Heterogeneous impact of air pollution exposures in midlife and late-life on cognitive trajectories in WHIMS-Y

Jiu-Chiuan Chen, M.D., MPH, Sc.D.

Departments of Population & Public Health Sciences and Neurology, University of Southern California, Los Angeles, USA

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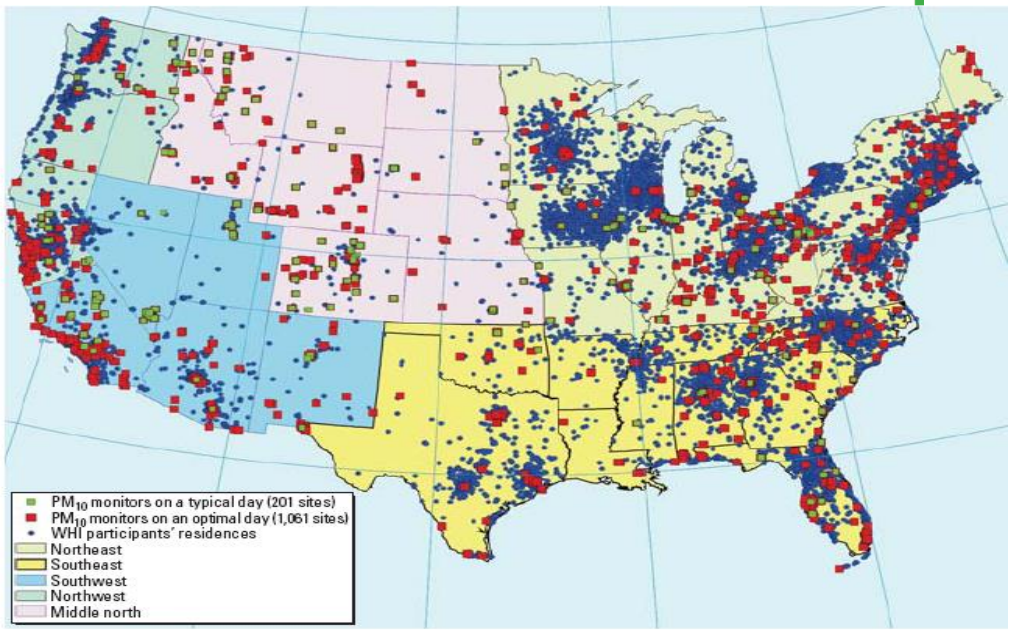
Neurotoxicity of Ambient Air Pollution

- **Extensive experimental data supporting neurotoxicity in animals exposed to airborne particles**
- **Human data growing on adverse effects on aging brains with late-life exposures**
- **2020, 2024 Lancet Commission Reports List of Modifiable Dementia Risk Factors: $PM_{2.5}$ (late-life)…**
- Very scant and limited epidemiological data on neurotoxic effects of midlife exposures (Franz 2023)
- We examined whether midlife and late-life exposures ($PM_{2.5}$; NO_2) affect the trajectories of general cognitive ability and domains sensitive to neuropathology of Alzheimer's disease in older women.

WHIMS-AIR Studies

- **Built on Women Health Initiative (WHI) Clinical Trials (WHI-CT) ancillary studies: WHI Memory Study (WHIMS) in Younger (WHIMS-Y) Women**
  - **geographically-diverse, multi-ethnic cohorts of old women** to study effects of hormone therapies on cognition,
  - WHIMS/WHIMS-Y followed annually with neuropsychological+ behavioral/social function+ clinical
  - 40^{+}-WHI-CT centers, cognitively-intact, from 48 states; ~95% in urban areas

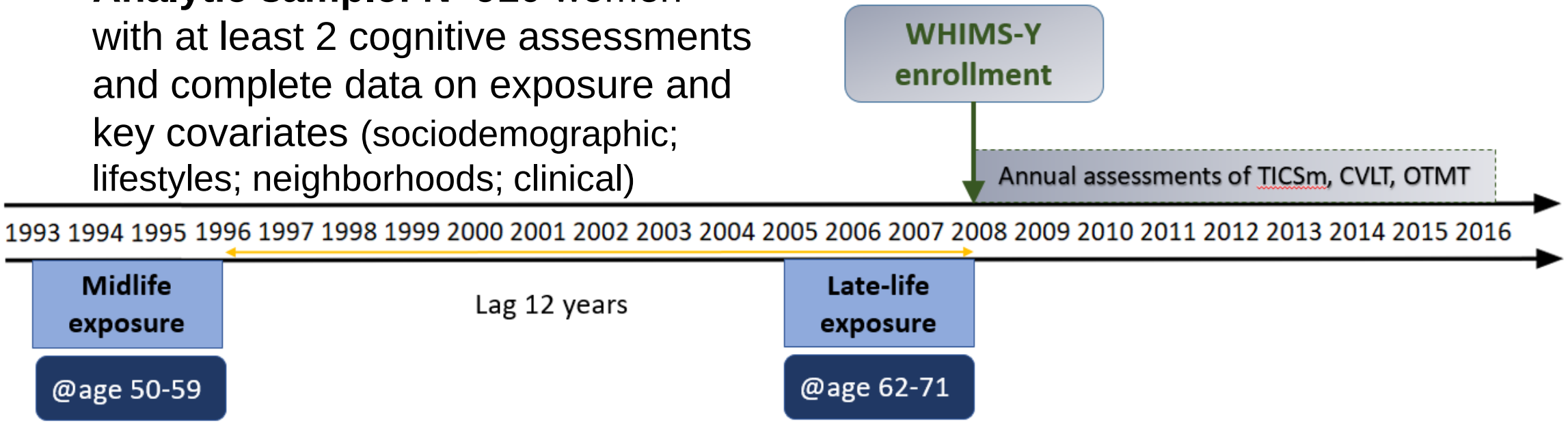


(Liao 2006)

Study Design and Exposure/Outcome Data Elements

WHIMS-Y: Women's Health Initiative Memory Study - Younger Women

Analytic sample: N=910 women with at least 2 cognitive assessments and complete data on exposure and key covariates (sociodemographic; lifestyles; neighborhoods; clinical)



$PM_{2.5}$ & NO_2: 3-year averages aggregated using monthly estimates predicted from regionalized universal kriging models

TICSm: modified Telephone Interview for Cognitive Status; measure general cognitive status

CVLT: California Verbal Learning Test; measure episodic memory

OTMT: Oral Trail Making Test; measure attention (Part A) and executive function (Part B)

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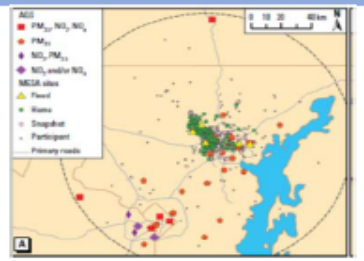
Framework of MESA Air spatio-temporal modeling

Observed concentrations



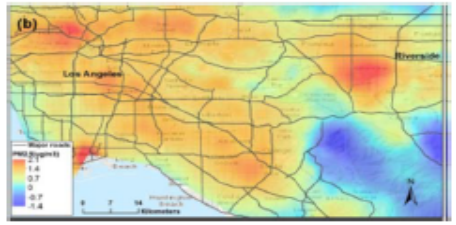
- AQS sites
- Fixed sites
- Snapshot sites
- Home sites

Covariate input data

- GIS covariates
- Meteorology
- Chemical transport model
- Satellite data

Statistical model

Predicted concentrations



- High spatial resolution
- High temporal resolution

- Long time series in relatively few locations
- Many locations with relatively short temporal coverage

- ~ 200 geocovariates
- CMAQ output from EPA for Ozone model

- Model accommodates complicated structure of input data
- Deals with missingness

- Predictions at fine scale
- Elucidate intra-urban exposure contrasts
- Capture emission gradients e.g. roadway

Yearly $PM_{2.5}$: >300 covariates; cross-validation R^2 0.88; pre-1999 $PM_{2.5}$
Yearly NO_2: >400 covariates; cross-validation R^2 0.85

Downscaled to monthly $PM_{2.5}$ and NO_2

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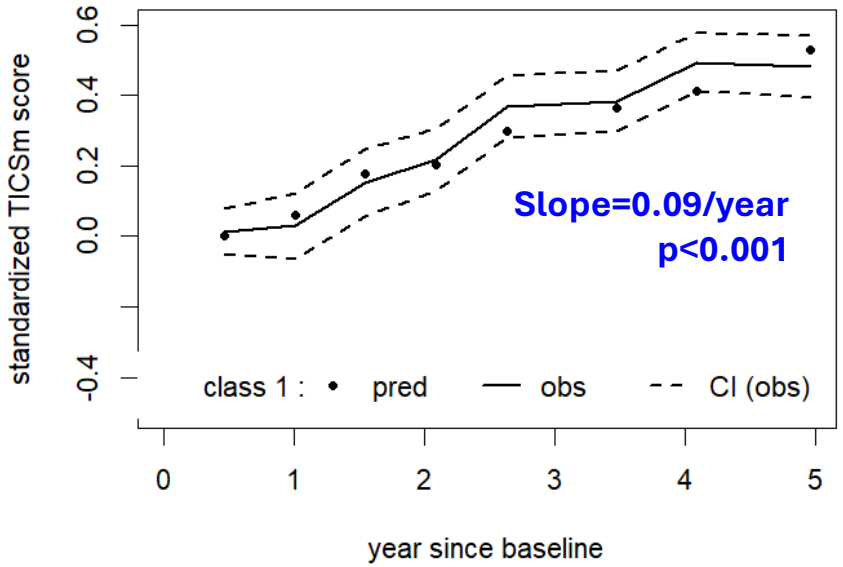
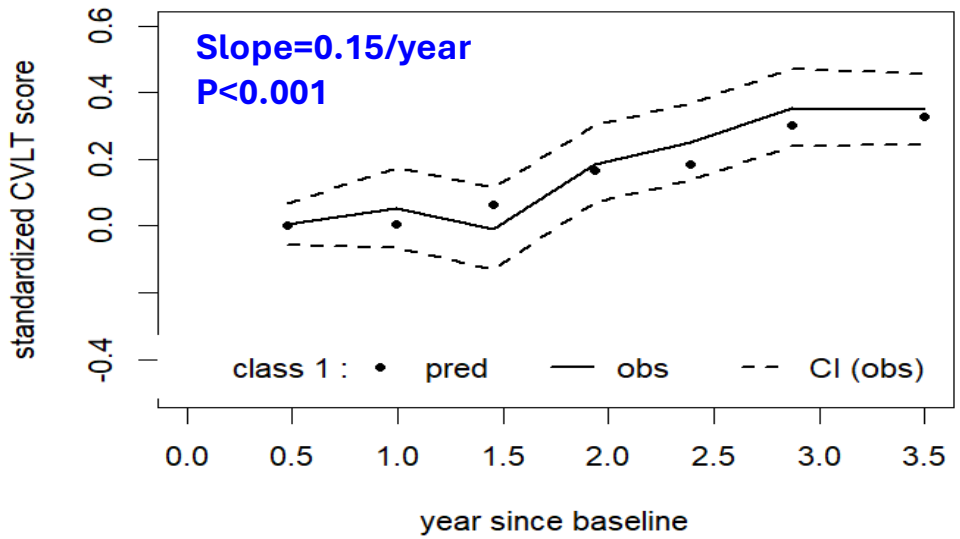
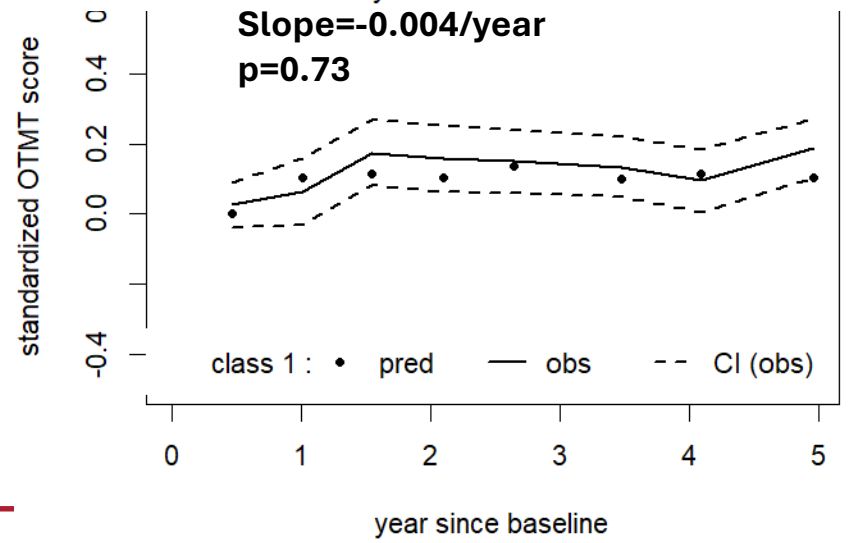
Credit: Joel Kaufman

Performance in global cognitive function and episodic memory improved over time







- The dots represent the marginal mean predicted standardized cognitive measures. The solid line and dashed lines represent the mean observed trajectories and the corresponding 95% confidence intervals.
- The models adjusted for the practice effects and a list of relevant covariates.

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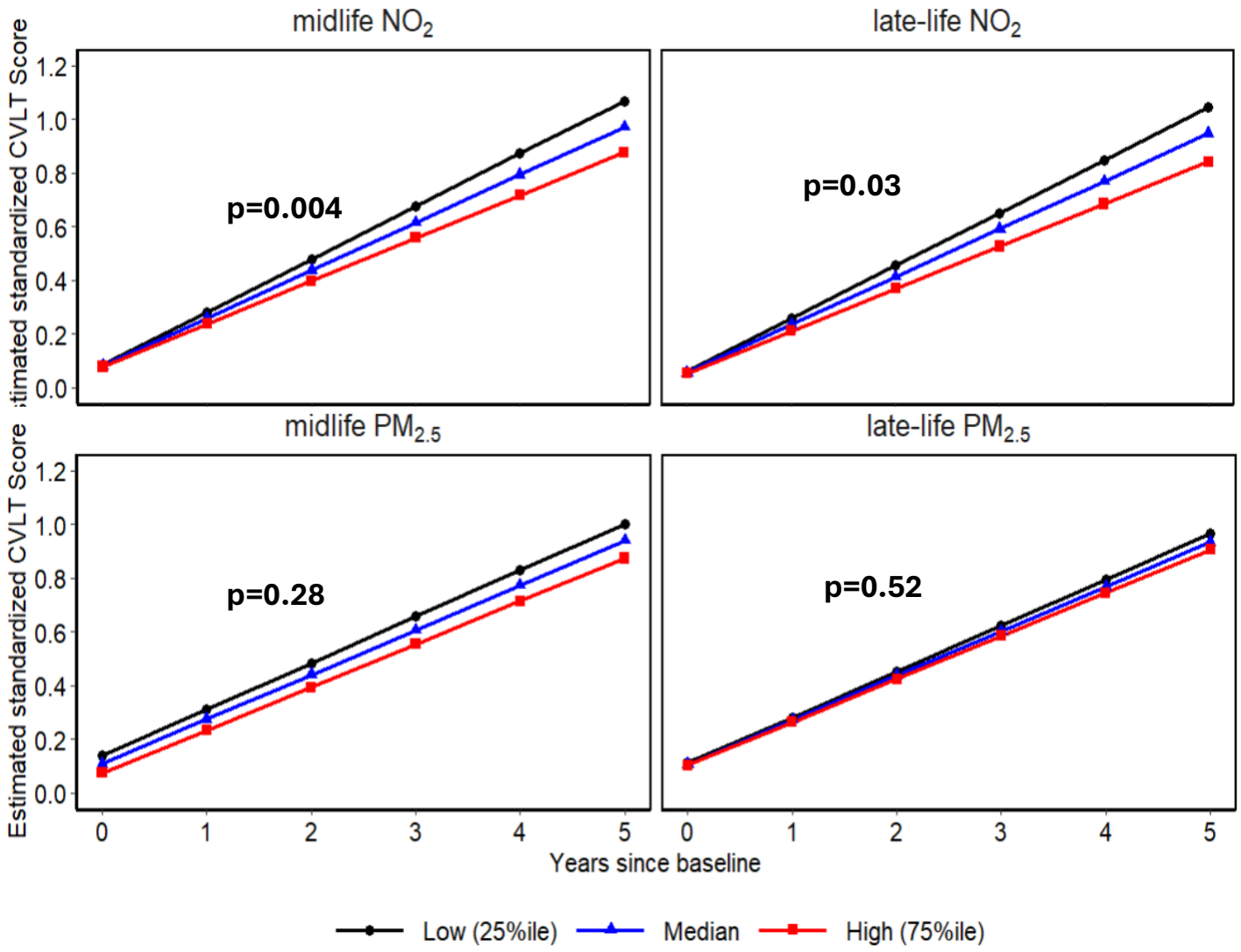
Estimated slopes of CVLT trajectories varied by different levels of NO_2 exposures



- Improvement in CVLT performance was attenuated in older women with higher NO_2 exposures.
- Similar for midlife and late-life NO_2 exposures

- $PM_{2.5}$ exposure →X→ CVLT slope

	25%ile	median	75%ile
midlife NO_2 (ppb)	8.7	13.4	17.9
late-life NO_2 (ppb)	5.5	8.4	11.6
midlife $PM_{2.5}$ (μg/m³)	12.1	13.8	15.5
late-life $PM_{2.5}$ (μg/m³)	7.9	9.7	11.2

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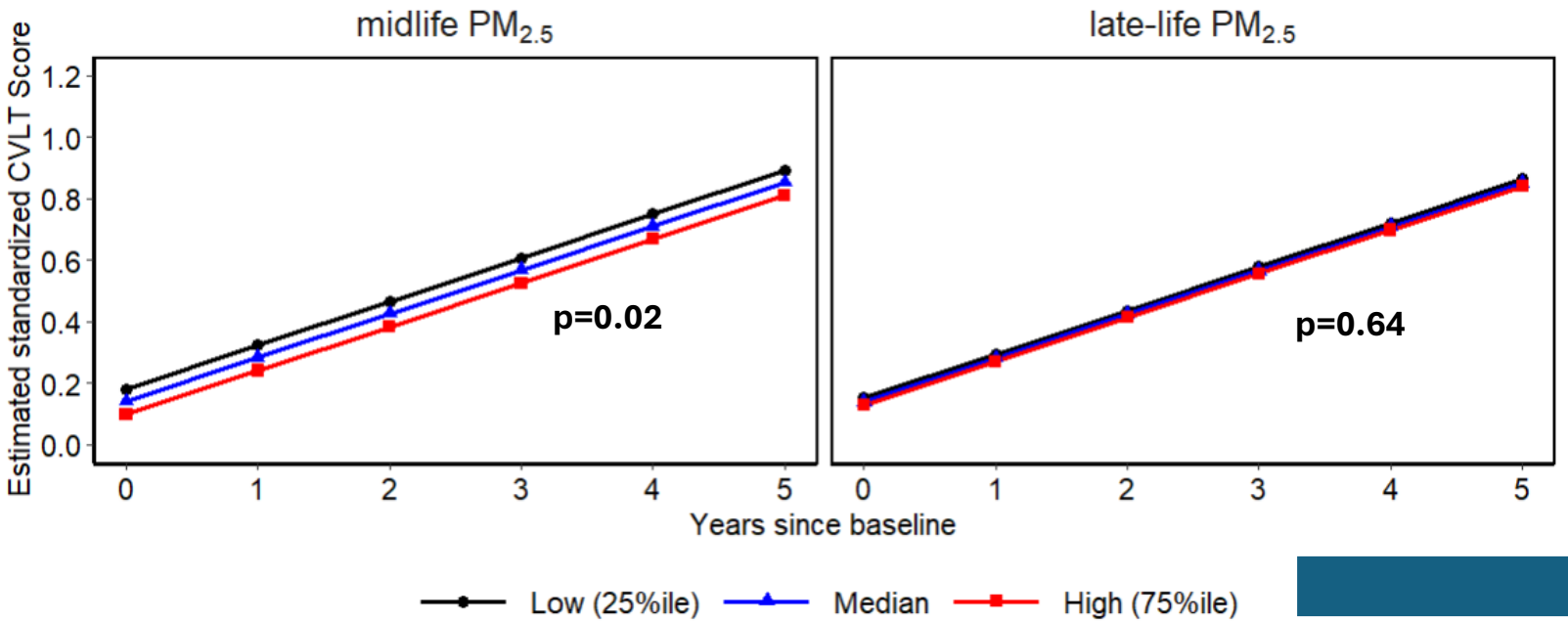
Lower CVLT scores were associated with higher $PM_{2.5}$ exposure in midlife, not with late-life exposure



	25%ile	median	75%ile
midlife $PM_{2.5}$ ($\mu g/m^3$)	12.1	13.8	15.5
late-life $PM_{2.5}$ ($\mu g/m^3$)	7.9	9.7	11.2

- Midlife $PM_{2.5}$ exposure was associated with lower CVLT scores
- No association found for late-life $PM_{2.5}$ exposure

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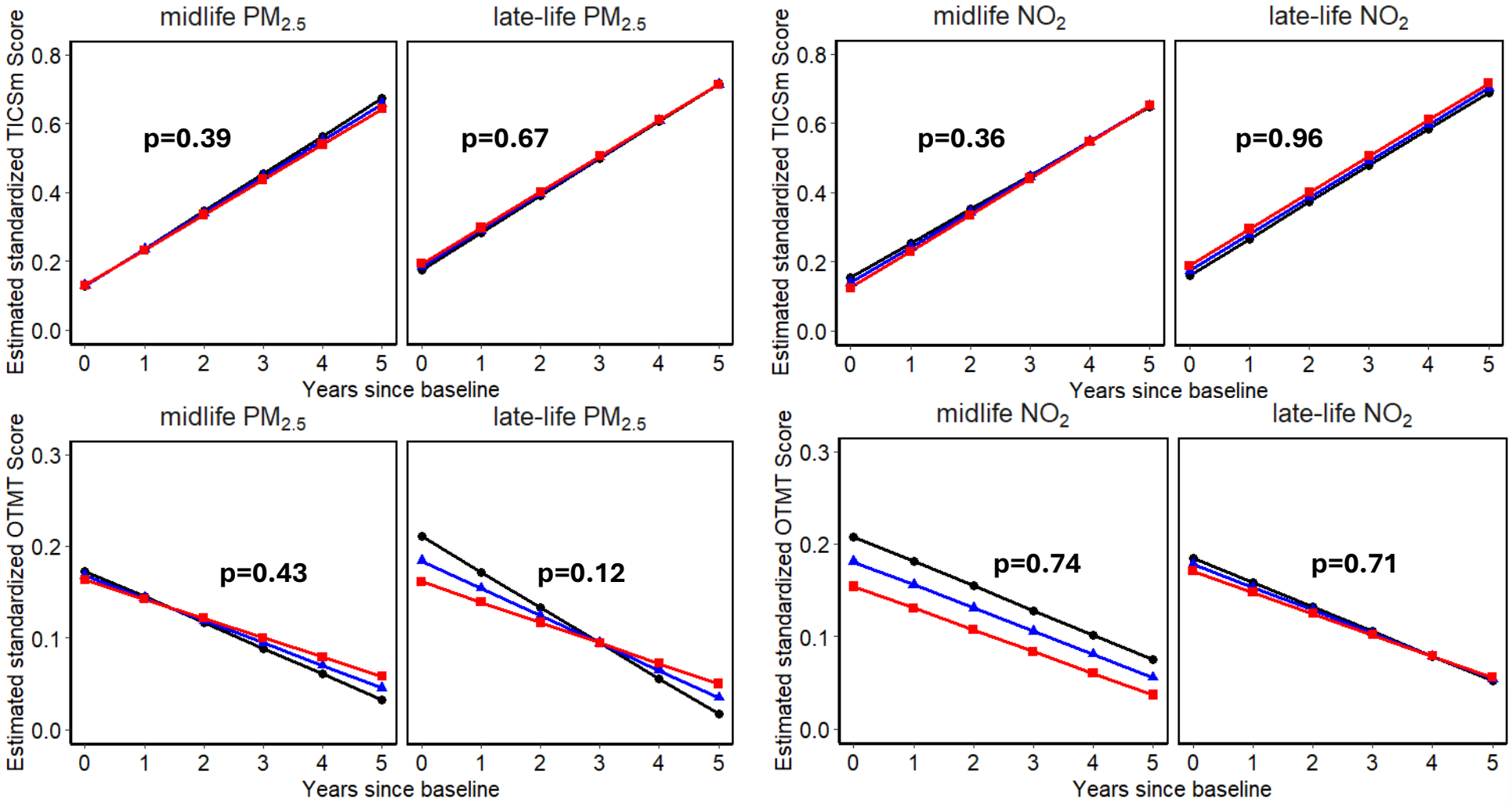
Trajectories of TICSm and OTMT were not affected by PM2.5 or NO2 exposure in midlife and late-life.



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Discussions & Conclusion

- Our study findings support the neurotoxicity of air pollution exposures in midlife and late life.
- Ambient air pollution may attenuate the cognitive learning of older women aged 62-71 years with improving episodic memory.
- The distinctive pattern of observed associations with NO_2 and $PM_{2.5}$ suggests the adverse effects of air pollutants may affect different neuropsychological processes with various underlying neuropathologies in late life.

- Strengths: geographically diverse, well-characterized cohort with annual longitudinal assessment
- Limitations: not generalizable to men and younger women; well-educated study samples; no PM2.5 constituents

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Linear mixed-effect models:
Air pollution (AP) exposures → Cognitive trajectory

- For AP effect on trajectory slope:

$$Y = \beta_0 + \beta_1 \cdot AP + \beta_2 \cdot time + \beta_3 \cdot AP \cdot time + \gamma \cdot \mathbf{cov} + \varepsilon$$

- For AP effect on trajectory level:

$$Y = \beta_0 + \beta_1 \cdot AP + \beta_2 \cdot time + \gamma \cdot \mathbf{cov} + \varepsilon$$

- Models adjusting for:
  - Socio-demographic factors: age; geographic region; race/ethnicity; education; income; employment status; neighbourhood SES
  - Lifestyle: smoking; alcohol use; physical activity
  - Clinical characteristics: depression symptoms; BMI; diabetes; high cholesterol; hypertension; CVD; prior hormone use; hormone therapy assignment
  - Time-varying propensity scores (TV-PS): to control for differential attr up