Choice of timescale and its implications for longitudinal cognitive aging research (work in progress)

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Background

- In longitudinal cognitive aging research (for example, cohort study), generalized linear mixed models (GLMM) are widely used to describe the change over time of outcomes and association with risk factors
  - With continuous outcomes, linear mixed models (LMM) are often used
- However, the timescale seems an arbitrary choice in the LMM literature
  - Time on study
  - Age
  - Age + adjust for baseline age

Aims

Use simulations to evaluate how different parameterizations of timescales affect longitudinal cognitive aging research results

- Estimated effects of education on the rate of cognitive decline
- Estimated within- and between-person age effects

Simulation- Procedure

1. Generate a hypothetical cohort
2. Create an analytical sample
3. Generate data according to data generating rules
4. Estimate parameters of interest
   - Timescale: study time / age / age + adjustment
5. Repeat 1-4 for multiple iterations (B=1000)
6. Quantify magnitude of bias

- Percentage bias = $\frac{\hat{\beta}-\beta}{\beta} * 100\%$

 Mayeda et al.(2016). A simulation platform for quantifying survival bias: an application to research on determinants of cognitive decline. American journal of epidemiology, 184(5), 378-387

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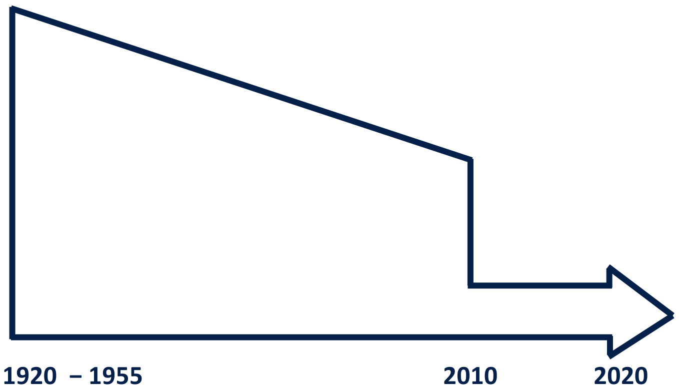
Simulation- Hypothetical cohort study

- Hypothetical cohort:
  - Study the effect of completion of high school education on late−life cognitive decline
  - $N = 50{,}000$ subjects born between 1920 and 1955 (uniformly)
  - In 2010, a random sample of $n = 2{,}000$ subjects who survived to late life (55-90 years old) enrolled in the study
    - $P(survial_i) = \frac{\exp(\gamma_{0t}+\gamma_1 educ_i+\gamma_2 U_i)}{1+\exp(\gamma_{0t}+\gamma_1 educ_i+\gamma_2 U_i)}$, γ_{0t} selected to match the age distribution based on the 2010 Census
  - Cognitive function was measured on 10 waves over 10 years



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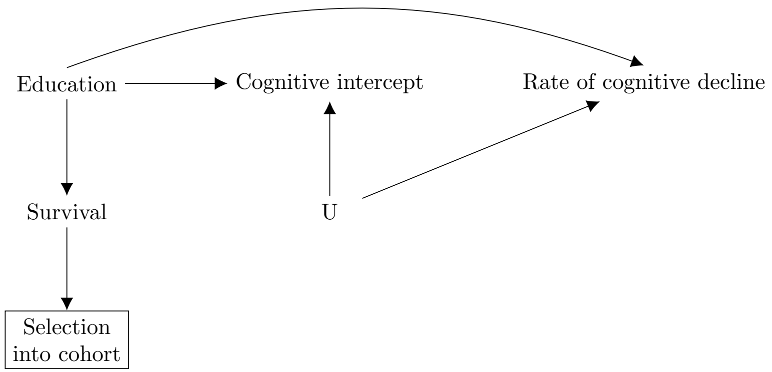
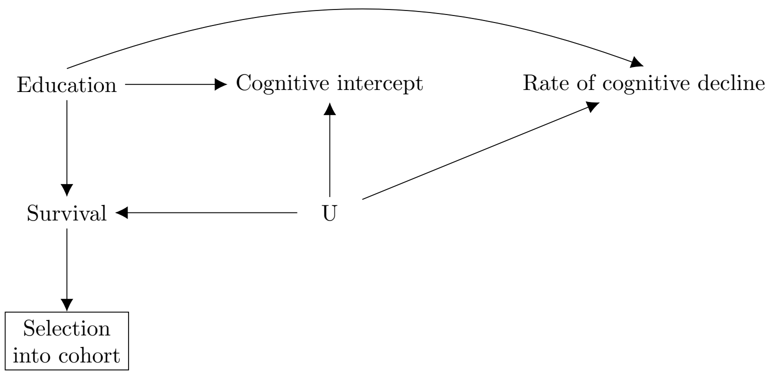
Simulation- Data generating rules

- Causal structures
  - Causal structure 1 (no bias anticipated)
    - U is the unmeasured determinants of cognitive decline



