

# Estimating cognitive trajectory and the changing effect of pathologies using a nonparametric time-varying effect model

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Rush Alzheimer's Disease Center

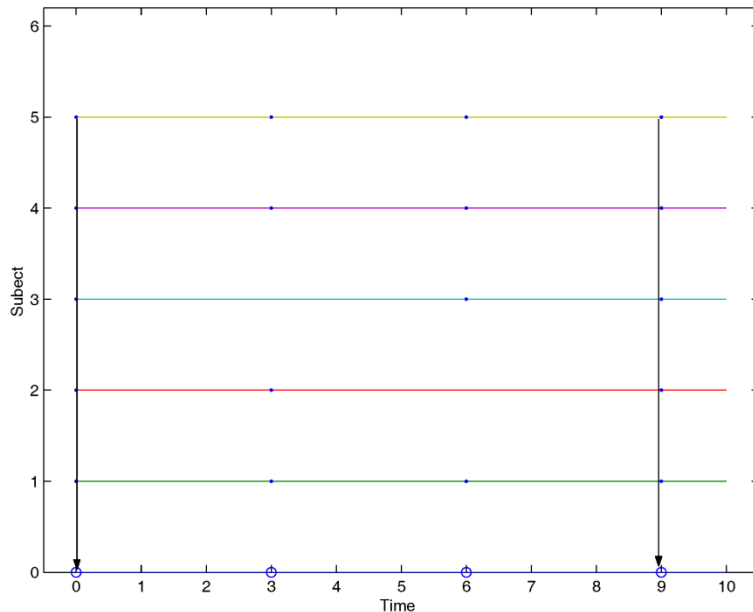
Rush University Medical Center

09/26/2015

Manuscript in progress

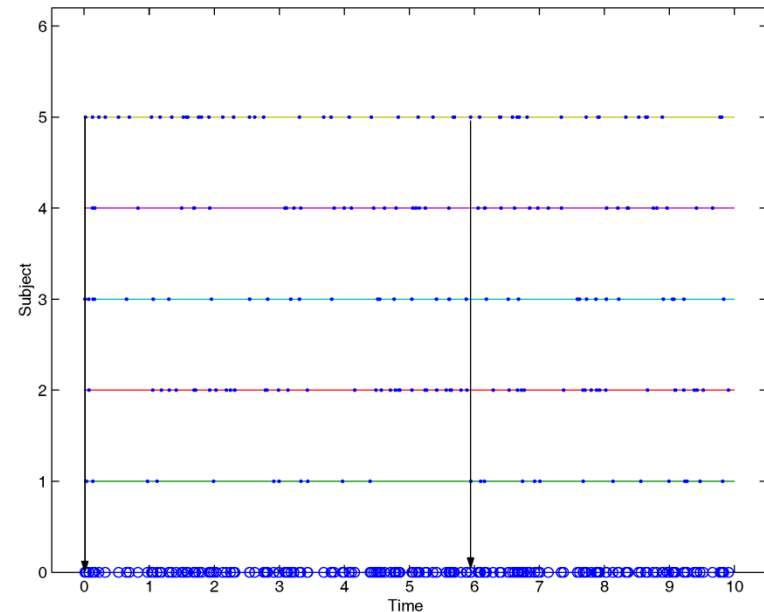
# Different longitudinal data

## Traditional longitudinal data



- Limited # of measurements
- Incapable of revealing
  - irregular ups and downs
  - temporal association or time-varying effects

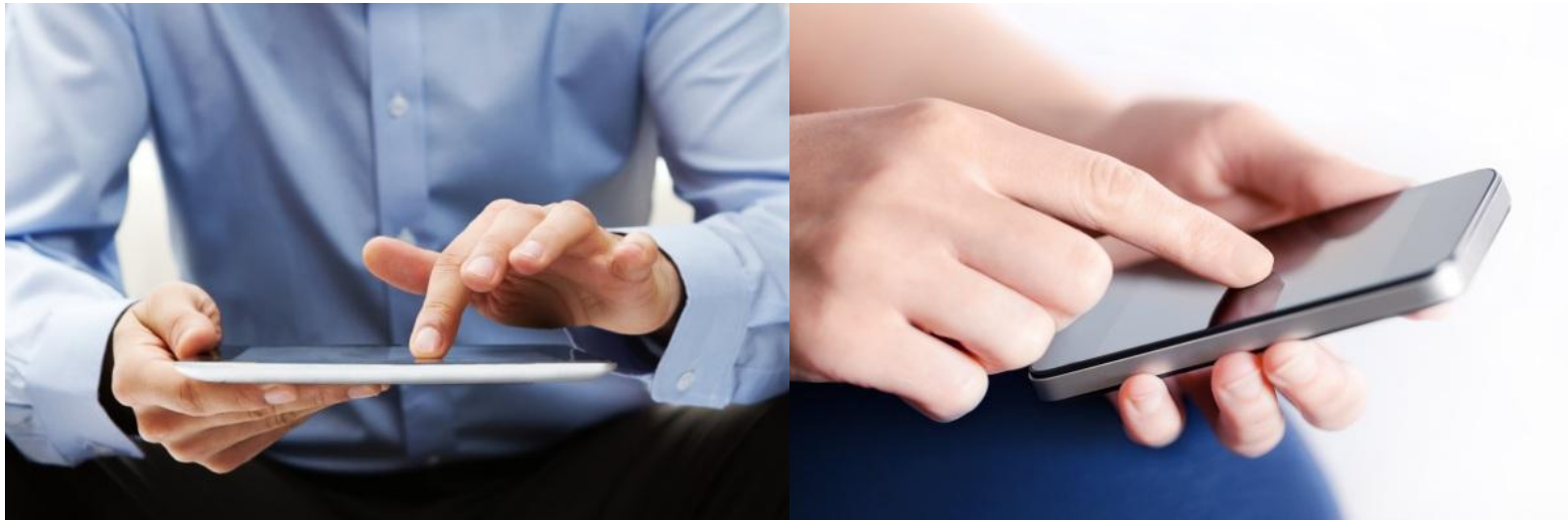
## Intensive longitudinal data (ILD)



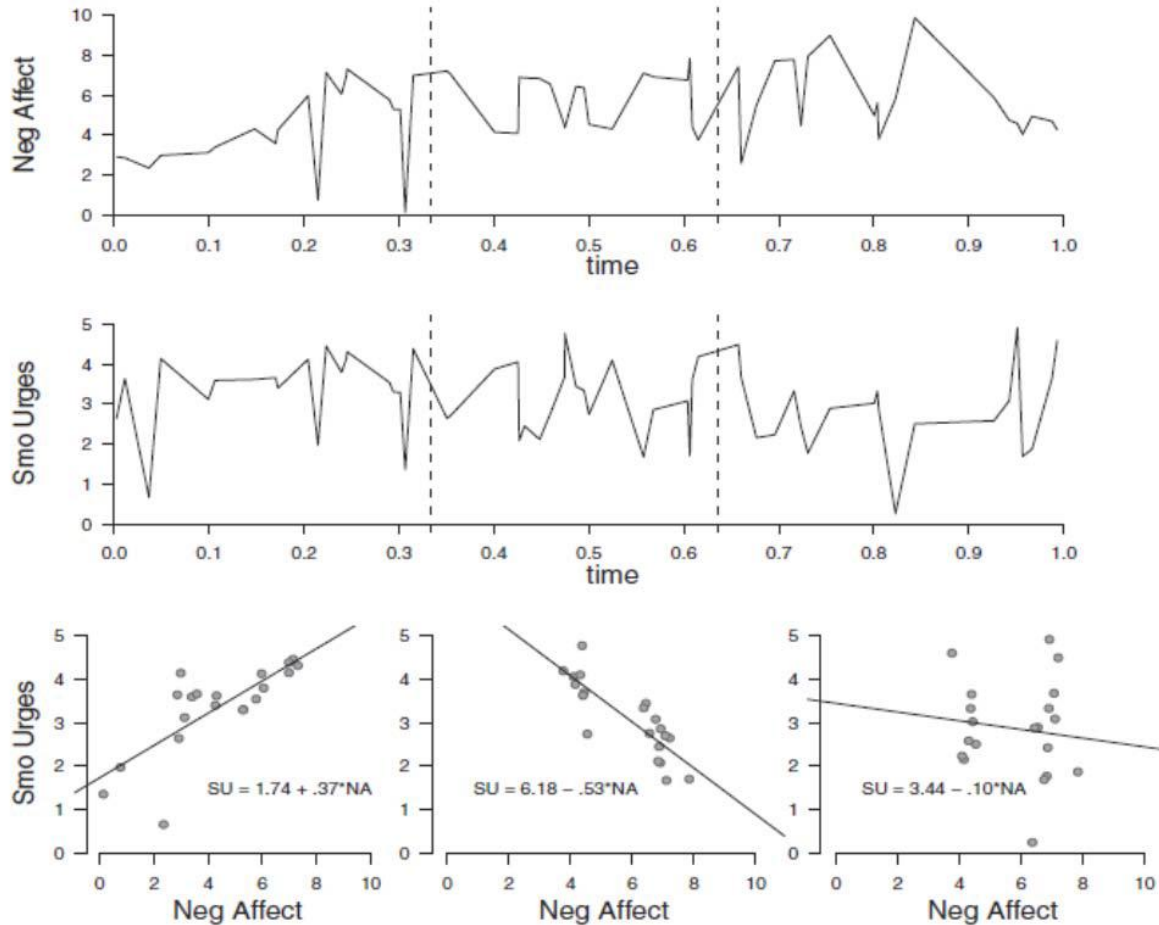
- Irregular time series
  - Partially missing
  - Unequally spaced
- Many observations at each time points

# Collection of ILD

- Web-based assessment
- Hand-held computers (e.g., PDA)
- Other portable devices (actigraph, GPS, iWatch, iPhone)
- Data collected from well-designed longitudinal studies that have a long time of follow-ups (e.g., data from ROSMAP)



# Time-varying effect model: A motivating example



# The time-varying effect model (TVEM)

- Does not impose a parametric form on the coefficient functions
- Can accurately reveal the underlying shape of coefficient functions
- Capable of handling different responses
  - Continuous
  - Binary
  - Poisson
  - ZIP
- User-friendly and easy-to-implement SAS macro suite

# Using TVEM to examine cognitive trajectory

<b>N</b>	641
<b>Study</b>	ROS (n=339)/MAP (n=302)
<b>Follow-up, mean (range)</b>	9.3 (4-19)
<b>Age at death</b>	89.7±6.3
<b>Gender, male</b>	31.8%
<b>Education</b>	16.4±3.6
<b>Global pathology</b>	0.6±0.7
<b>Lewy bodies</b>	23.9%
<b>Hippocampal sclerosis</b>	12.6%
<b>Arteriolar sclerosis</b>	30.9%
<b>Gross chronic cerebral Infarcts</b>	0.4±0.5
<b>Gross subacute cerebral Infarcts</b>	0.1±0.3
<b>Gross acute cerebral Infarcts</b>	0.1±0.3
<b>Cerebral amyloid angiopathy</b>	1.1±1.0
<b>TDP-43</b>	0.6±1.0

# Using TVEM to examine cognitive trajectory

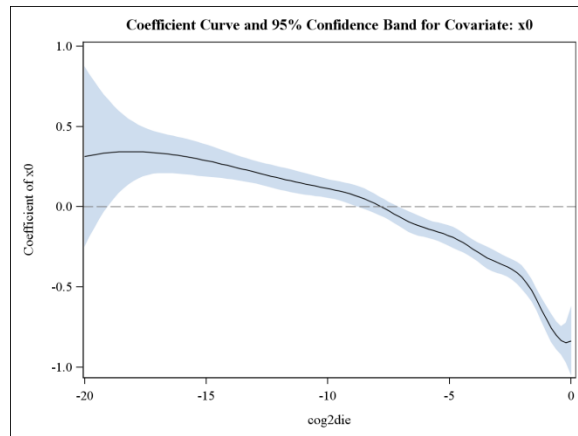
- Outcome: global cognition
- Adjust for sex, education, age at death, APOE4
- Type of coefficients:
  - Time-invariant: sex, education, age at death
  - Time-varying: APOE, pathologies
- Time: time to death
- Strategy:
  - Examine each pathology individually
  - Examine all pathologies simultaneously

# Using TVEM to examine cognitive trajectory: sample code

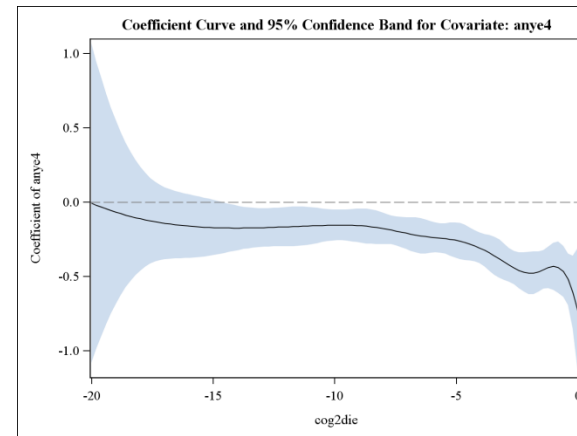
```
%TVEM_normal(method=B-spline,  
mydata=e4_path_all_mod,  
id=projid_new,  
time=cog2die,  
dep=cogn_global,  
class_var=msex,  
tcov=x0 anye4 gpath,  
cov=msex educ16 age_death_c,  
cov_knots=6 6 6  
);
```



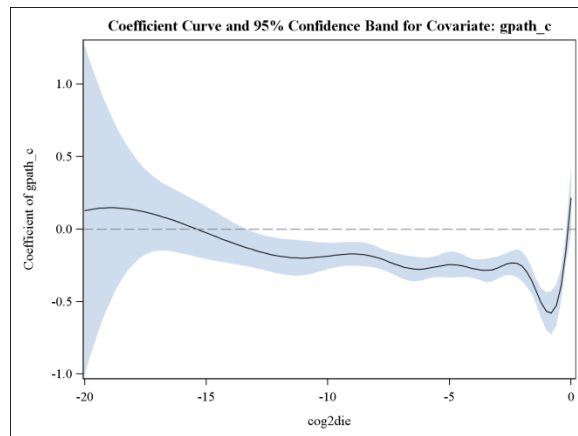
# Cognitive trajectory and effect of APOE and pathologies: individual examination



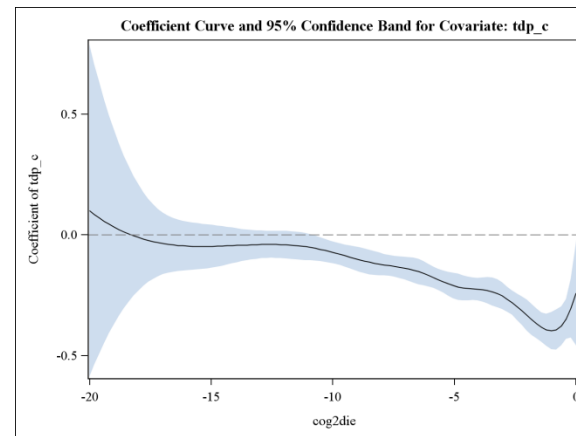
Mean trajectory



APOE4

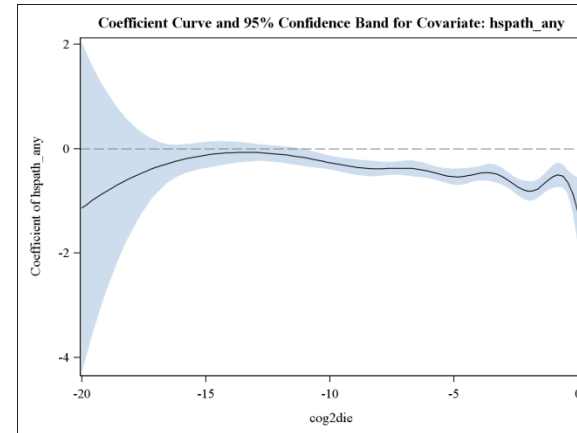
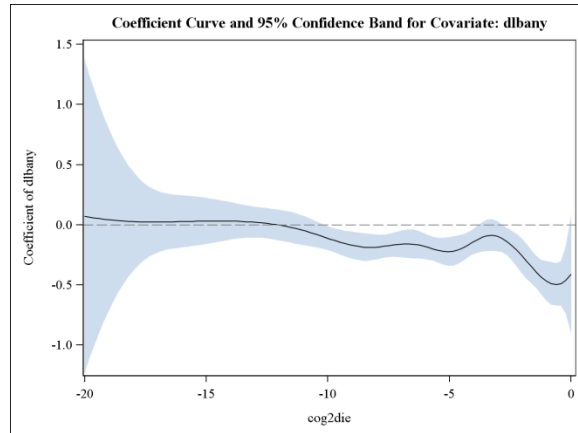


Global pathology



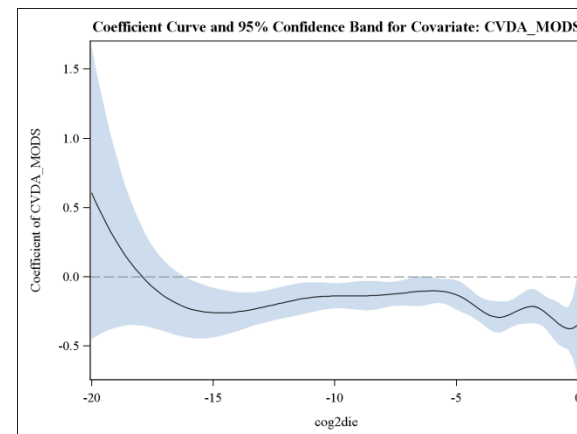
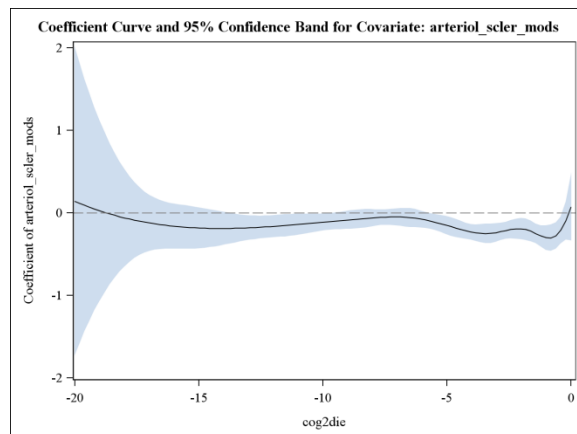
TDP-43

# Cognitive trajectory and effect of APOE and pathologies : individual examination



Lewy bodies

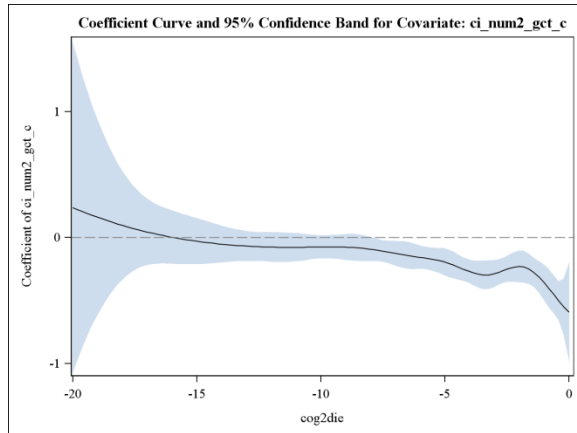
Hippocampal sclerosis



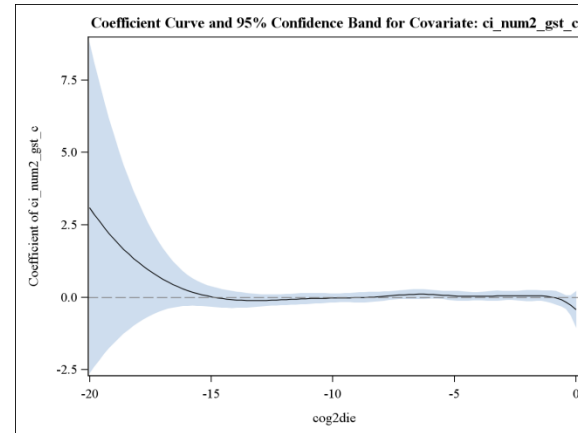
Arteriolar sclerosis

Cerebral atherosclerosis

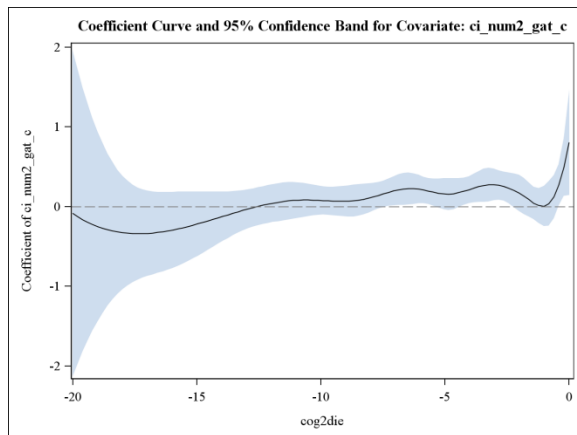
# Cognitive trajectory and effect of APOE and pathologies: individual examination



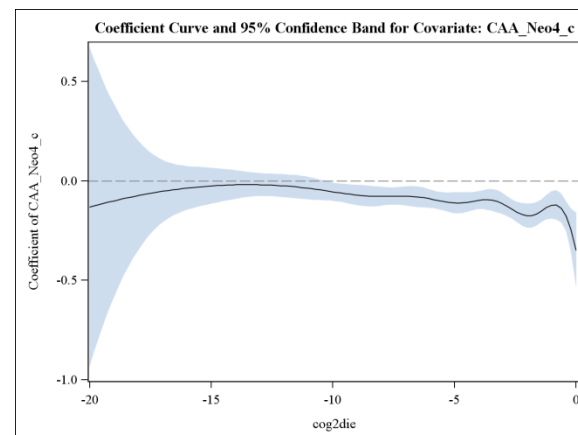
Gross chronic cerebral infarcts



Gross subacute cerebral infarcts

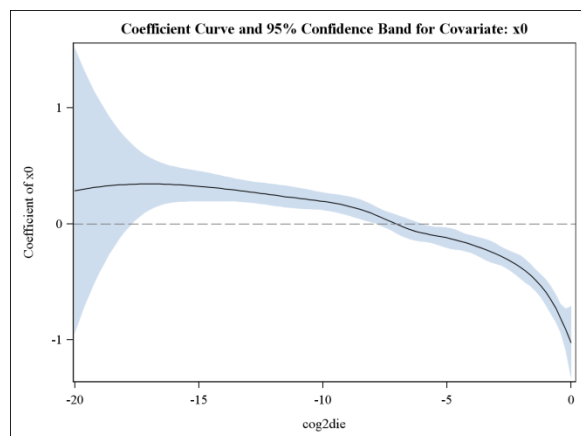


Gross acute cerebral infarcts

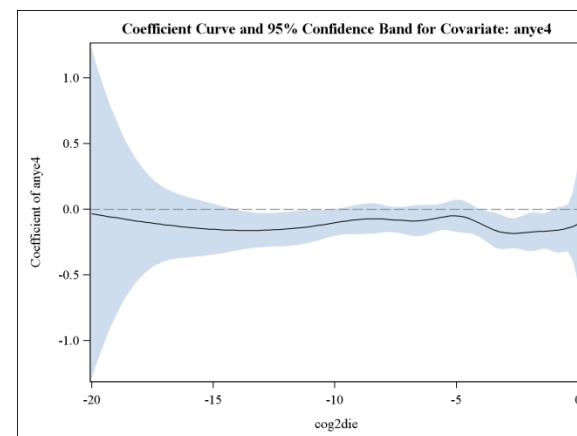


Cerebral amyloid angiopathy

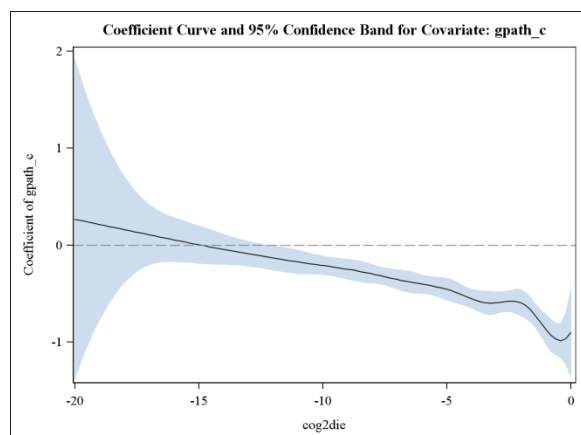
# Cognitive trajectory and effect of APOE and pathologies: simultaneous examination



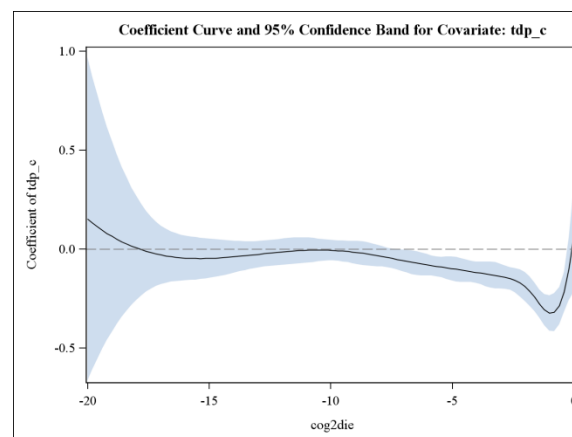
Mean trajectory



APOE4

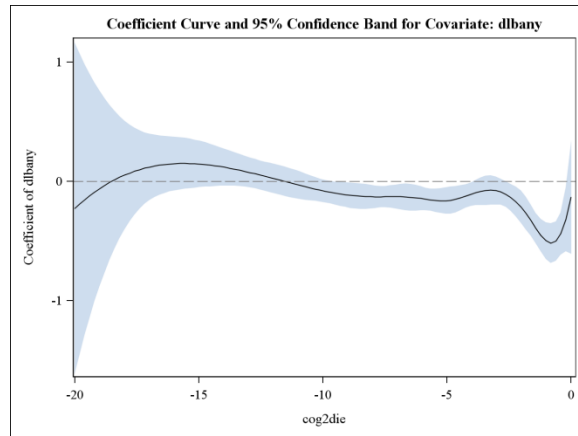


Global pathology

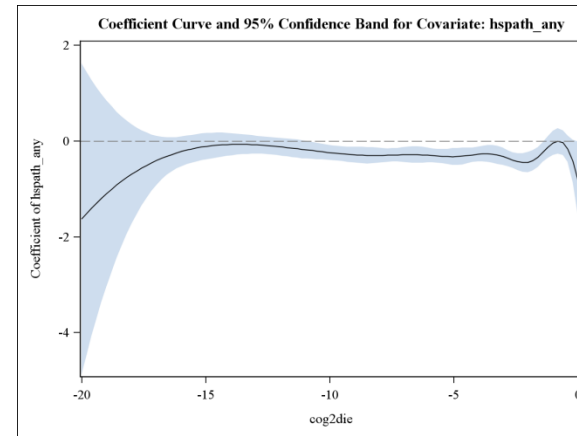


TDP-43

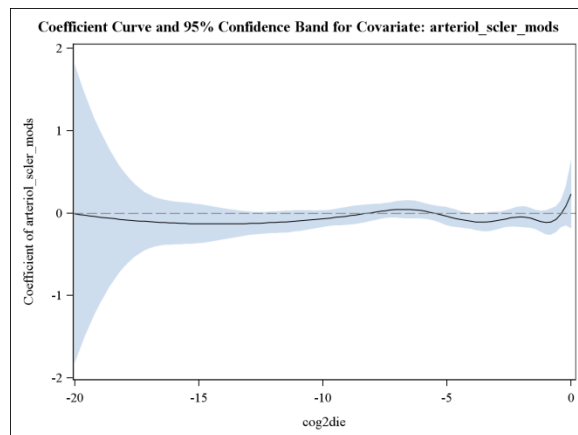
# Cognitive trajectory and effect of APOE and pathologies: simultaneous examination



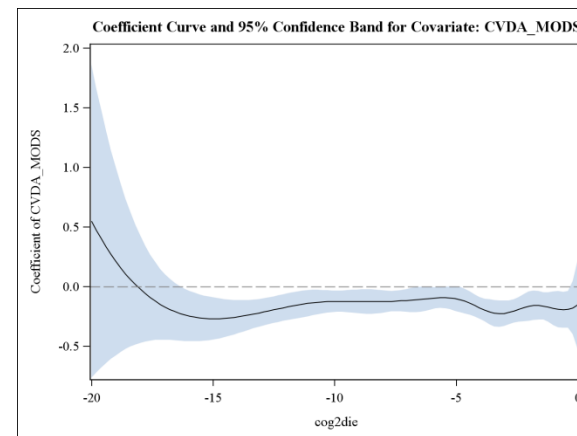
Lewy bodies



Hippocampal sclerosis

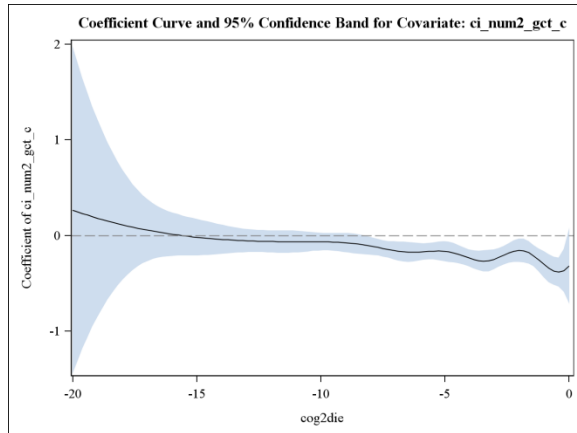


Arteriolar sclerosis

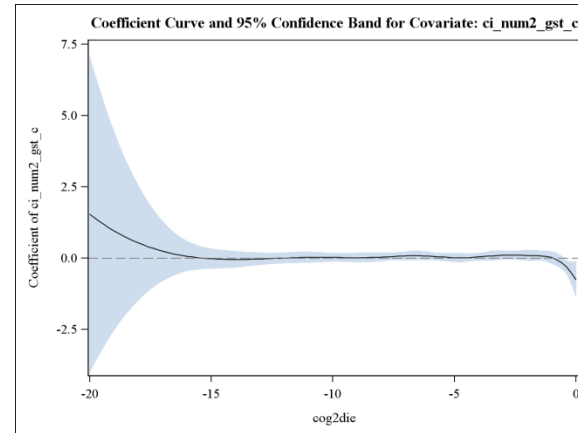


Cerebral atherosclerosis

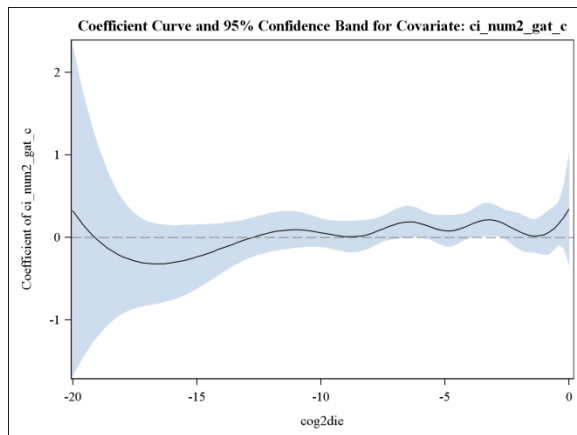
# Cognitive trajectory and effect of APOE and pathologies: simultaneous examination



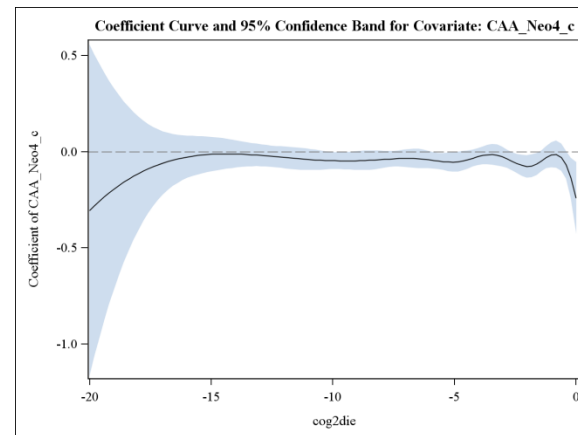
Gross chronic cerebral infarcts



Gross subacute cerebral infarcts



Gross acute cerebral infarcts

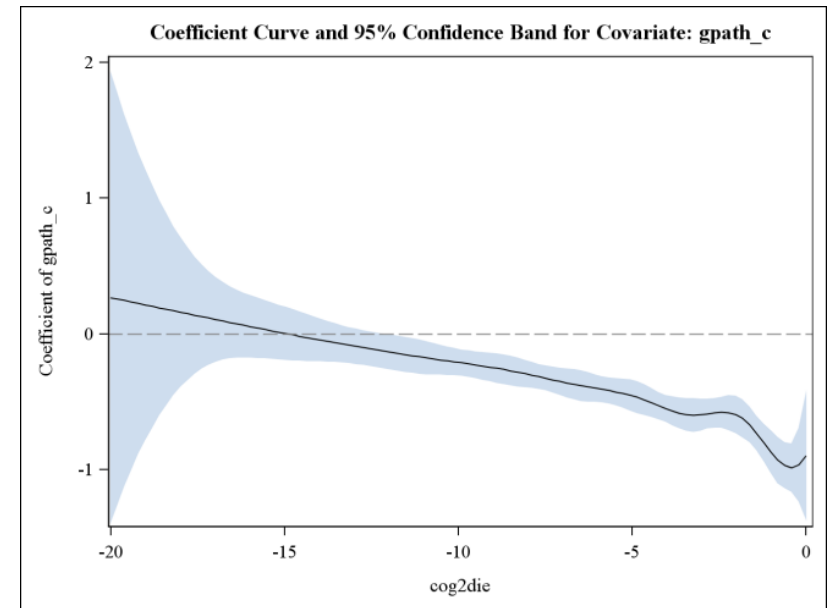
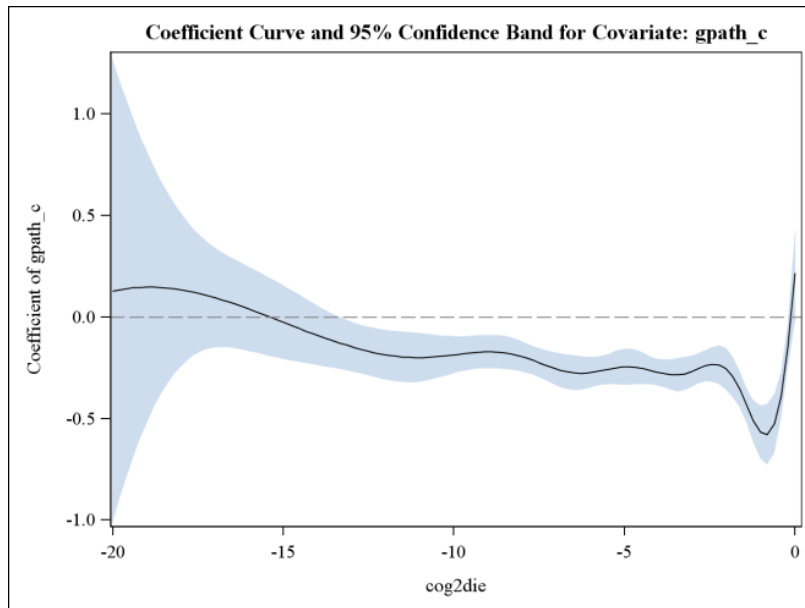


Cerebral amyloid angiopathy

# Comparison of the time-varying effect:

Individual

Simultaneous

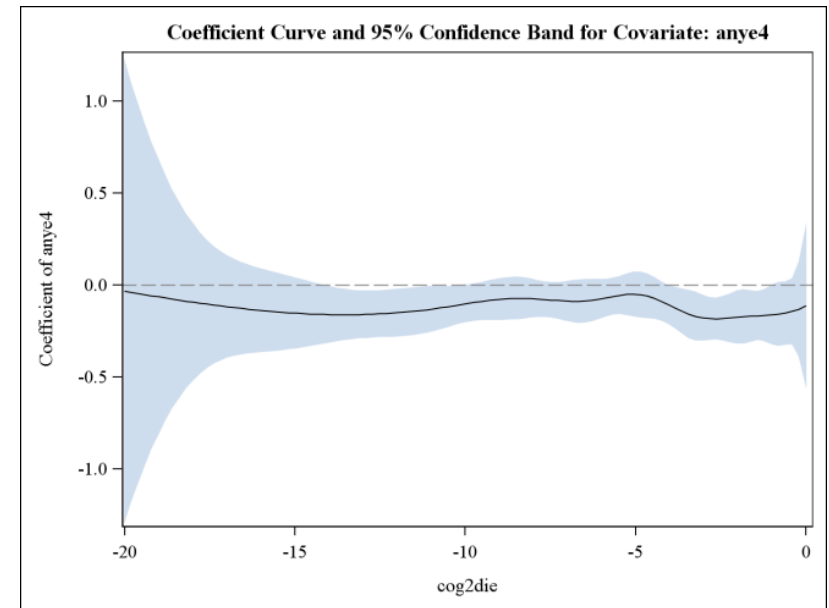
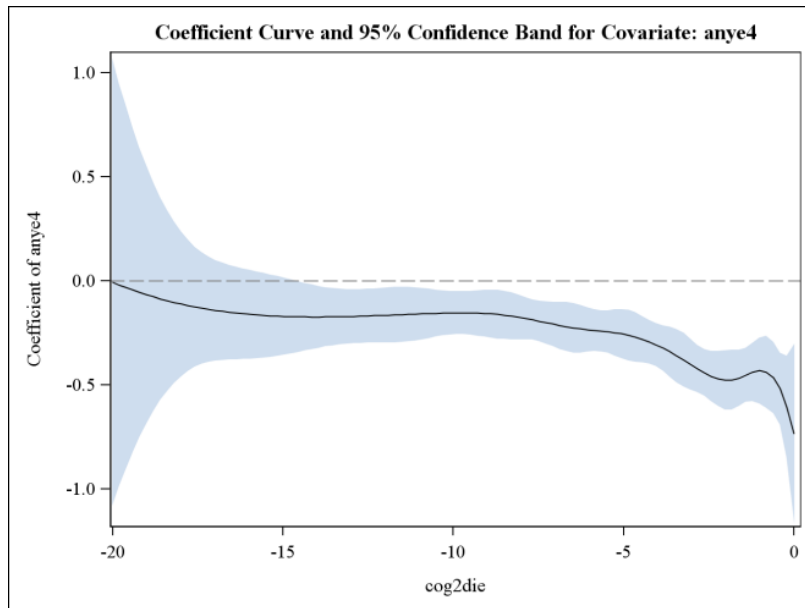


Global pathology

# Comparison of the time-varying effect:

Individual

Simultaneous



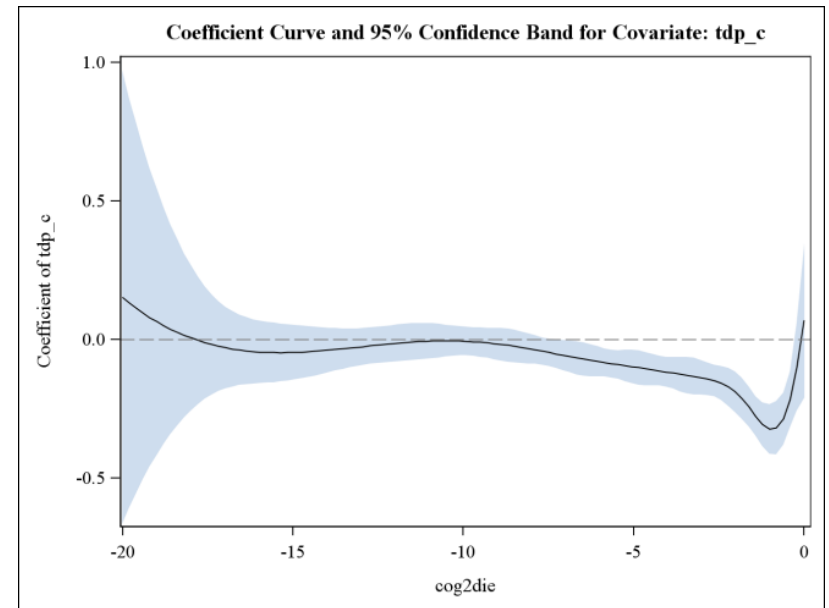
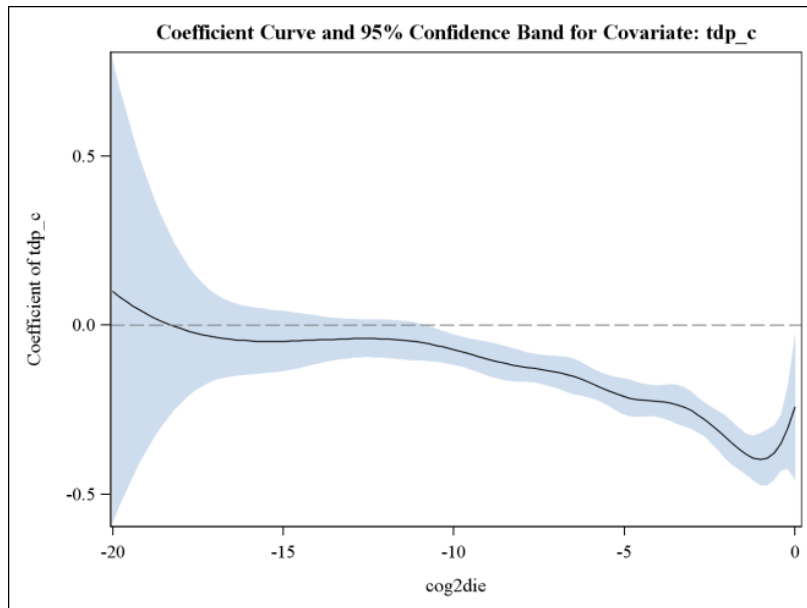
APOE4



# Comparison of the time-varying effect:

Individual

Simultaneous



TDP-43

# Summary of results

- Older adults experienced gradual cognitive decline along aging, and sharp decline before death (terminal decline)
- Pathologies exerted effect on cognition about 10 years before death
- The effect of APOE is similar as pathologies
- After controlling for other pathologies, the effect of APOE on cognition is only minimally significant in the 4 years before death
- Cerebral infarcts had little effect on cognition over time, after controlling for other pathologies

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