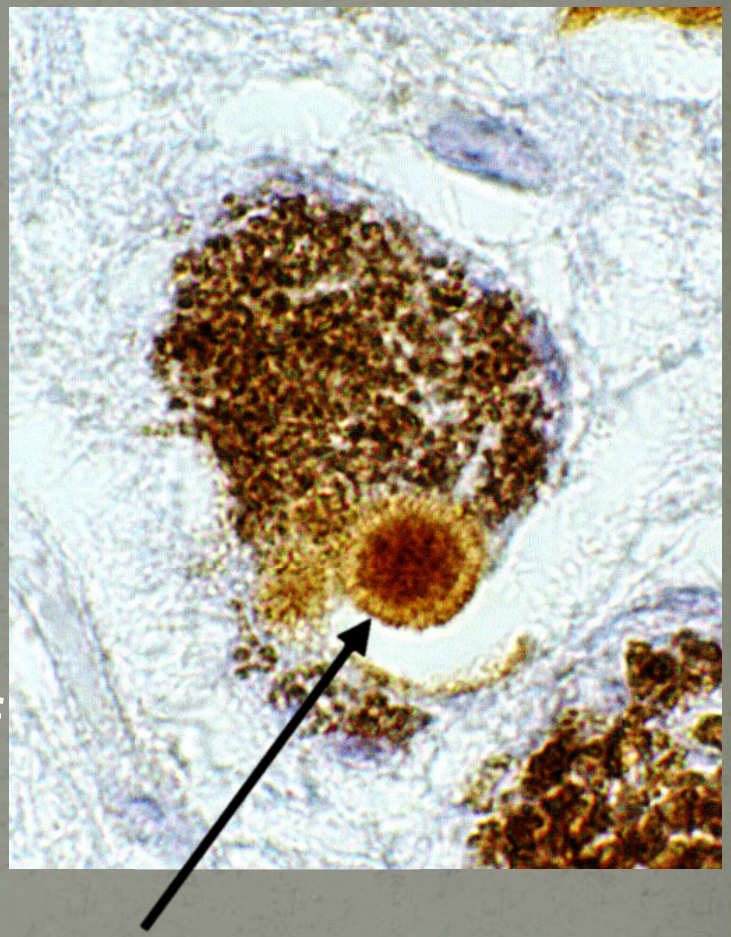


Normal Substantia Nigra

Substantia Nigra in PD

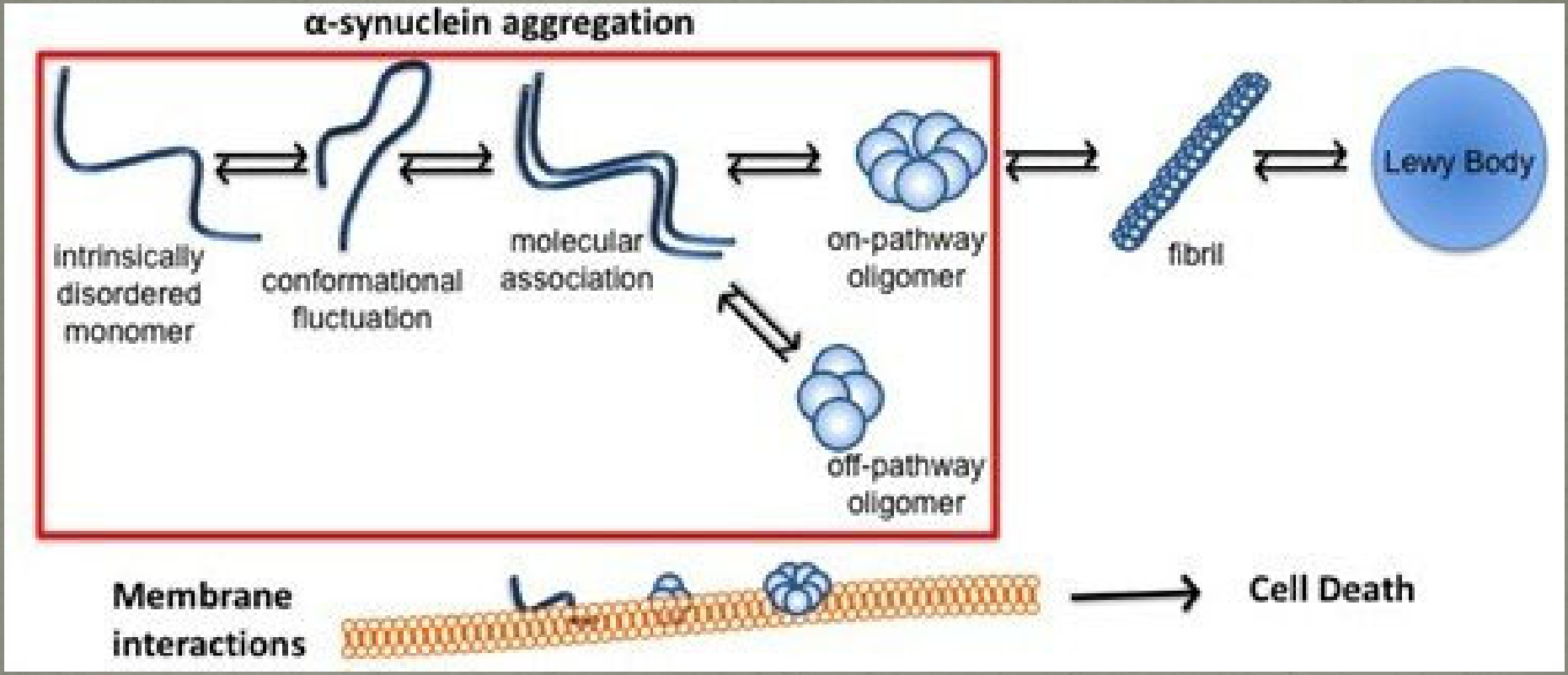
α-Synuclein is Central to PD

- 1st gene linked to PD.
- Point mutations and gene duplication cause typical PD.
- Major component of Lewy Body in sporadic PD.
- Overexpression in animals recreates many of the features of PD.