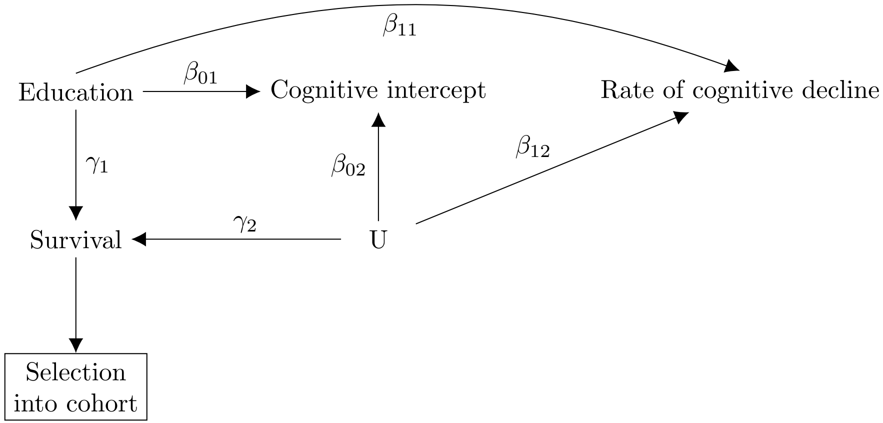
  - Causal structure 2 (selection bias)
    - U is the unmeasured determinants of cognitive decline



Mayeda et al. (2018). Does selective survival before study enrolment attenuate estimated effects of education on rate of cognitive decline in older adults? International journal of epidemiology, 47(5), 1507-1517

Simulation- Data generating rules

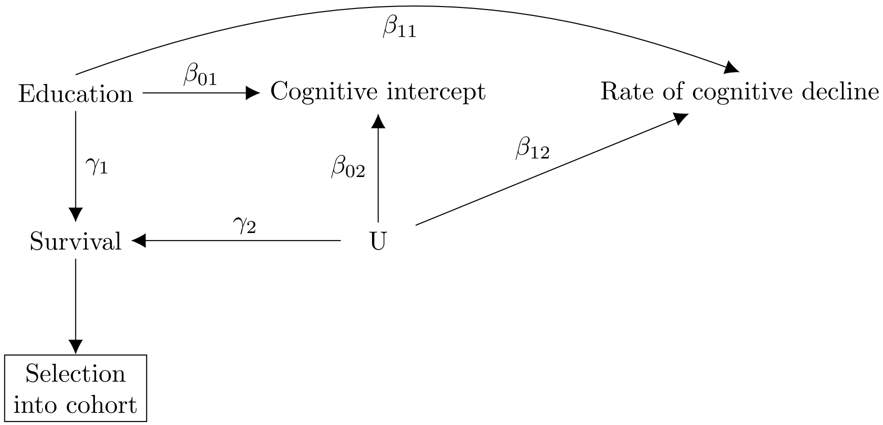
- Unified causal structures
- Generation of repeated measures of cognitive function
  - $Y_{it} = \beta_{00} + b_{0i} + \beta_{01} educ_i + \beta_{02} U_i + \beta_{03} pe_{ij}$
    $+(\beta_{10} + b_{1i} + \beta_{11} educ_i + \beta_{12} U_i) \times age_{it} + \epsilon_{ij}$
  - Age as timescale
  - $\begin{bmatrix} b_{0i} \\ b_{1i} \end{bmatrix} \sim N(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_0^2 & \rho\sigma_0\sigma_1 \\ \rho\sigma_0\sigma_1 & \sigma_1^2 \end{bmatrix}), \epsilon_{ij} \sim N(0, \sigma^2)$
  - $educ_i \sim Bernulli(0.4)$
  - $U_i \sim N(0,1)$
  - True within-person age effect = true between-person age effect



Simulation- Input parameter values

Causal structure	Cognitive intercept			Cognitive decline			Mortality	
	β_{00}	β_{01}	β_{02}	β_{10}	β_{11}	β_{12}	γ_1	γ_2
1: no bias anticipated	0	-0.05	-0.005	-0.05	-0.05	-0.005	-log(2)	0
2: selection bias	0	-0.05	-0.005	-0.05	-0.05	-0.005	-log(2)	-log(2)

Parameter	Definition	Value
β_{03}	Practice effect	0.05
σ_0^2	Variance of random cognitive intercept	0.2
σ_1^2	Variance of random cognitive slope	0.005
ρ	Correlation between random intercepts and random slopes	0.01
σ^2	Variance of measurement error	0.7



Simulation- Model fitting

- Three parameterizations

Timescale	**LMM model with a random intercept and slope**
Time on study	$E[Y_{ij}] = (\beta_{00} + b_{i0}) + (\beta_{10} + b_{i1})time_{ij} + \beta_2 baseline\_age_i$ $+\beta_{02} educ_i + \beta_{03} pe_{ij} + \boxed{\beta_{11}} time_{ij} \times educ_i$
Age	$E[Y_{ij}] = (\alpha_{00} + v_{i0}) + (\alpha_{10} + v_{i1})age_{ij}$ $+\alpha_{02} educ_i + \alpha_{03} pe_{ij} + \boxed{\alpha_{11}} age_{ij} \times educ_i$
Age + adjustment	$E[Y_{ij}] = (\gamma_{00} + u_{i0}) + (\gamma_{10} + u_{i1})age_{ij} + \gamma_2 baseline\_age_i$ $+\gamma_{02} educ_i + \gamma_{03} pe_{ij} + \boxed{\gamma_{11}} age_{ij} \times educ_i$

Simulation- