The effect of air pollution on aggravation of neurodegenerative diseases

An analysis of long-term exposure to fine particulate matter and its components

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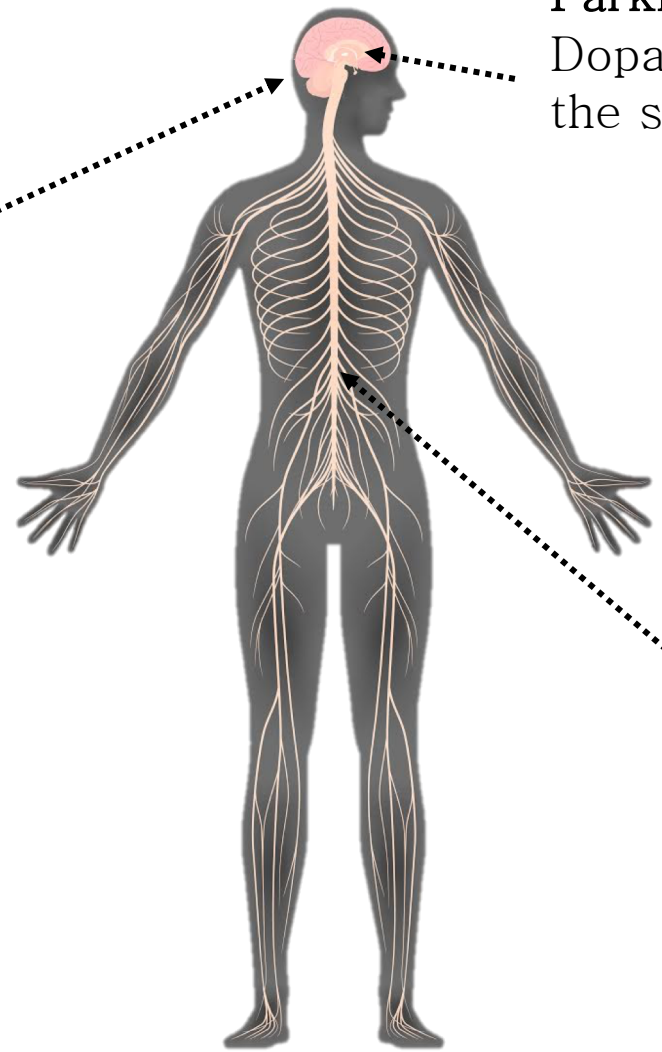
Background

Neurodegenerative diseases

Parkinson's disease (PD)
Dopaminergic-neuron loss in the substantia nigra

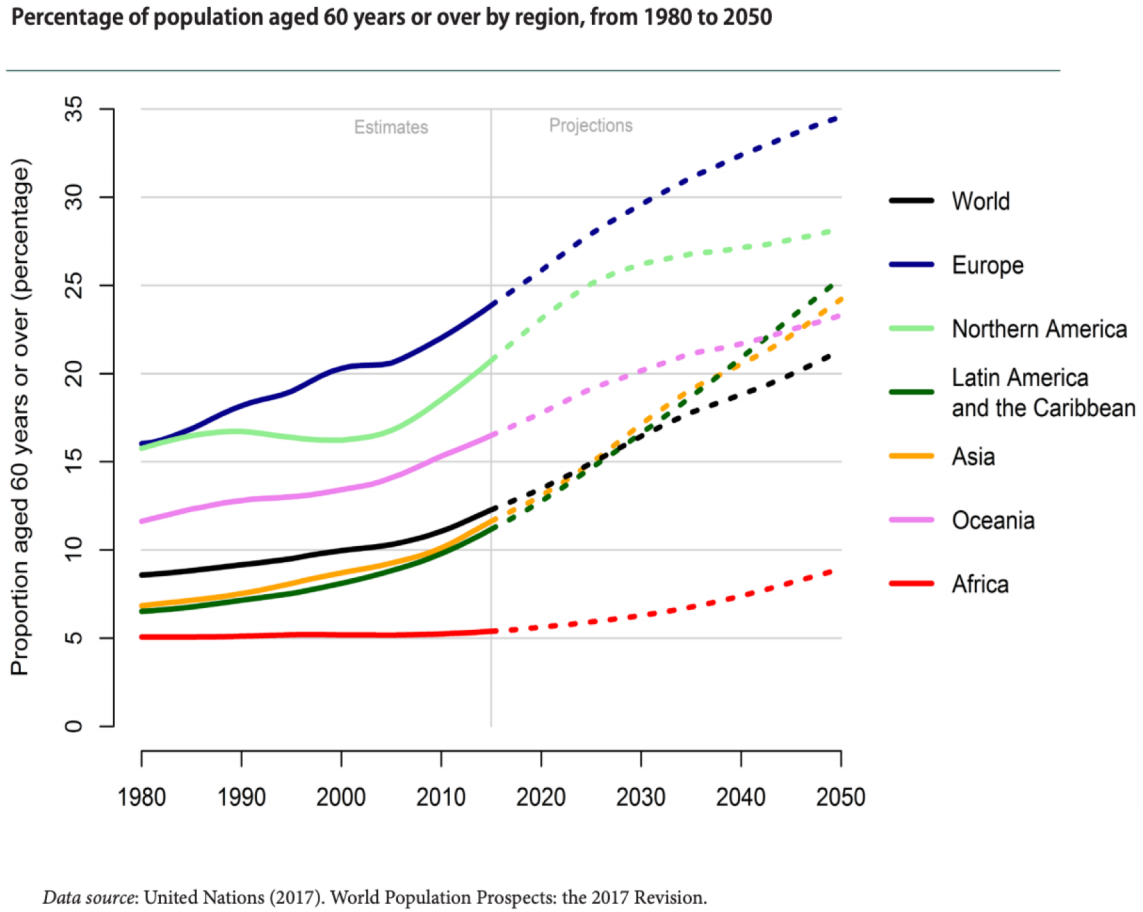
Alzheimer's disease (AD)
Progressive neuronal cell death in various brain regions



Amyotrophic lateral sclerosis (ALS)
Motor neuron degeneration and death

Neurodegenerative diseases

- Long asymptomatic pre-clinical state
- Clinical symptoms begin in older adulthood
- Disease prognosis highly variable
  - A couple years to decades
- Little known about factors that determine disease aggravation and no treatment available



Neurodegenerative diseases are costly

Average annual per-person payments for health care. Medicare beneficiaries age ≥65 years with and without Alzheimer's or other dementias, in 2018 dollars

Service	Beneficiaries with Alzheimer's or other dementias	Beneficiaries without Alzheimer's or other dementias
Inpatient hospital	$11,306	$3652
Medical provider	5728	3568
Skilled nursing facility	6977	477
Nursing home	15,984	774
Hospice	2060	156
Home health care	2578	374
Prescription medications	3503	3005
	$48, 136	$12,006

Alzheimer's Association. Alzheimer's & Dementia, 2019

Environmental and genetic factors

Genetic factors

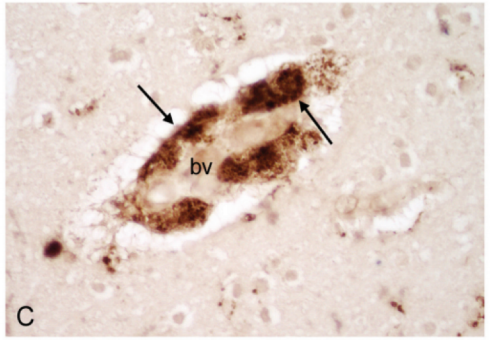
- Multiple genetic variants identified
- Majority of cases are sporadic
- Age of clinical symptom onset is variable
- Differences in disease progression rate

Environmental factors

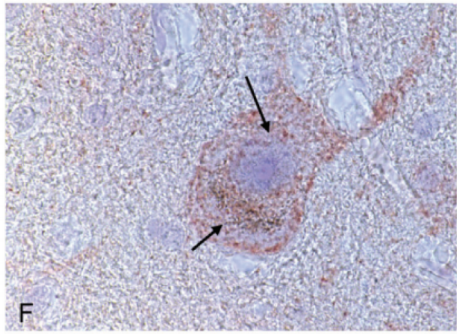
- Multiple exposures suggested but nothing confirmed
    - Metals
    - Pesticides

Air pollution effects on the nervous system

- Evidence suggests air pollution affects the central nervous system
- Linked with neuropathological changes
  - Neuroinflammation
  - Proteinopathies
  - Oxidative stress



CD68 & microglia in blood vessels of the brain



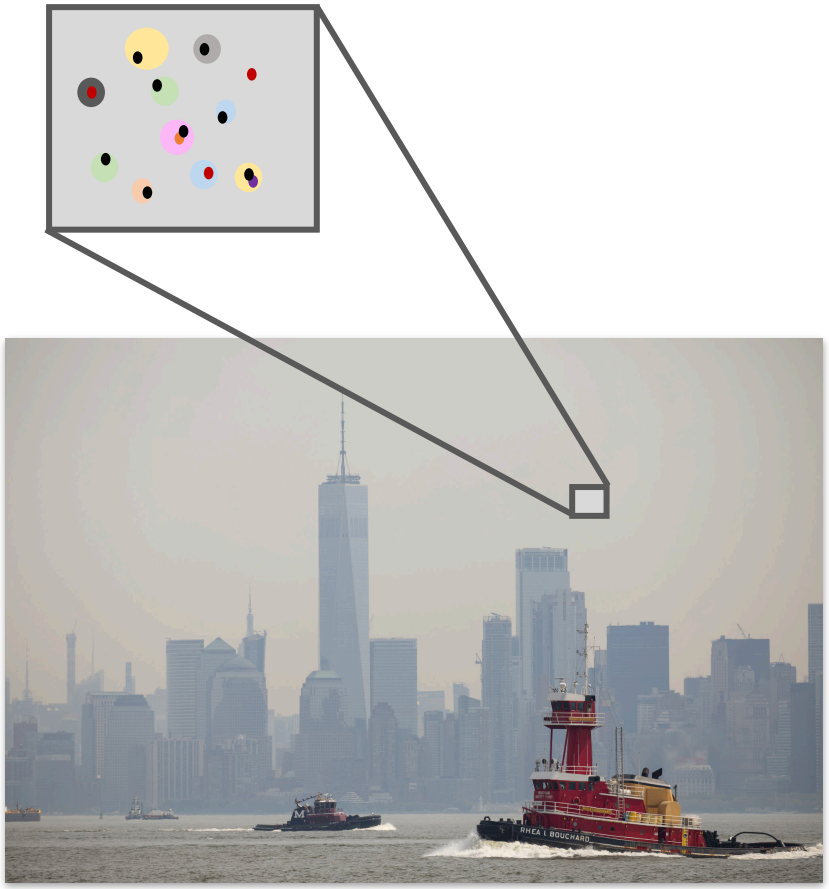
α-synuclein-positive granular stain in substantia nigra cells

Fine particulate matter has most consistently been implicated in adverse neurological processes

Calderon-Carciduenas, L., et al. Toxicologic Pathology, 2008

Fine particulate matter is a mixture

- Fine particulate matter ($PM_{2.5}$)
  - Any particle ≤ 2.5 μm in diameter
  - Total $PM_{2.5}$ mass consists of different chemical components
- $PM_{2.5}$ total mass represents a mixture of pollutants
- Local sources of pollution and other factors (e.g. weather) influence $PM_{2.5}$ composition



$PM_{2.5}$ composition varies

- Main $PM_{2.5}$ components
  - Organic matter
  - Sulfates
  - Nitrates
  - Black carbon
  - Trace amounts of metals
- Proportion of each component varies temporally and geographically

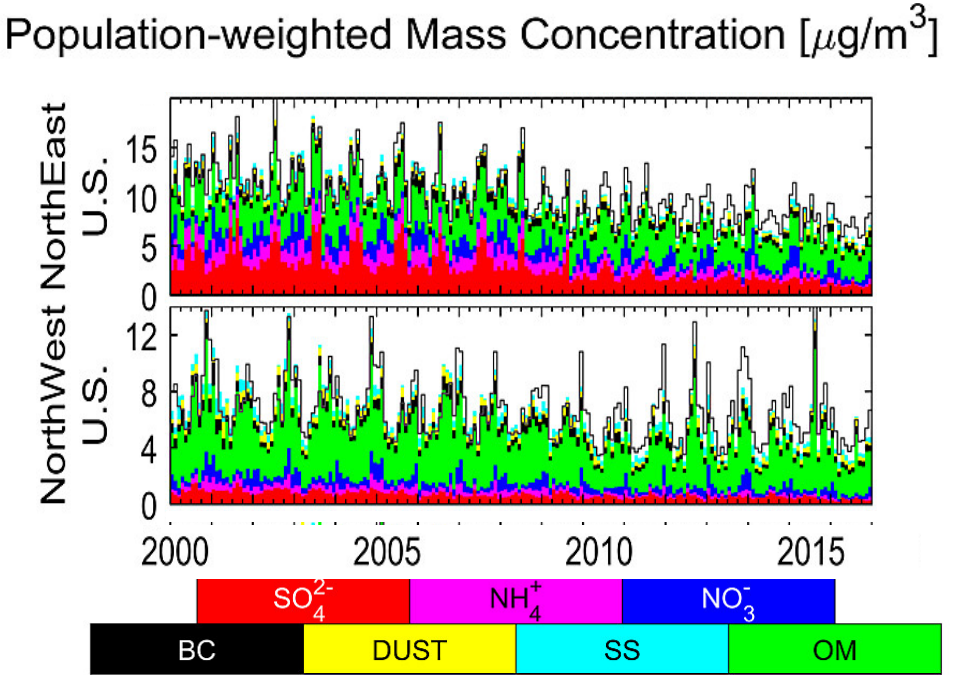
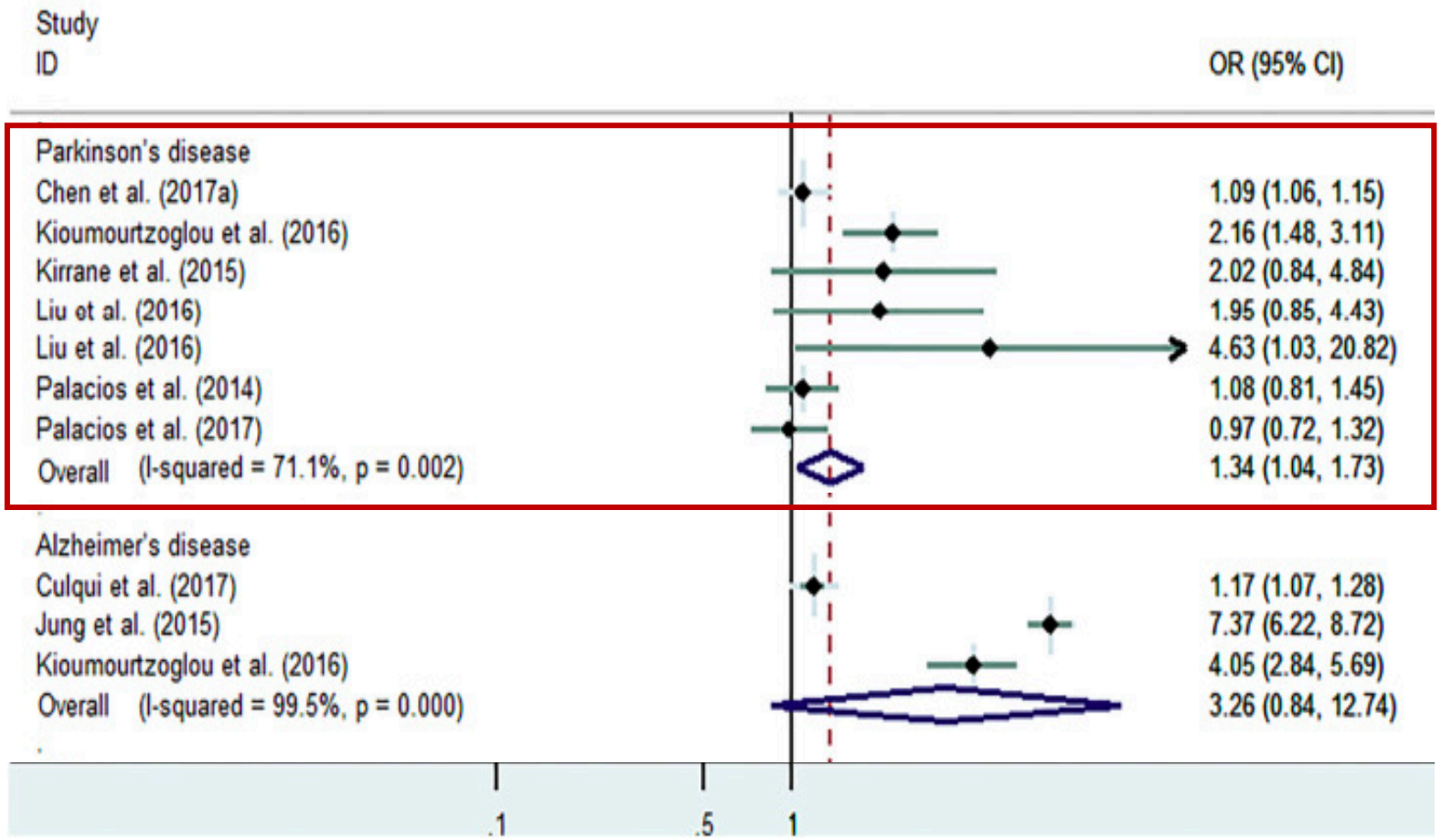


Fig. adapted from Donkelaar, A., et al. American Chemical Society, 2019

$PM_{2.5}$ and neurodegenerative diseases

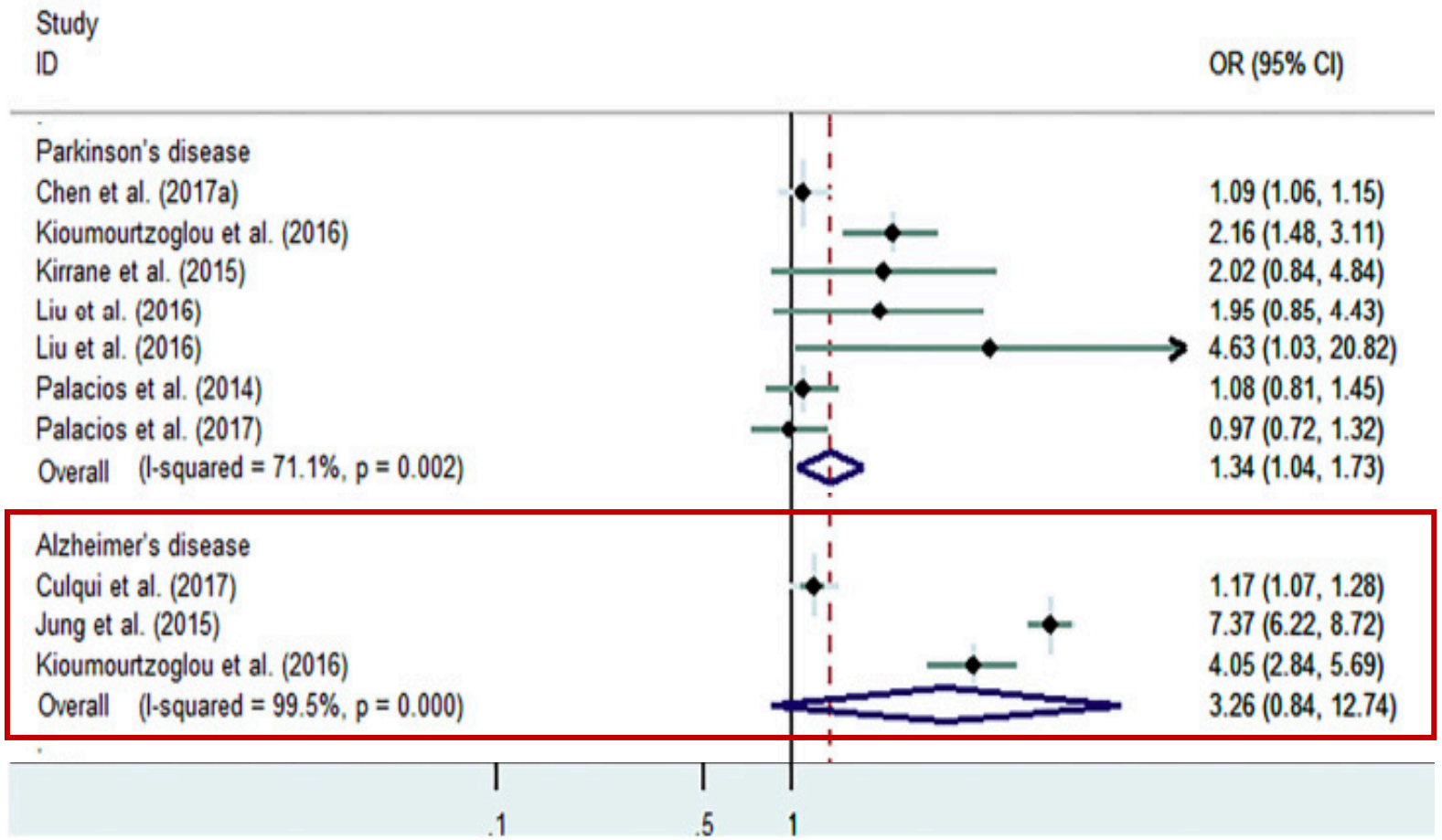
- $PM_{2.5}$ composition
- Differences across results



Plot adapted from Pengfei, F., et al. Sci of the Total Env., 2019

$PM_{2.5}$ and neurodegenerative diseases

- $PM_{2.5}$ composition
- Differences across results
- Disease aggravation less studied



Plot adapted from Pengfei, F., et al. Sci of the Total Env., 2019

Overall Research Question

Does long-term $PM_{2.5}$ exposure contribute to **disease aggravation** in neurodegenerative diseases?

1. **Total $PM_{2.5}$ mixture effect**
   - Parkinson's disease
   - Alzheimer's disease
   - Amyotrophic lateral sclerosis

2. **Effect of specific $PM_{2.5}$ components**
   - Parkinson's disease

Fine Particle Exposure and Hospital Admissions for Neurodegenerative Diseases in New York State

Yanelli Nunez, Amelia K. Boehme, Marc G. Weisskopf, Diane B. Re, Ana Navas-Acien, Aaron V. Donkelaar, Randall V. Martin, and Marianthi-Anna Kioumourtzoglou

Hospitalization data

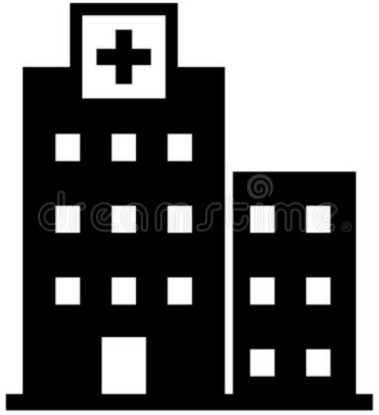
- SPARCS
- 98% of all hospitalizations in non-federal acute care facilities
- International Classification of Diseases 9 (ICD-9)
- Annual-county-counts of first hospitalization
- Years 2000-2014
- Years 1995-1999 to remove prevalent cases

NEW YORK STATE | SPARCS Statewide Planning and Research Cooperative System

First hospitalization: surrogate of aggravation

Crossing point to a more severe stage of the disease

Discharge to nursing home care



Disease Progression Timeline

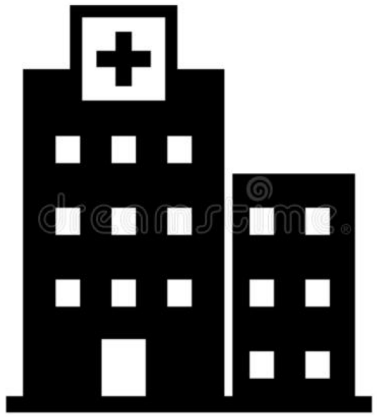
Disease onset

Clinical diagnosis

First hospitalization

Advanced disease stage

First hospitalization: surrogate of aggravation



First hospitalization

Primary diagnosis code

Health events **directly** related to the disease

1. Symptoms not exclusive to motor and cognitive deficits
2. Collateral health damage

Secondary diagnosis code

Health events **indirectly** related to the disease

Better representation of the stage of disease

- More hospitalizations in patients with a neurodegenerative disease
- Increased hospital visits as disease progresses
- 50% of admissions at advanced stages of disease

Annual per-county counts of first hospitalizations from 2000—2014 in NYS

	Mean	St Dev	25%	Median	75%
Outcome					
AD	283.9	469.1	45.0	82.0	260.0
Female	191.0	319.0	29.0	53.0	173.0
Male	93.6	151.0	16.0	30.0	87.7
<70 years	19.9	35.5	3.0	6.0	17.0
≥70 years	265.0	436.0	42.0	76.0	244.7
PD	131.1	222.0	21.0	37.0	121.0
Female	57.8	98.8	9.0	16.0	52.0
Male	65.4	110.0	11.0	19.0	60.0
<70 years	29.0	51.6	4.0	9.0	26.0
≥70 years	94.9	160.0	15.0	26.0	86.0
ALS	6.0	9.5	1.0	2.0	6.0
Female	2.7	4.5	0.0	1.0	3.0
Male	3.3	5.3	0.0	1.0	3.0
<70 years	4.2	6.49	1.0	2.0	4.0
≥70 years	2.9	3.9	1.0	1.0	3.0

Nunez, Y., et al. Env. Health Perspectives. *Under revision*

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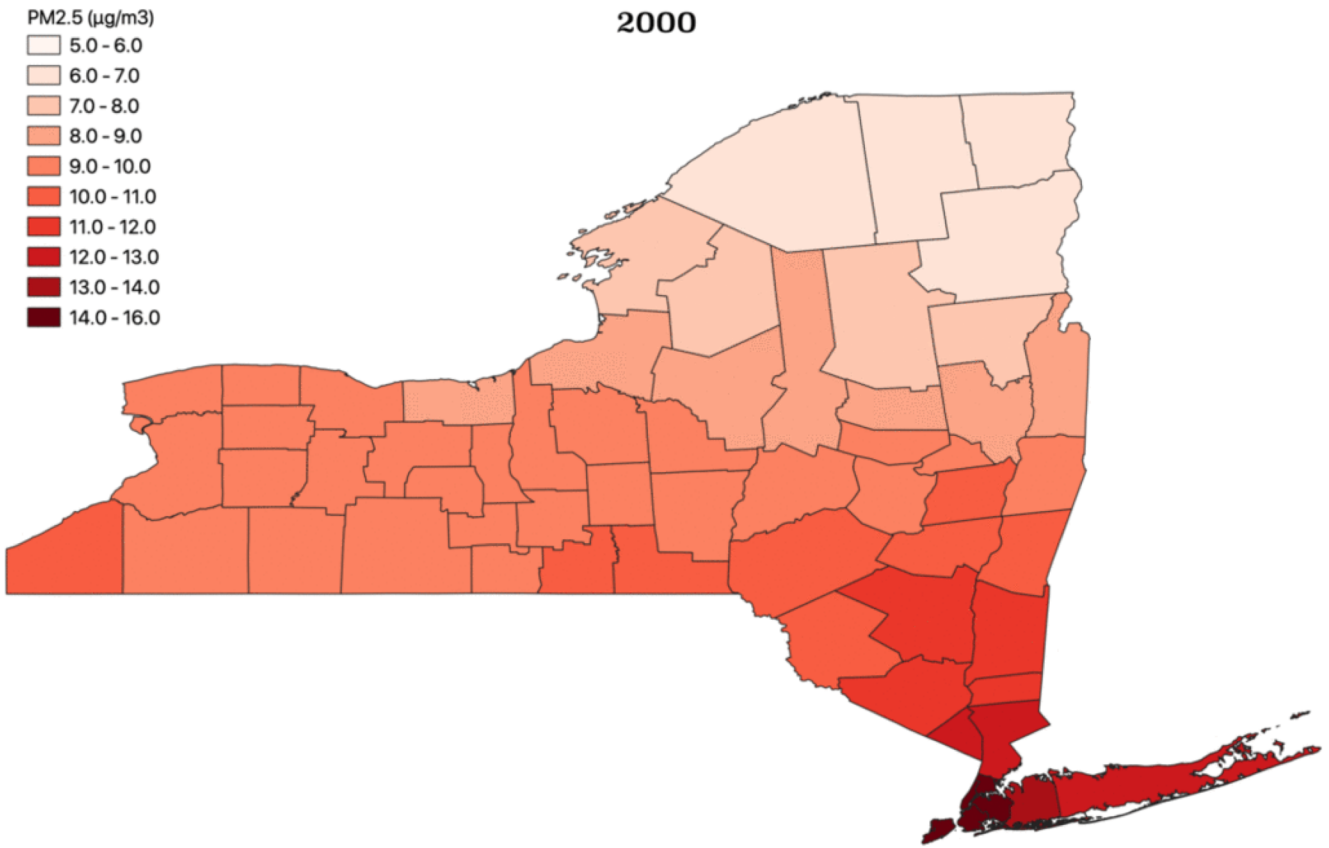
Exposure assessment

- $PM_{2.5}$ prediction model by Van Donkelaar et al., 2019
- Based on aerosol optical depth estimates, chemical transport models and geographically weighted regression
- High accuracy ($R^2 = 0.76$)
- 1km × 1km grid resolution
- Annual county-level averages
- Years 2000-2014

Geographic & temporal contrast

Annual concentrations of $PM_{2.5}$ per county from 2000–2014



Nunez, Y., et al. Env. Health Perspectives. *Under revision*

Statistical model

- Separate models for each disease: AD, PD, ALS
- Quasi-Poisson generalized additive mixed model to estimate rate ratio (RR) and 95% confidence intervals (CIs)

Counties as random term

Exposure: Annual $PM_{2.5}$ average concentrations per county

Account for county population size

$$\text{Log}(E[y_{ct}]) = (\beta_0 + b_{0\{c\}}) + s(PM_{2.5\{ct\}}) + s(C_{\{ct\}}) + \text{offset}(\text{population})$$

Outcome: Annual first hospitalization counts per county

- Sex
- Age (≥70 & <70 years)

Assess nonlinearity

Covariates:

- Socioeconomic status
- Weather
- Year

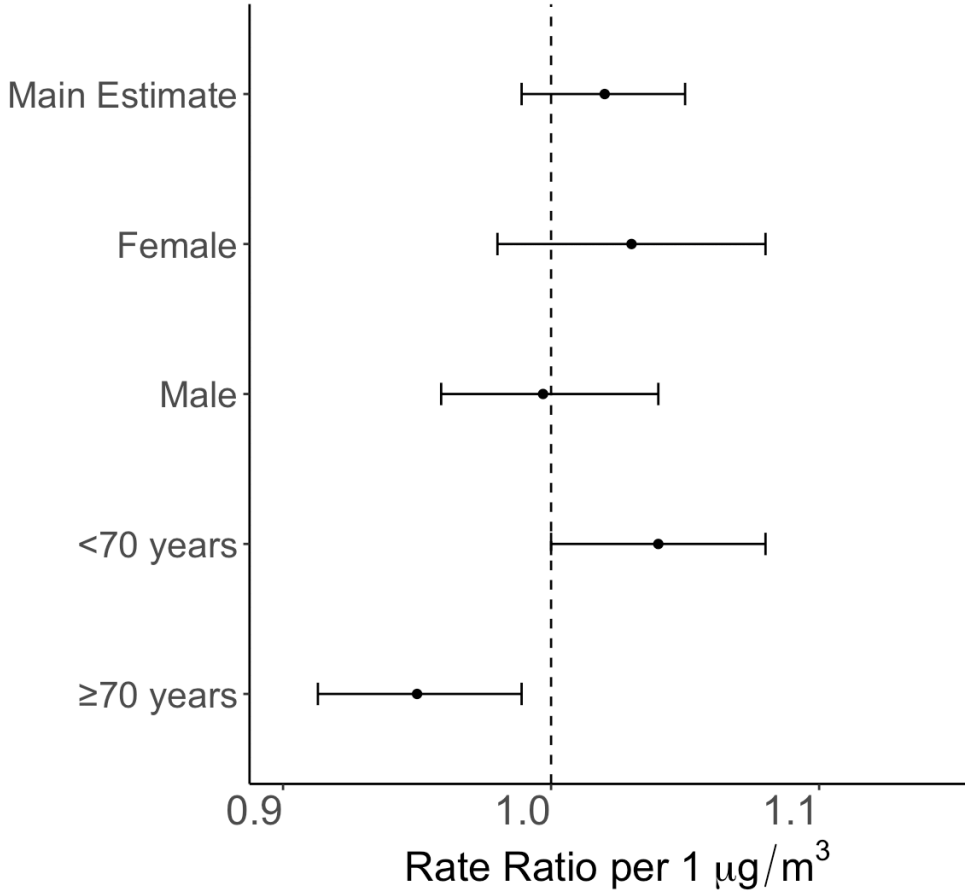
Sensitivity analysis

Minimize false positives due to disease misclassification

- At least two hospitalizations with primary or secondary diagnosis for the disease
- Second hospitalization as a diagnosis verification

Results

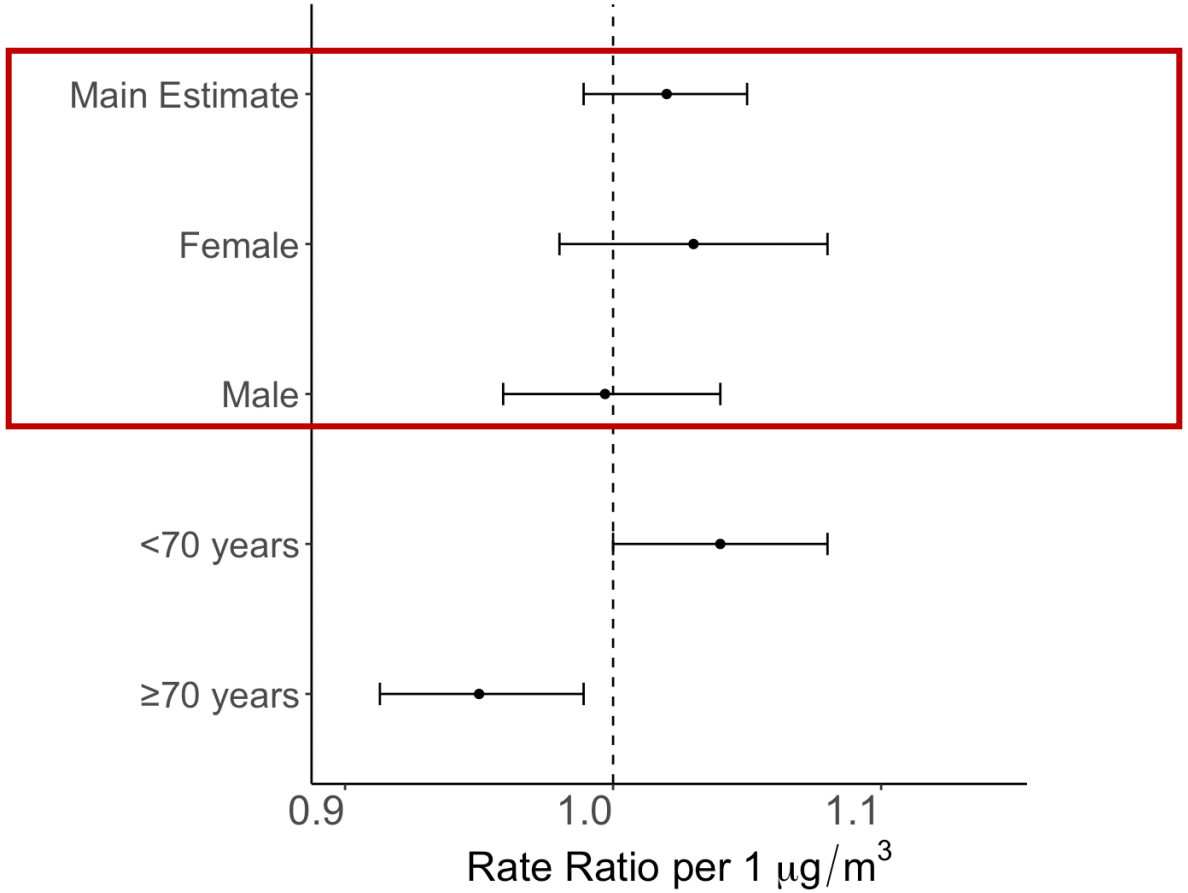
$PM_{2.5}$ and ALS first hospitalizations



No deviations from linearity

Nunez, Y., et al. Env. Health Perspectives. *In revision*

$PM_{2.5}$ and ALS first hospitalizations



No significant overall association or effect modification by sex

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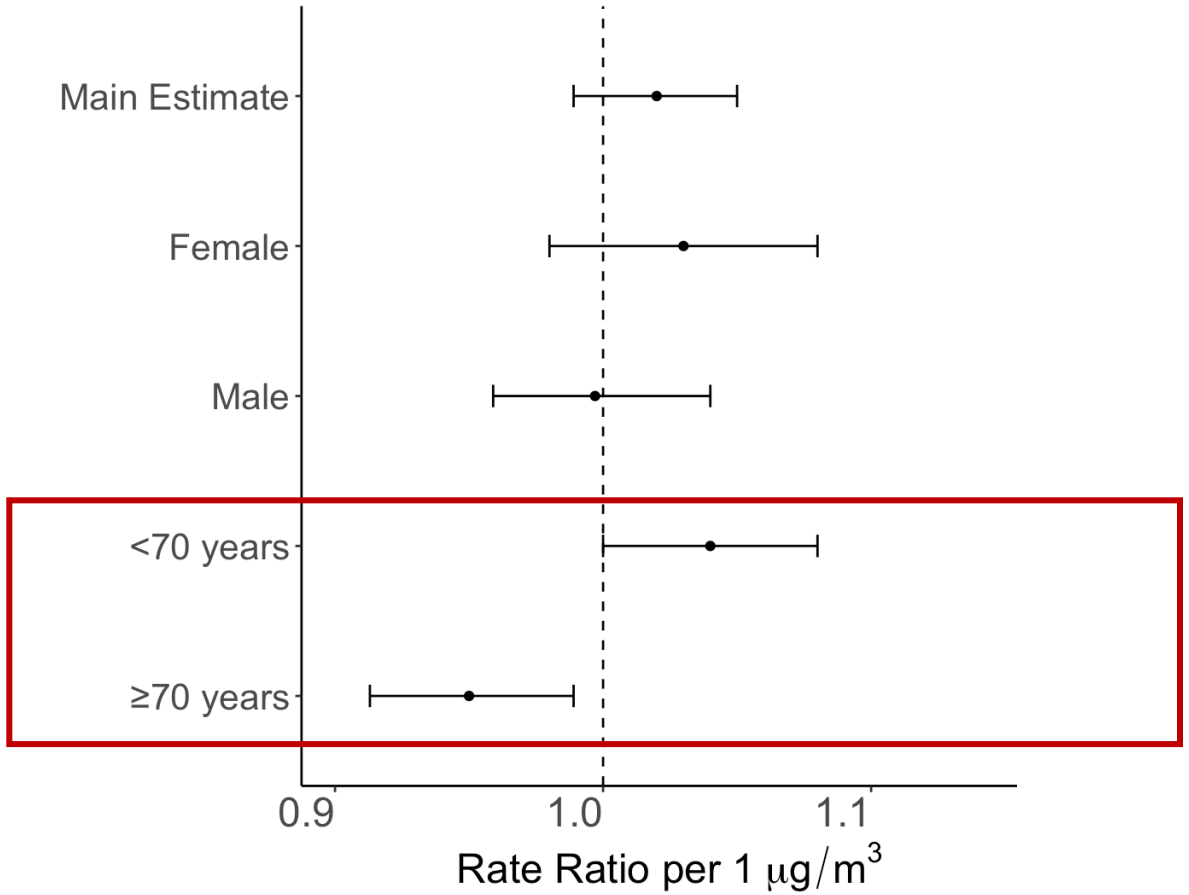
$PM_{2.5}$ and ALS first hospitalizations



Effect modification by age

- Positive association <70 years old (RR = 1.04, 95% CI: 1.00-1.08)
- Negative association ≥ 70 years old (RR = 0.95, 95% CI: 0.91-0.99)

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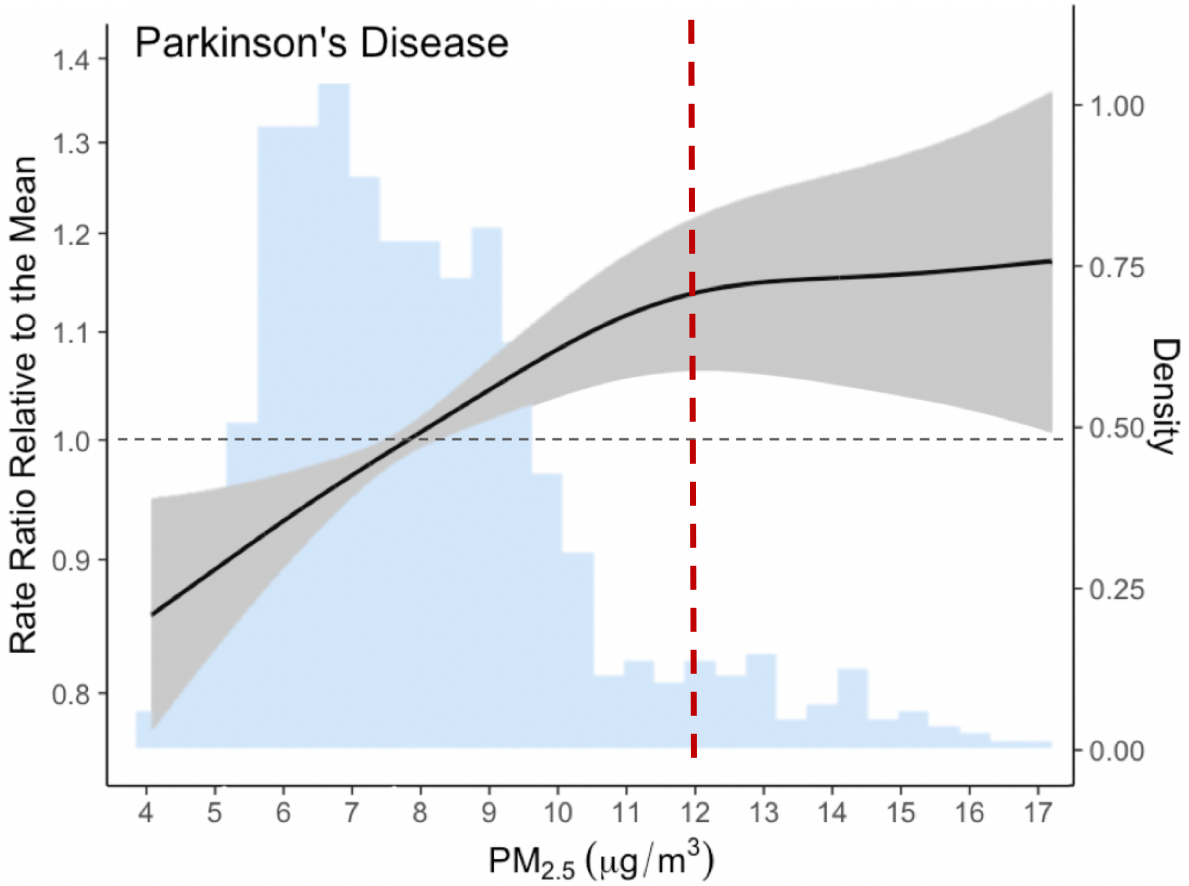
$PM_{2.5}$ and PD first hospitalizations



Nonlinear positive association

- Steeper slope at lower concentrations
- Significant association even at concentrations below current National Ambient Air Quality Standards (NAAQS)

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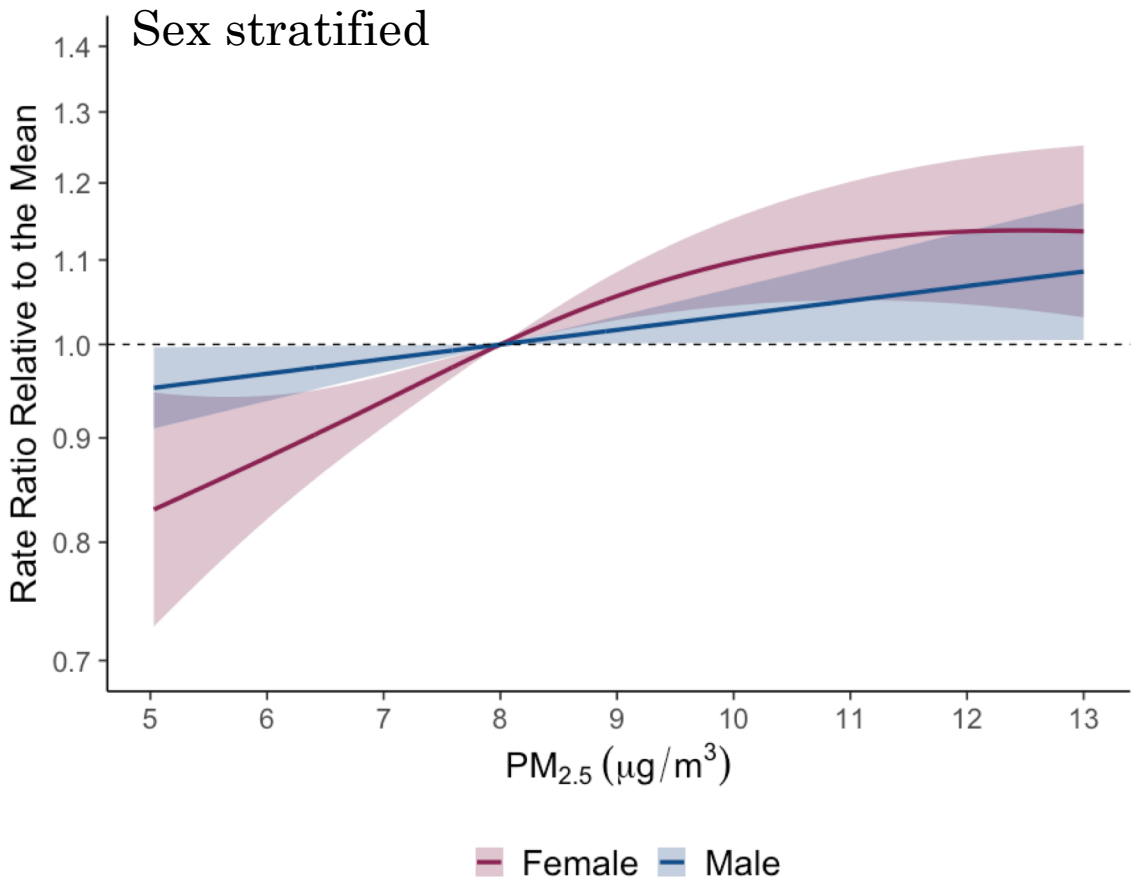
No sex effect modification in PD



- No effect modification by sex
- Positive significant associations in both male and female

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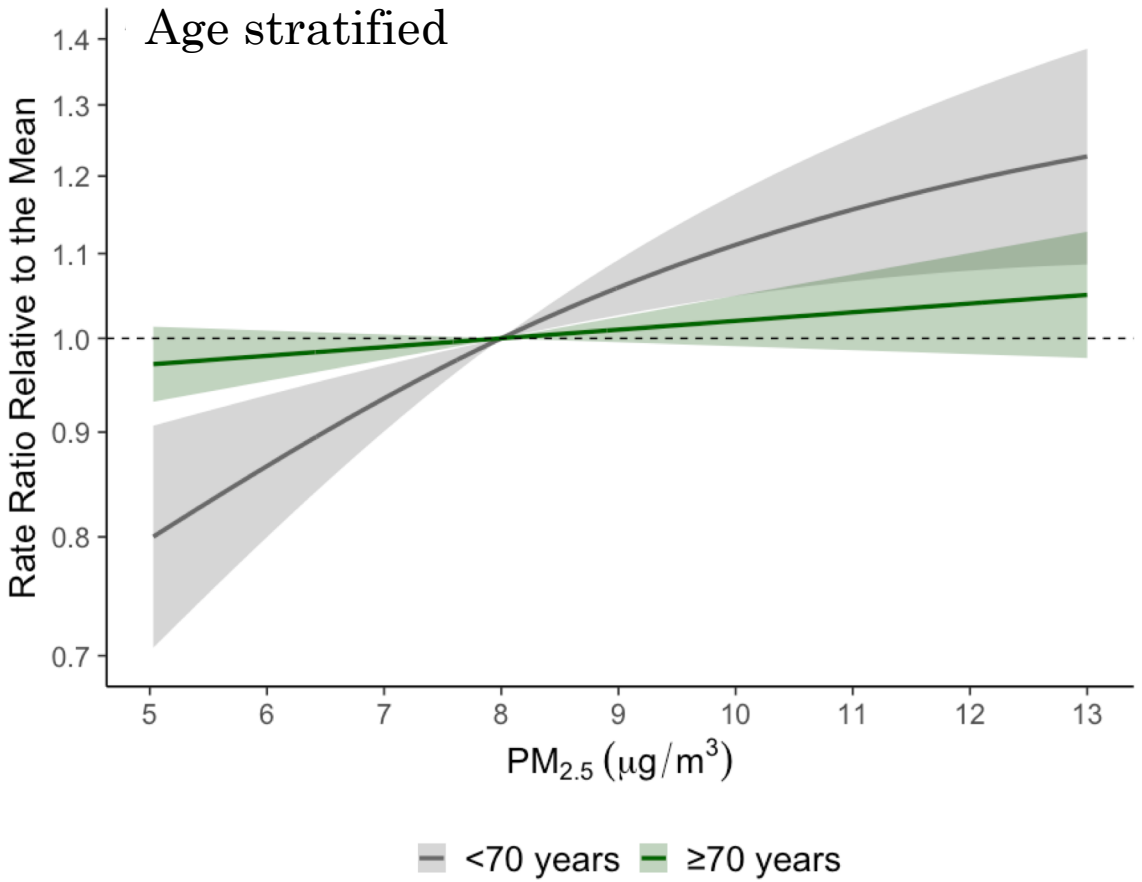
Effect modification by age in PD



- Effect modification by age at low concentrations
  - < 70 years of age, stronger effect

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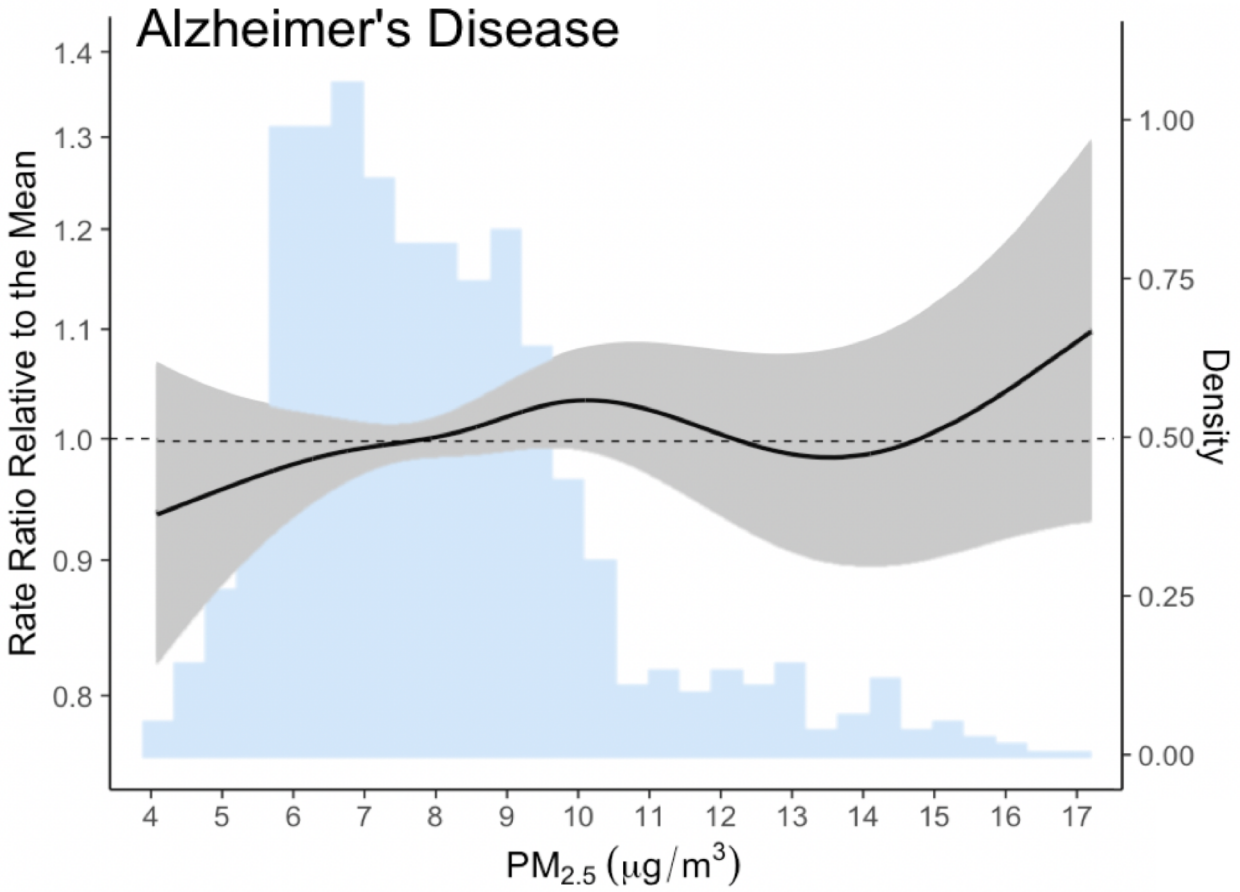
$PM_{2.5}$ and AD first hospitalizations



- Null association
- No effect modification by sex
- No effect modification by age

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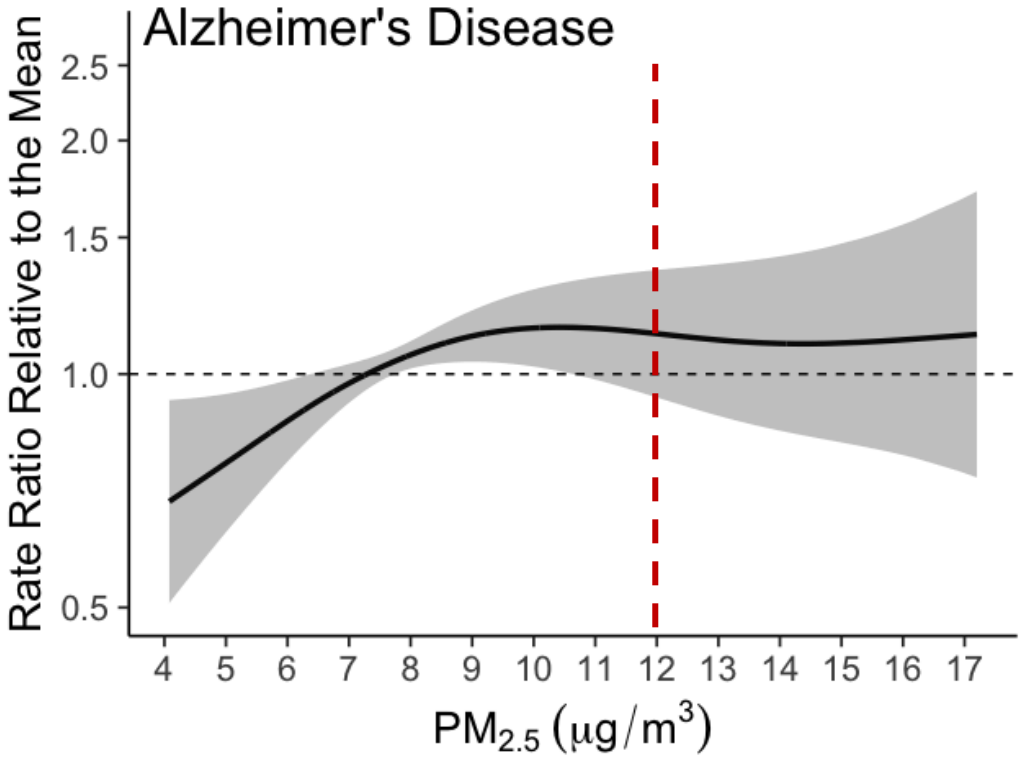
AD sensitivity analysis



- Removed potential false positives
- Positive association in lower $PM_{2.5}$ concentrations
- Significant association even at concentrations below NAAQS

Nunez, Y., et al. Env. Health Perspectives. *In revision*

Summary

Does long-term $PM_{2.5}$ exposure contribute to **disease aggravation** in neurodegenerative diseases?

1. Total $PM_{2.5}$ mixture effect

- Consistent $PM_{2.5}$—PD association
- Stronger association in PD patients <70 years old
- Potential $PM_{2.5}$—AD association
- Inconclusive results for ALS

2. Effect of specific $PM_{2.5}$ components

- Parkinson's disease

Strengths & limitations

Limitations:

- Limited statistical power in ALS
- Disease misclassification
- Exposure measurement error

Strengths:

- Large and diverse geographical region
- Flexible models
- 15 years of data
- Disease aggravation

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2. Effect of specific $PM_{2.5}$ components

- Parkinson's disease

Parkinson's disease hospitalizations in association with fine particle components in New York State

Yanelli Nunez, Amelia K. Boehme, Marc G. Weisskopf, Jeff Goldsmith, Ana Navas-Acien, AaronV. Donkelaar, Diane B. Re, Randall V. Martin, Marianthi-Anna Kioumourtzoglou

$PM_{2.5}$ components and PD first hospitalization

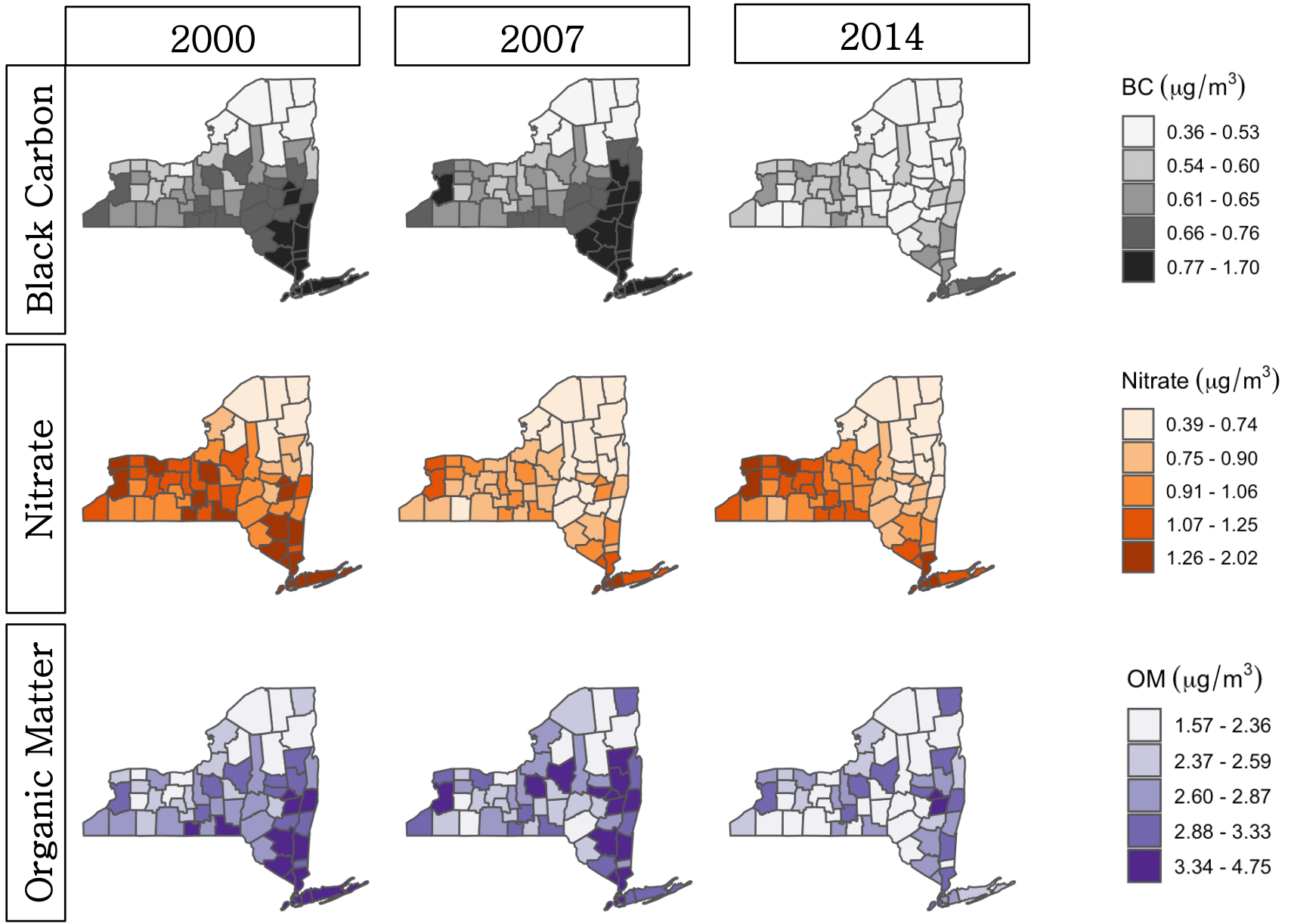
- SPARCS
  - PD county-level annual counts
  - Years 2000-2014
  - Years 1995-1999 to remove prevalent cases
- $PM_{2.5}$ components prediction model by Van Donkelaar et al., 2019
  - Six main $PM_{2.5}$ components
  - Population-weighted averages