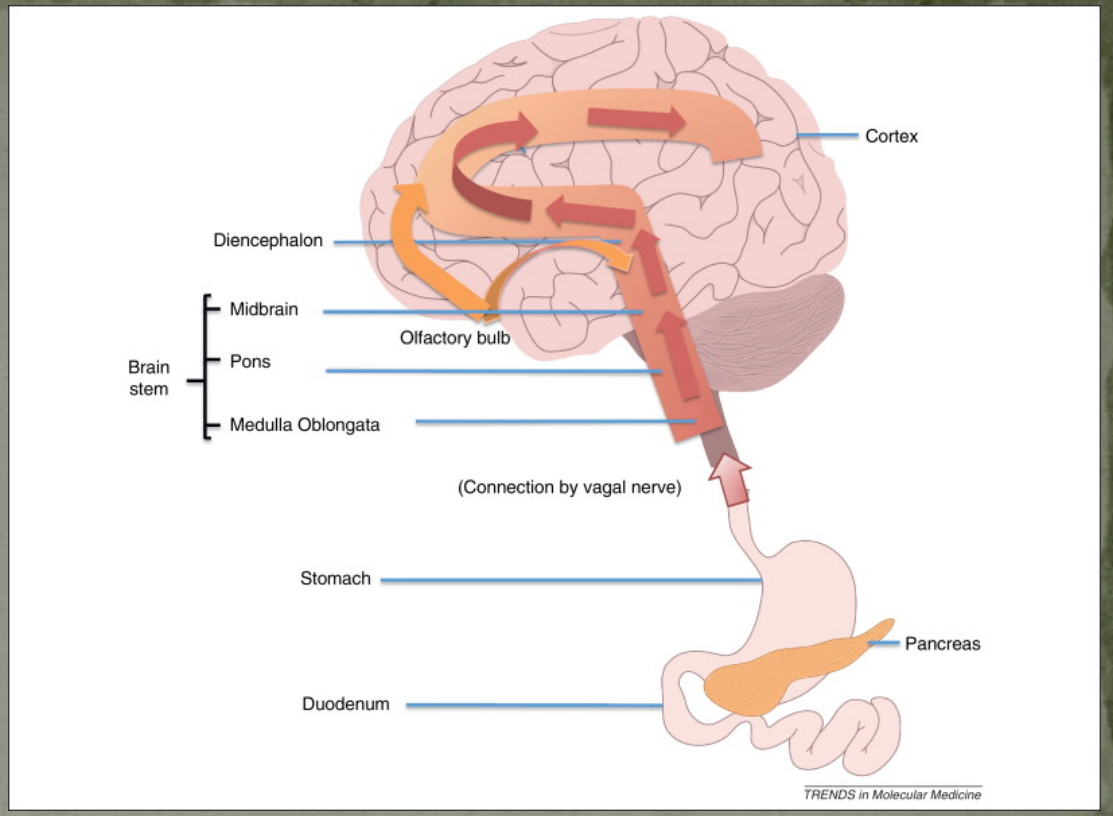


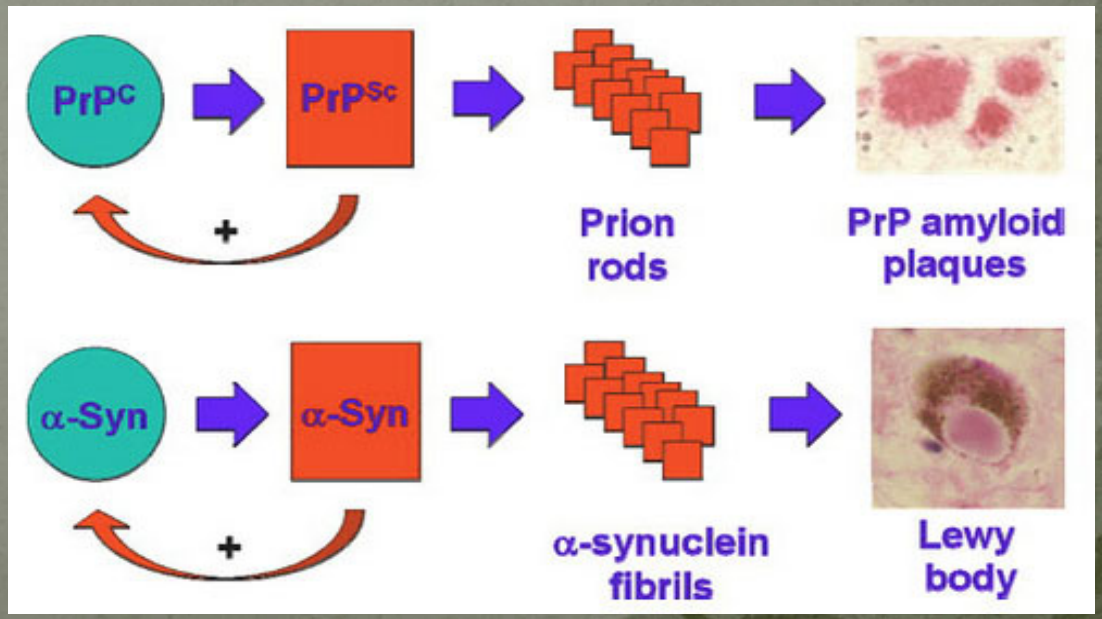
Lewy Body

α-Synuclein Oligomers Confer Toxicity



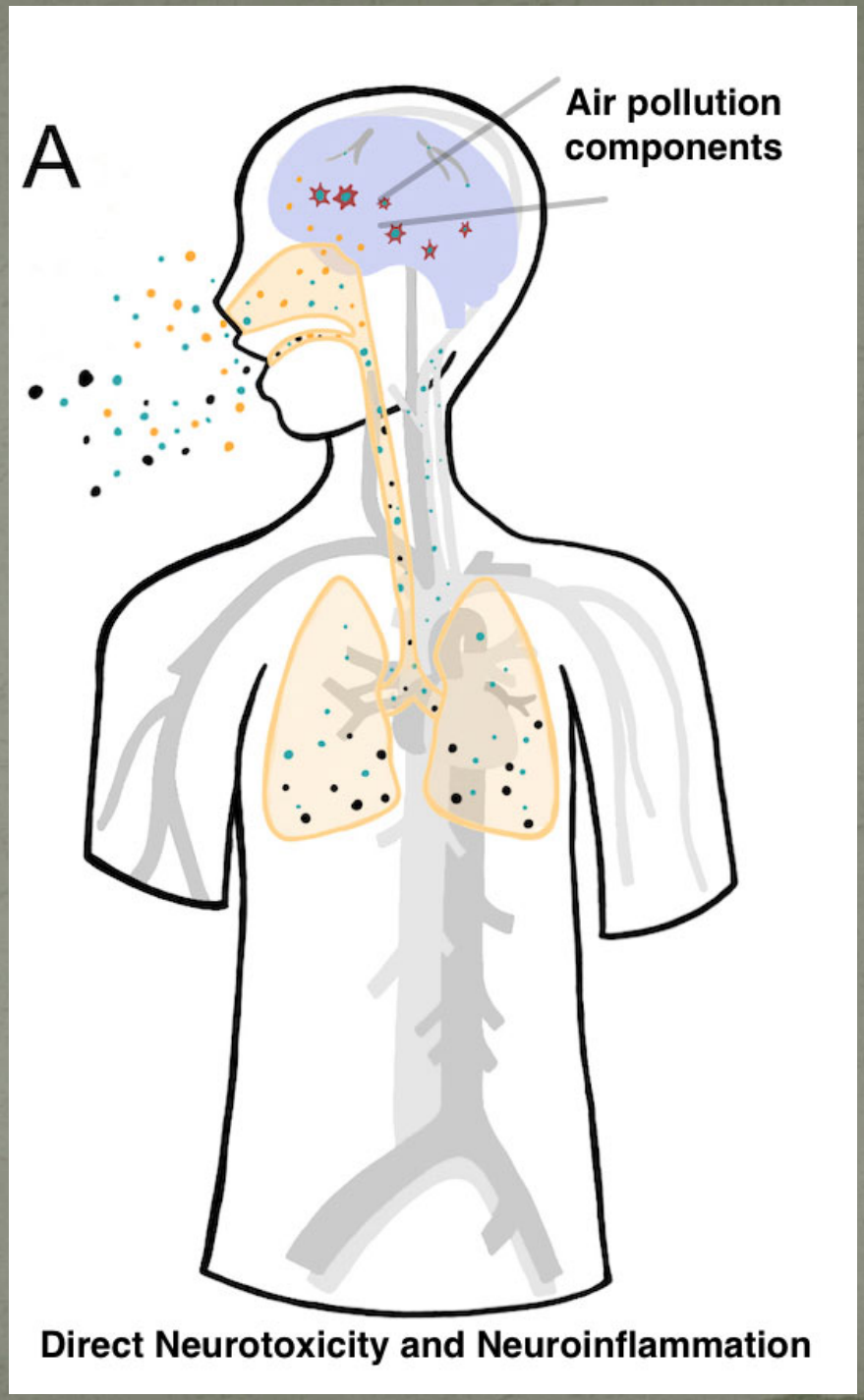
PD appears to start in the gut and/or olfactory bulb and propagate in a prion-like manner





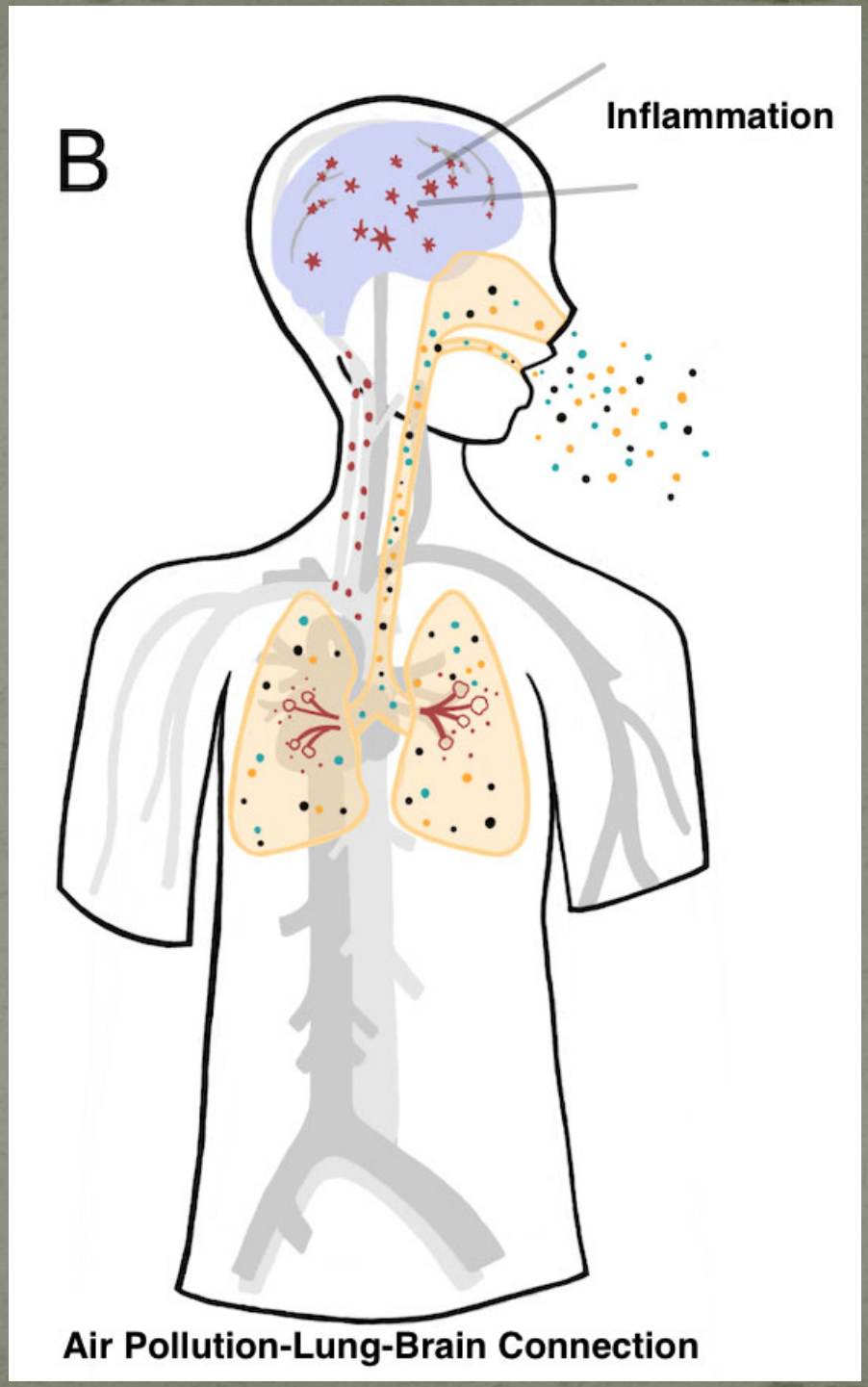
How might AP increase the risk of PD and Dementia?

- Many components of AP reach the brain and can accumulate (PAHs, metals etc.)
- These toxins can be neurotoxic and/or inflammatory



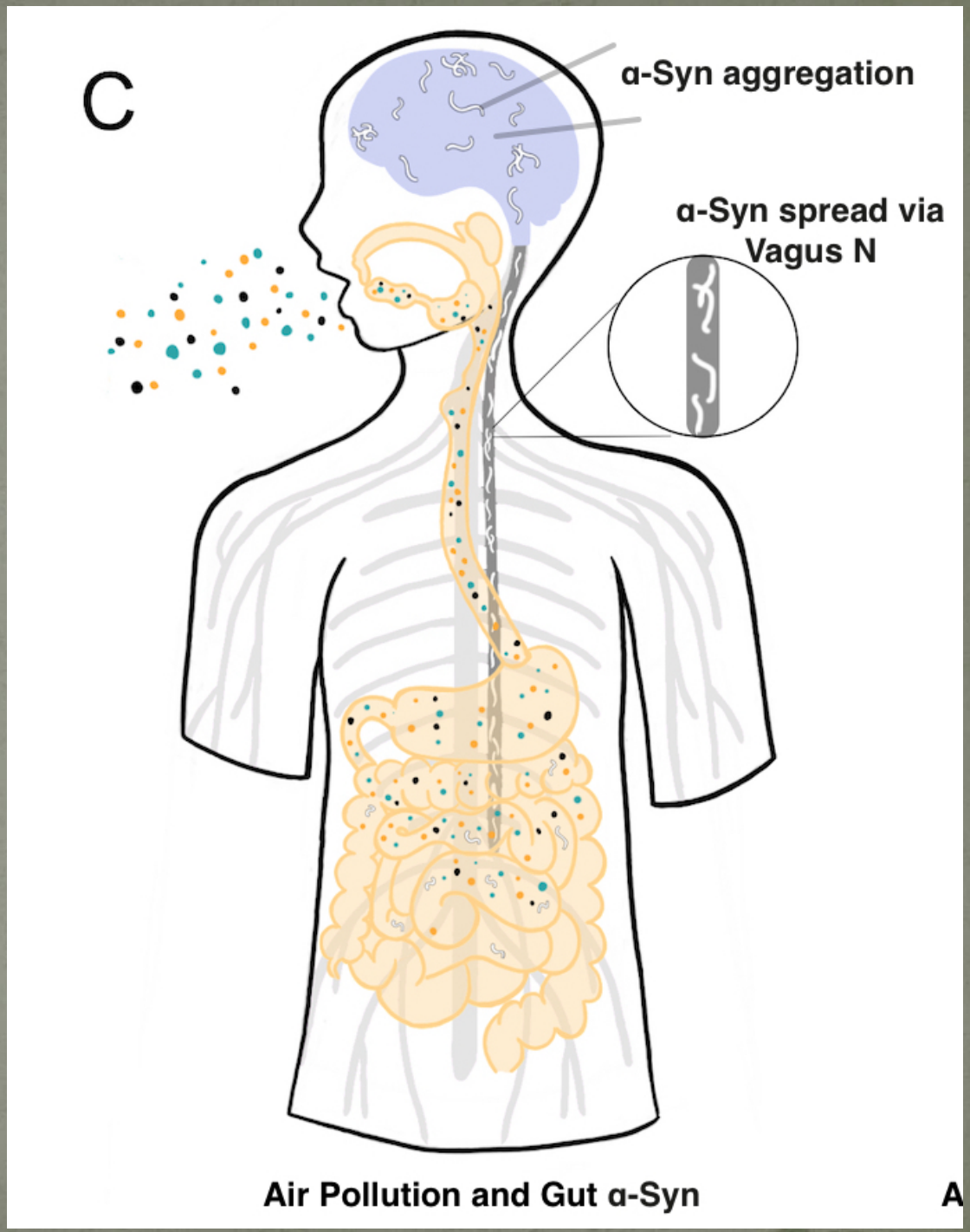
How might AP increase the risk of PD and Dementia?

- AP causes systemic inflammation (increased TNF, IL-1ß)
- In animal models, systemic inflammation can cause loss of DA neurons.
- IBD and hepatitis associated with increased risk of PD.



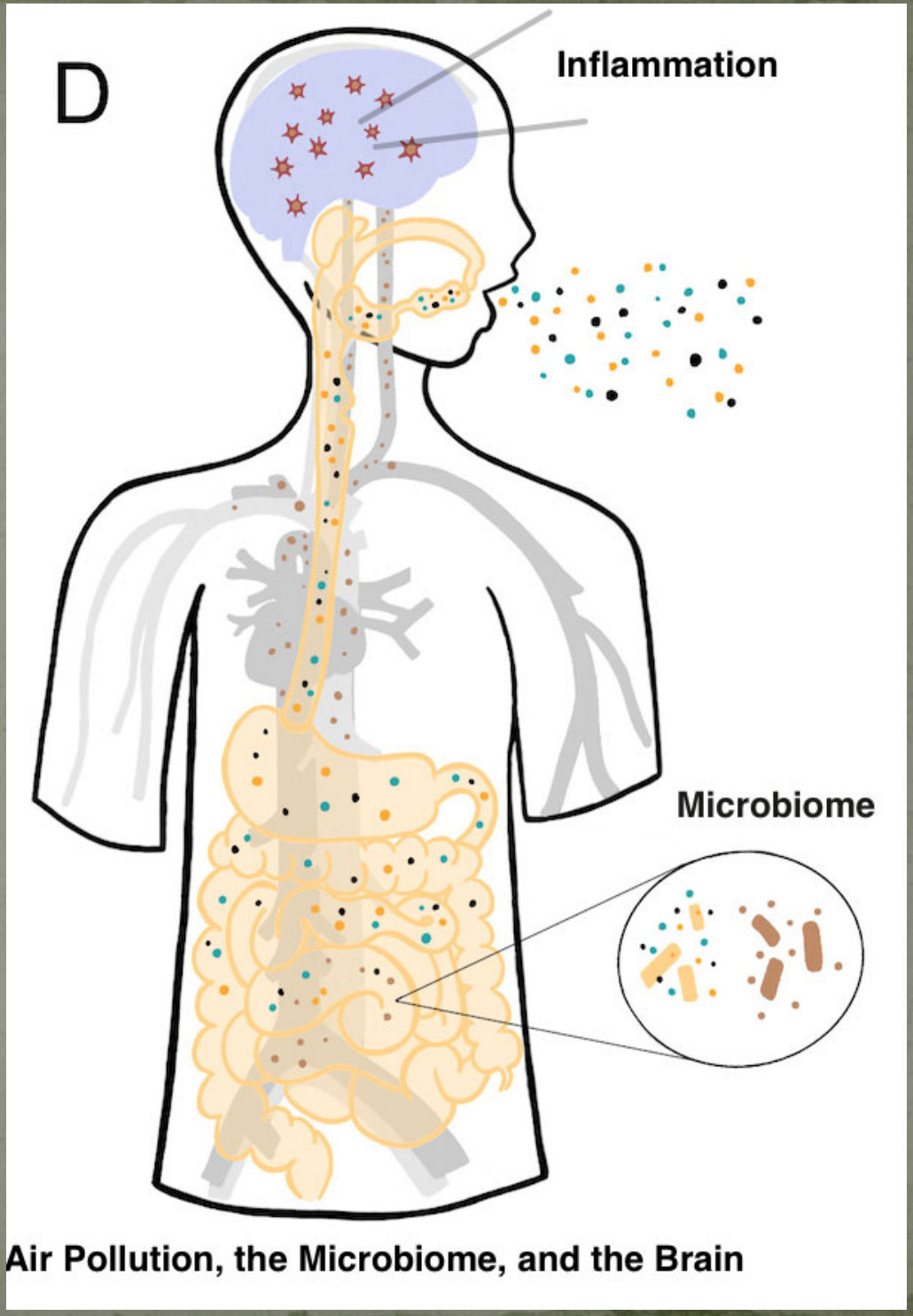
How might AP increase the risk of PD and Dementia?

- α-Synuclein found in gut neurons and can spread via vagus.
- AP causes gut inflammation and leakiness which promotes α-synuclein pathology



How might AP increase the risk of PD and Dementia?