Descriptive statistics based on annual per-county estimates from 2000—2014 in NYS

	Mean	St Dev	25%	Median	75%
Outcome					
PD	131.1	222.0	21.0	37.0	121.0
Component ($\mu g/m^3$)					
$PM_{2.5}$	8.10	2.30	6.40	7.60	9.20
Black Carbon	0.66	0.24	0.51	0.59	0.71
Nitrate	0.96	0.33	0.73	0.91	1.14
Organic Matter	2.87	0.67	2.36	2.74	3.30
Sulfate	2.51	0.87	1.79	2.41	3.09
Soil	0.29	0.10	0.22	0.28	0.33
Sea Salt	0.26	0.16	0.15	0.21	0.32

Nunez, Y., et al. *Manuscript in prep*

Geographic & temporal contrast



Nunez, Y., et al. *Manuscript in prep*

Statistical models

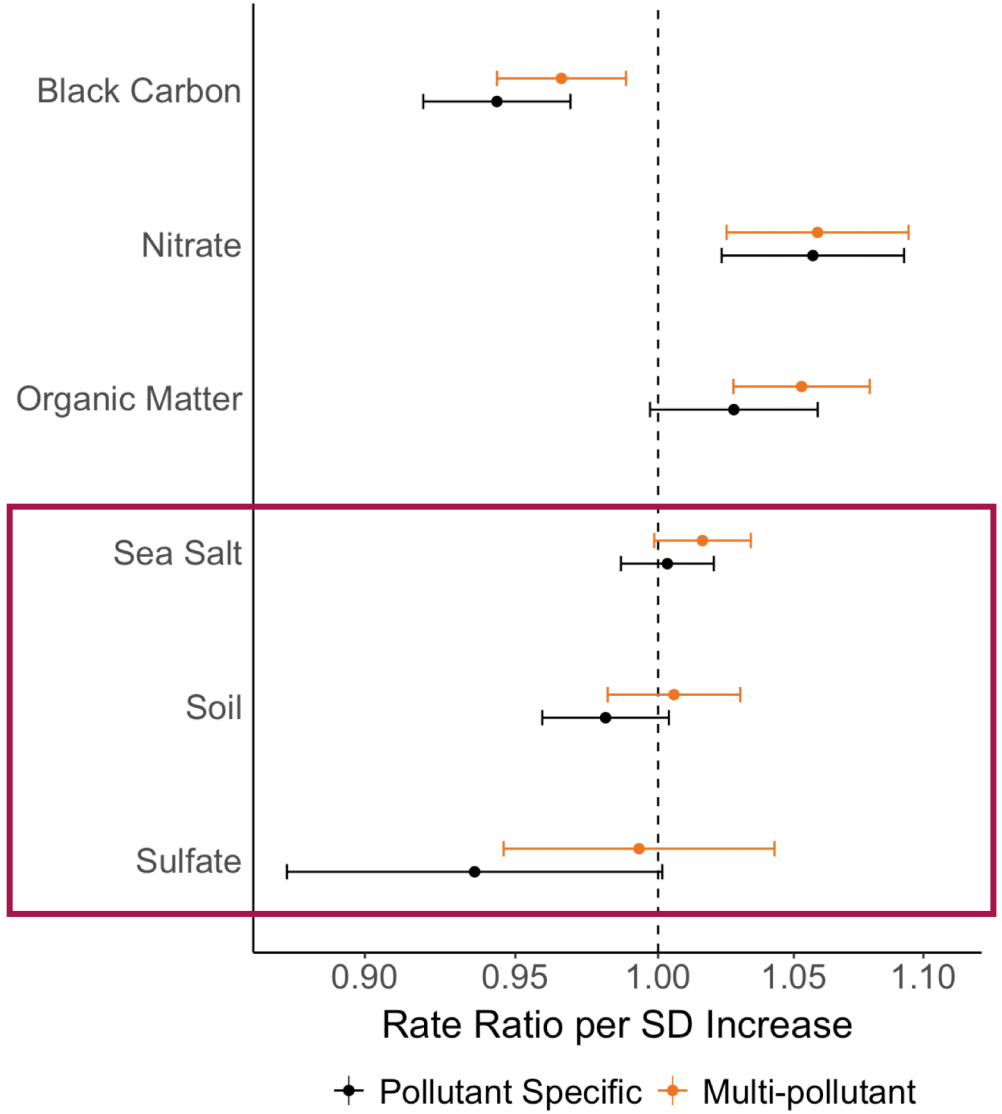
- Quasi-Poisson generalized additive mixed model to estimate RR and 95% CIs
  - Evaluated nonlinearities
  - Adjusted for potential confounder
  - Population offset

- Outcome:
  - Annual county counts of first PD hospitalizations

- Exposure:
  - Multi-pollutant model: included all $PM_{2.5}$ components
  - Specific-pollutant model: included only one $PM_{2.5}$ component at a time, adjusted for total $PM_{2.5}$ mass

Results

$PM_{2.5}$ components and PD first hospitalizations



No significant association for sea salt, soil, sulfate

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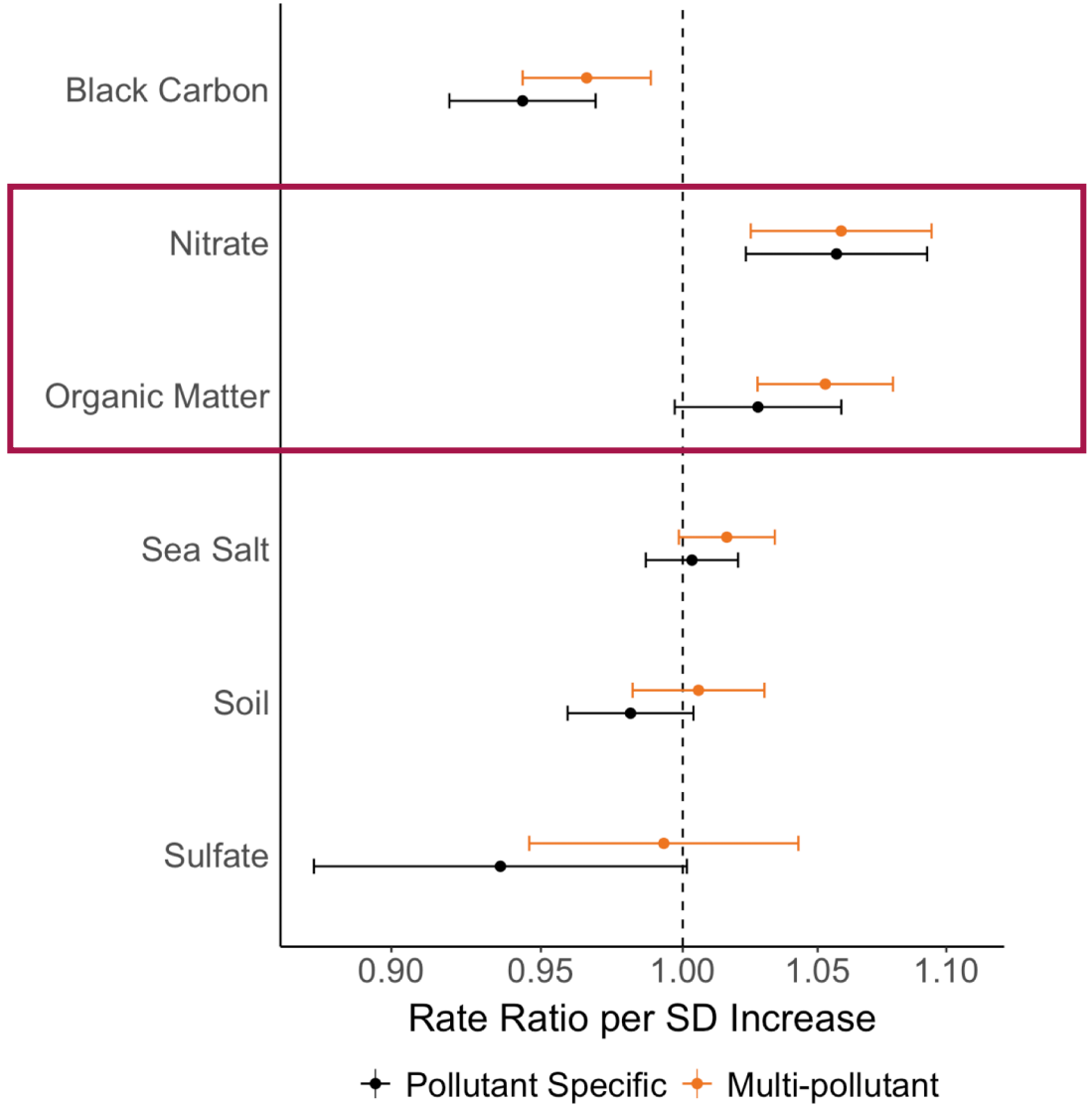
$PM_{2.5}$ components and PD hospitalizations