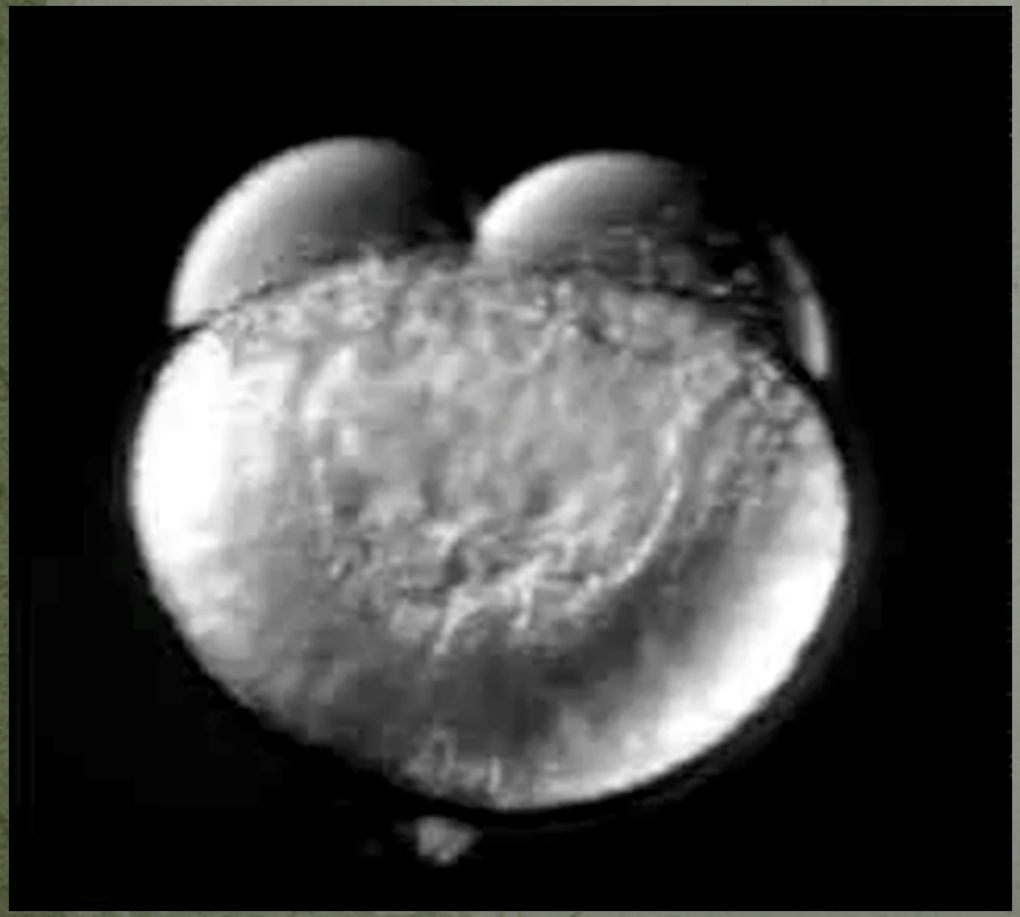
- AP alters microbiome
- Microbiome can be inflammatory
- PD is associated with altered microbiome

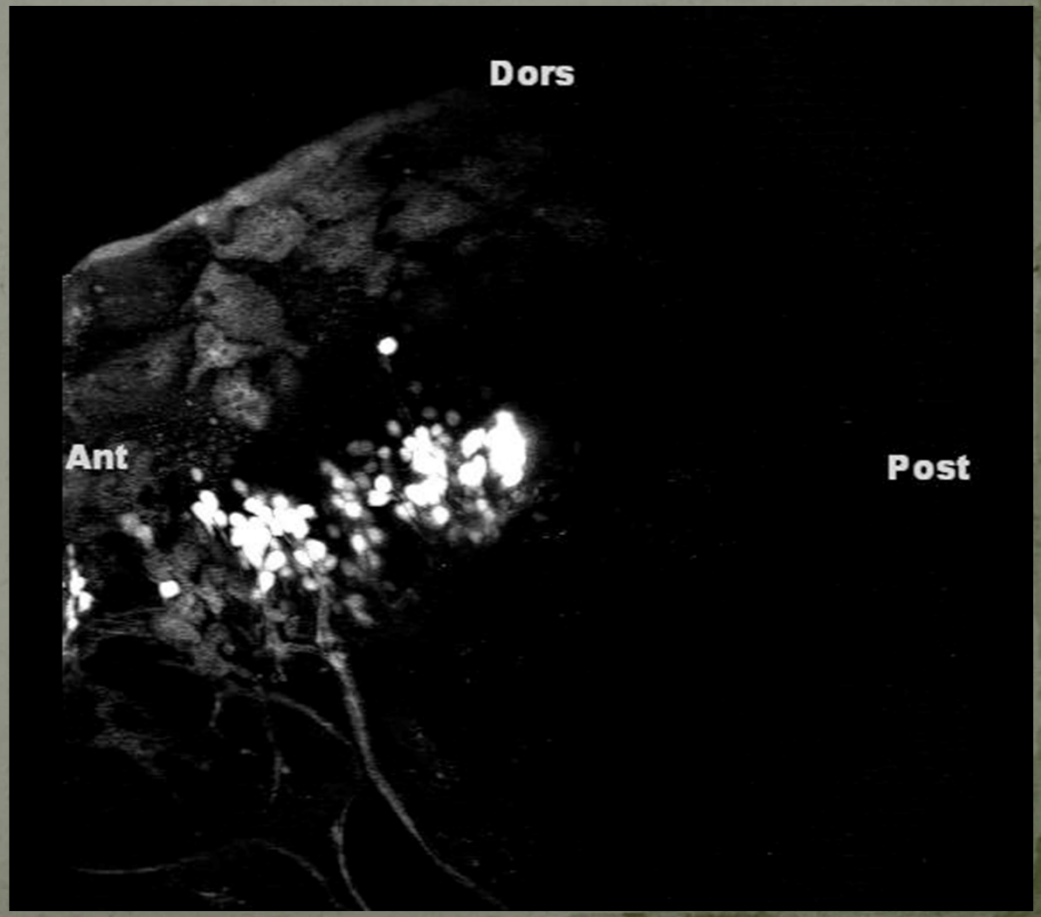


Our Studies on Direct Toxicity and Inflammation Caused by Diesel Exhaust

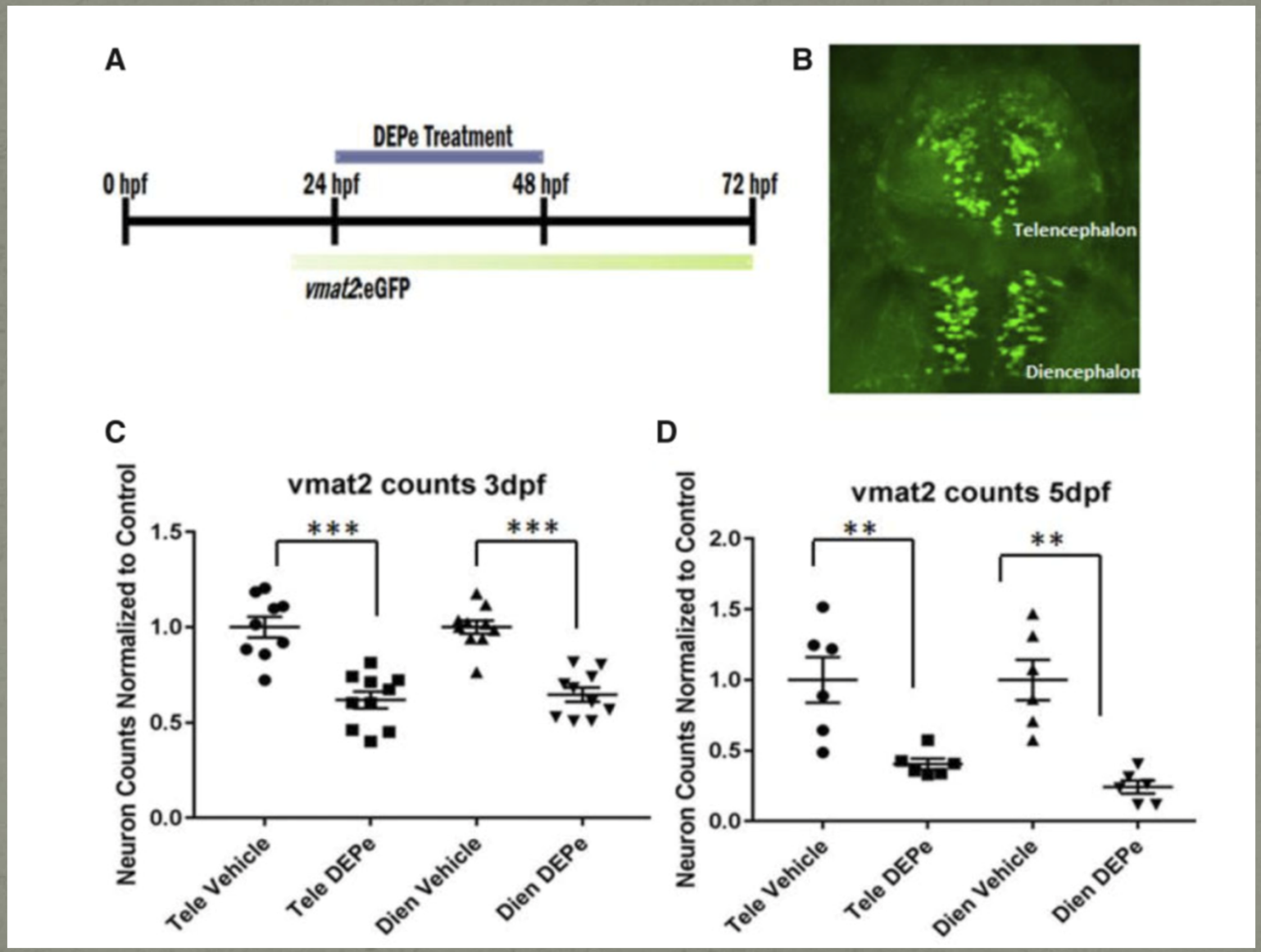
Zebrafish as a Tool to Study Molecular Mechanisms

- They develop quickly, are transparent and it is easy to modify them genetically and expose them to toxins



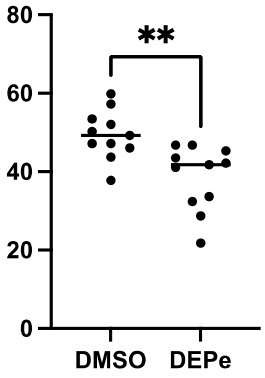


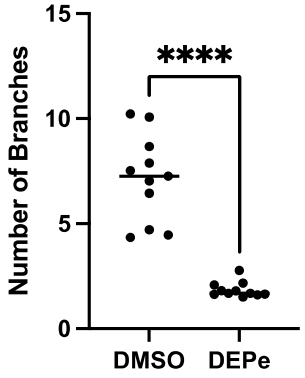
DEPe is Toxic to Aminergic Neurons

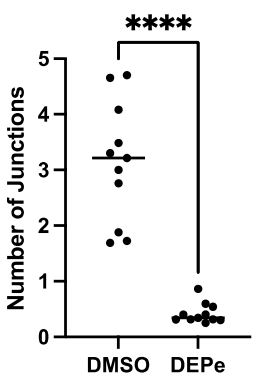


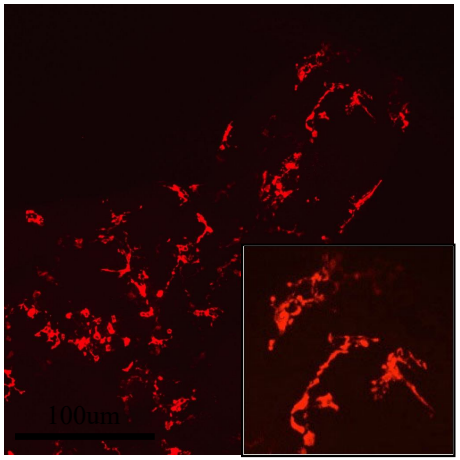
Barnhill et al (2020)

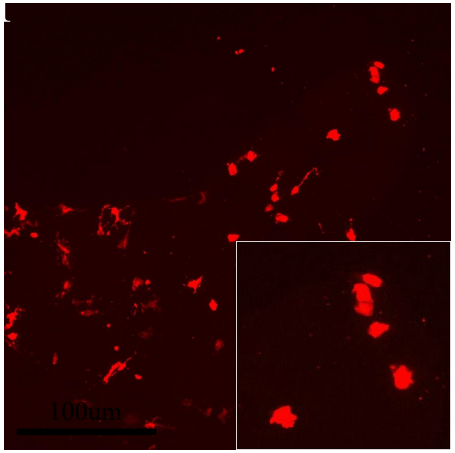
Inflammatory Response to DEPe

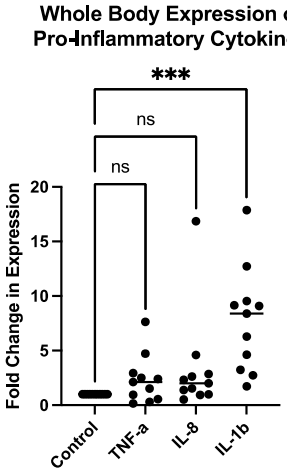


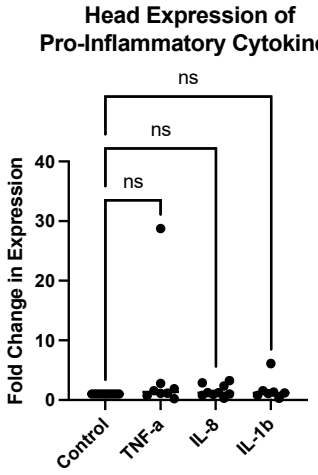


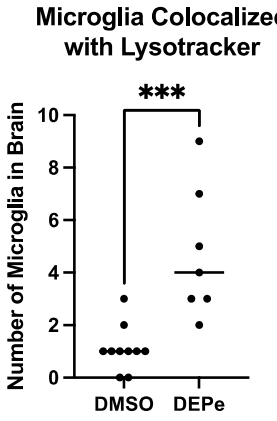


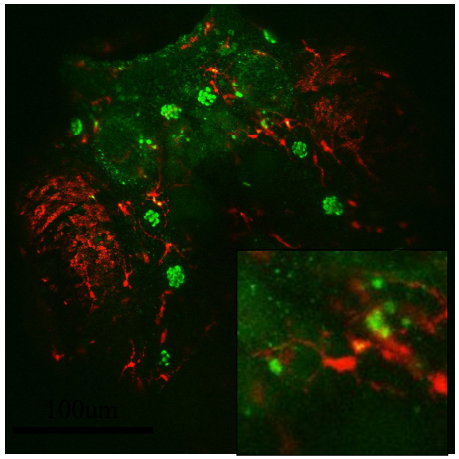


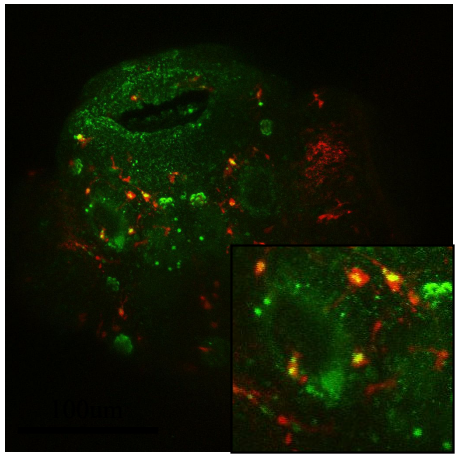




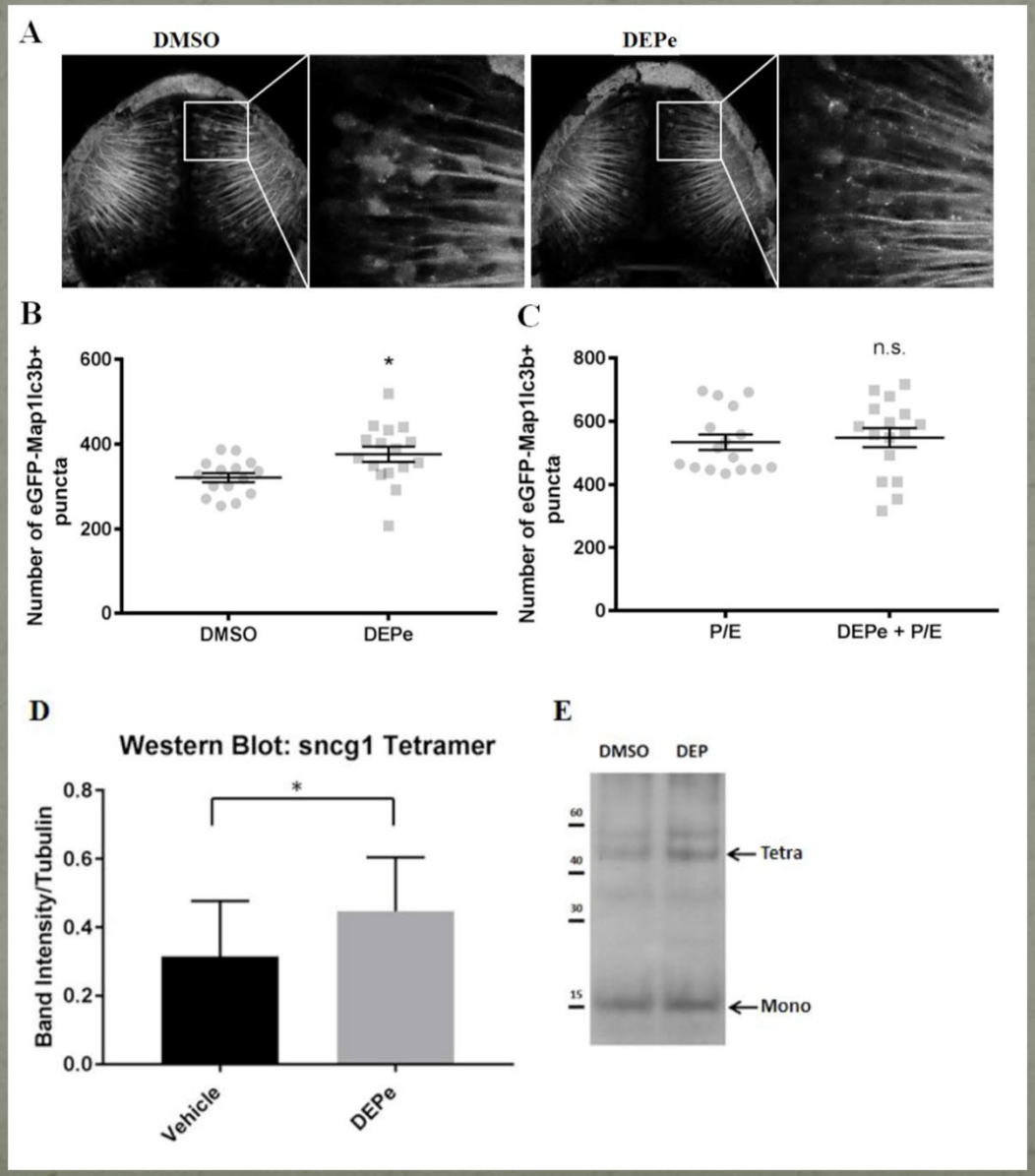






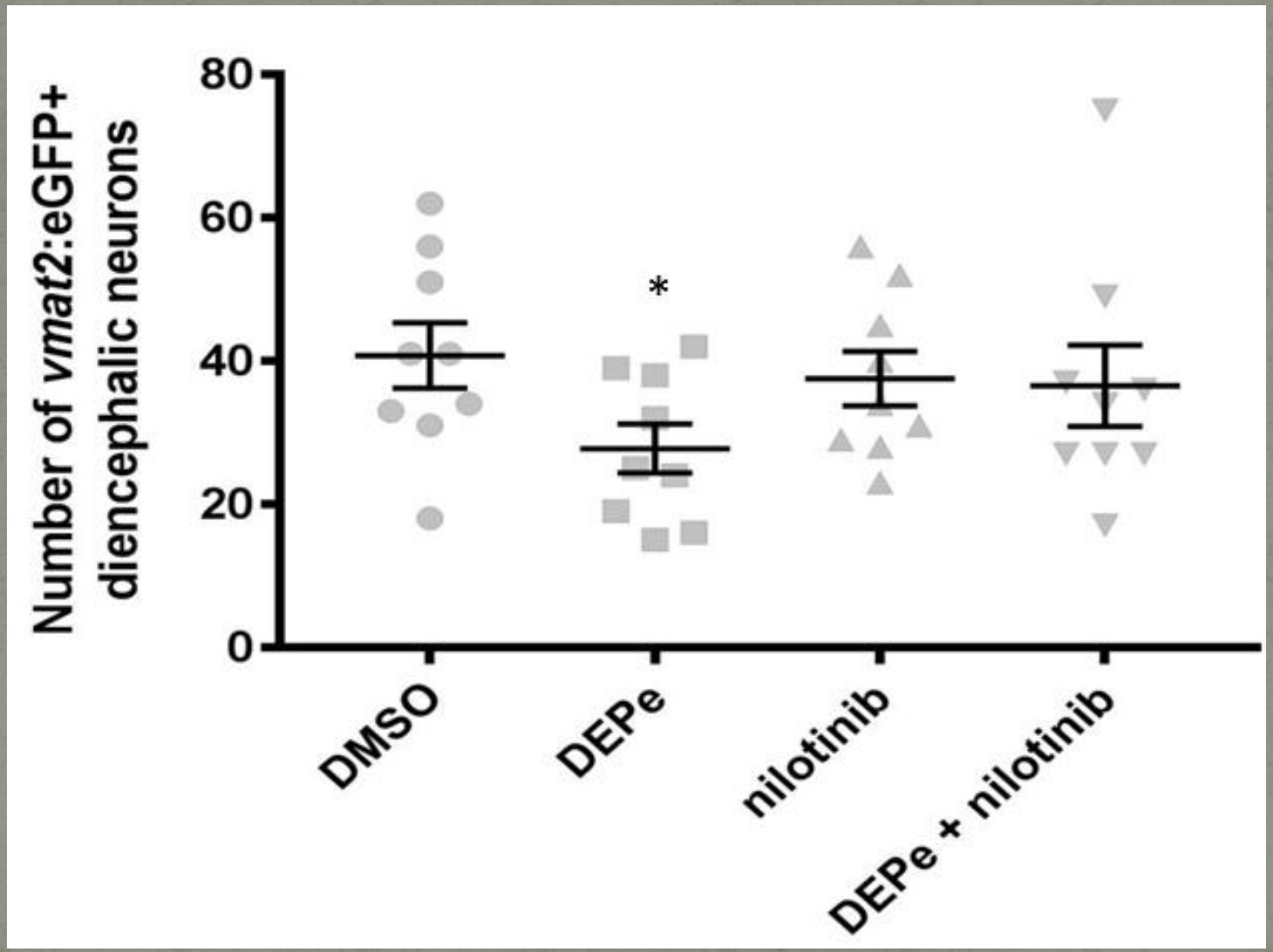


DEPe Inhibits Autophagic Flux



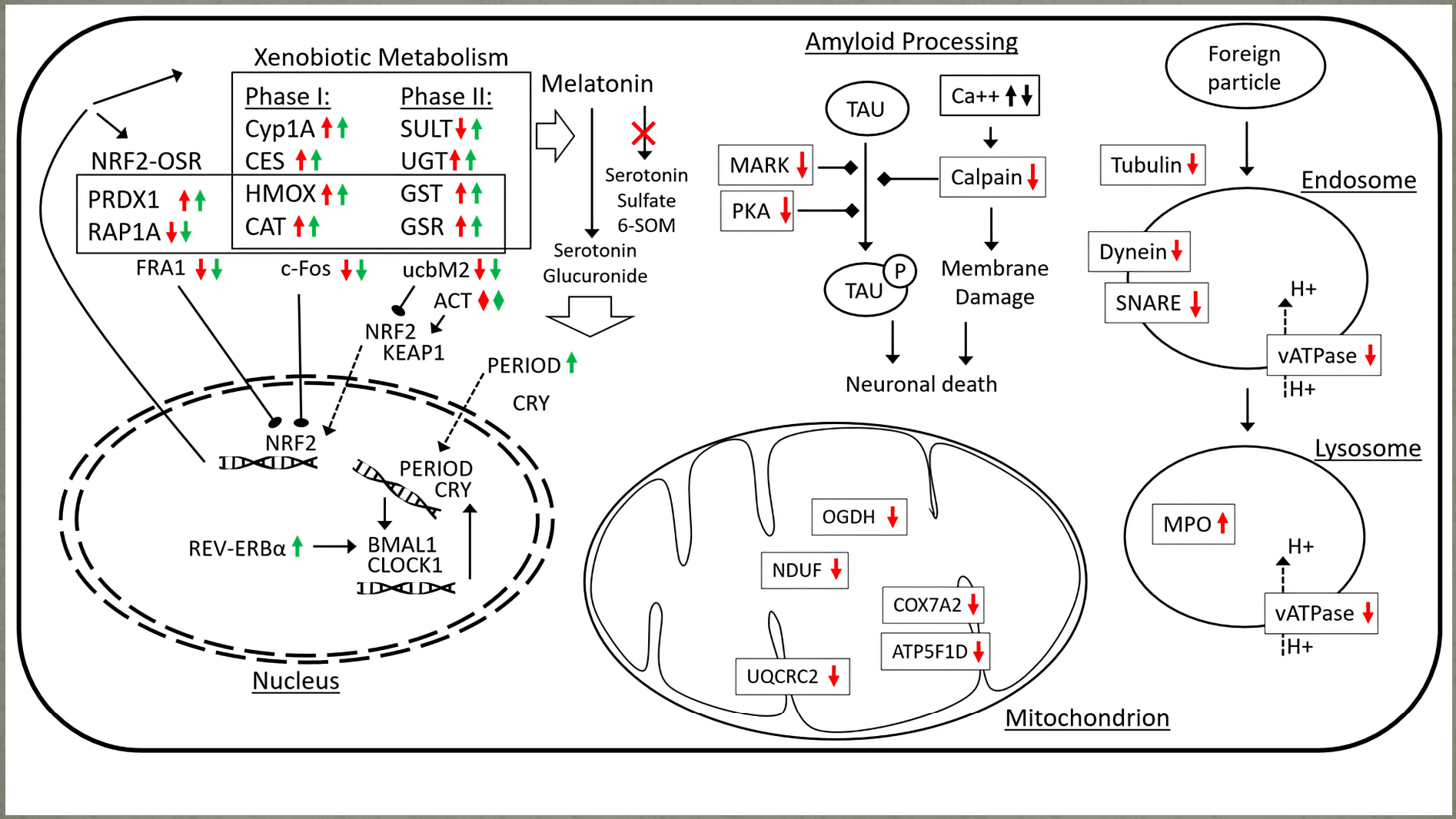
Barnhill et al (2020)

Stimulating Autophagy Rescues DEPe-Induced Neuronal Loss



Barnhill et al (2020)

Transcriptomics and Proteomics of ZF Brains



Jami et al., 2021

Overall Conclusions

- Epidemiological studies support an association of air pollution and Parkinson's disease
- Animal studies support biological plausibility
- Air pollution is likely an important risk factor for Parkinson's disease

Acknowledgments

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