Nitrate and organic matter have a consistent positive association

- 5% increased in first hospitalization per standard deviation increase

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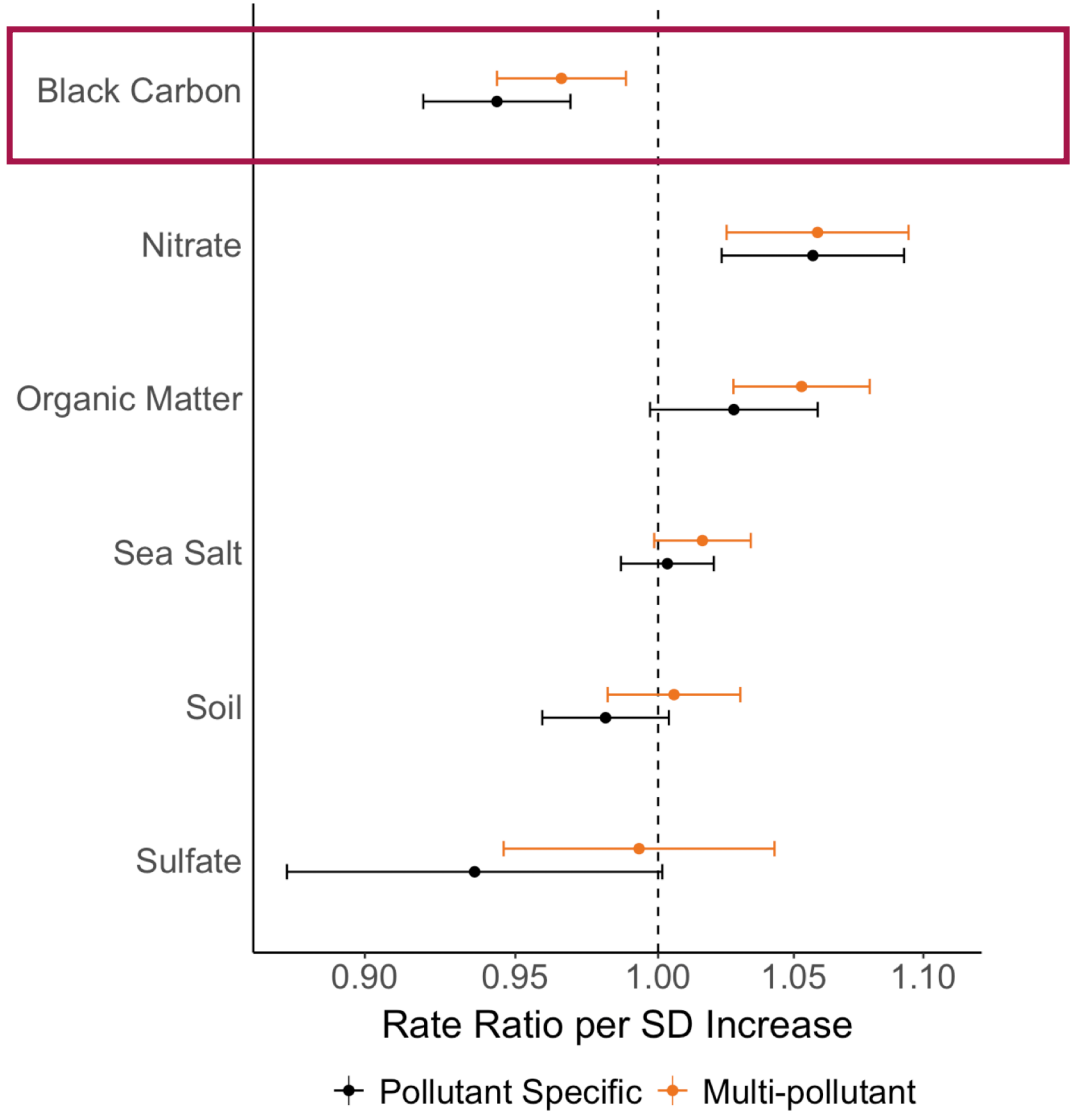
$PM_{2.5}$ components and PD first hospitalizations



Negative association between black carbon and PD

- Deviated from linearity

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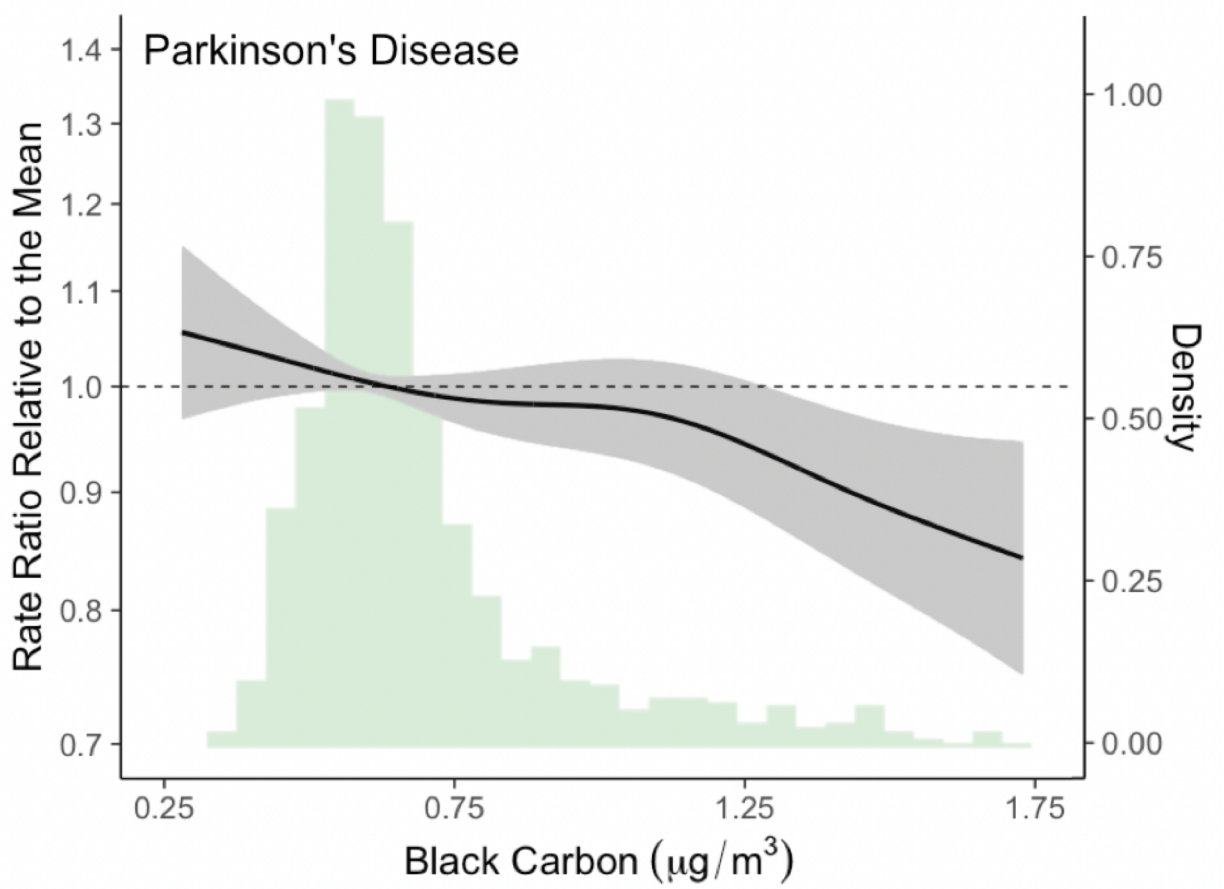
Black carbon: nonlinear association



- Exposure–response from multi-pollutant model
- Negative association at high concentrations

Nunez, Y., et al. *Manuscript in prep*

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- Consistent $PM_{2.5}$—PD association
- Stronger effect in PD patients <70 years old
- Potential $PM_{2.5}$—AD association

2. Effect of specific $PM_{2.5}$ components

- Not all components were associated with the outcome
- Harmful components:
  - Nitrate
  - Organic matter

Strengths & limitations

Limitations:

- Exposure data do not include all $PM_{2.5}$ components
- Exposure measurement error varies by component

Strengths:

- First analysis of $PM_{2.5}$ components in association with disease aggravation in Parkinson's disease
- Population-weighted averages for $PM_{2.5}$ components
- Results consistent across models

Conclusions & Implications

Conclusions & implications, study 1

1. Annual $PM_{2.5}$ exposure is associated with first hospitalization in PD and possibly in AD but limited power in ALS
   - $PM_{2.5}$ exposure may contribute to disease aggravation in these conditions
   - Significant harmful effects in $PM_{2.5}$ exposure levels below current National Ambient Air Quality Standards

2. Stronger effect in PD patients with a first hospitalization before age 70
   - Certain patient subpopulations may be more sensitive to exposure
     - Comorbidities?
     - Genetic variants?
     - Psychosocial stress?

Conclusions & implications, study 2

1. Not all $PM_{2.5}$ components are associated with the first hospitalization in Parkinson's disease
   - Different $PM_{2.5}$ compositions may affect neurodegenerative diseases differently
   - May explain some of the variability in results across studies

2. Nitrate and organic matter most harmful components in the $PM_{2.5}$ mixture
   - Source identification → Targeted regulation
   - Mechanistic toxicological studies

Future studies

- **Individual-level analyses**
  - Extrapolating results from area- to the individual-level presents challenges, particularly for the inference of causation
  - Individual-level studies or a combination of group- and individual-level analyses needed

- **Specific markers of disease progression**
  - Disease scale scores
  - Time from clinical diagnosis to death

- **Mediators & modifiers**

Other projects

1. Overview of Methods to Address Distinct Research Questions on Environmental Mixtures: An Application to Persistent Organic Pollutants and Leukocyte Telomere Length

- Biostatistical methods in the study of environmental exposure to mixtures

2. Good Practices for Applied Statistical Learning in Epidemiology

- Stability of seed-dependent methods over different seeds

3. Gene X Environment in ALS: Environmental exposure to metals and TDP-43 genetic variants in clinical onset of ALS

- Interaction of low-level metal exposures with ALS genetic variants to influence time of clinical onset

Gibson, L. & Nunez, Y., et al. Env. Health, Aug. 2019
Nunez, Y. & Gibson, L., et al. Int. Journal of Epi. *Under revision*
Merwin, S., Obis, T., Nunez Y., et al. Archives of Toxicology, Jan. 2017

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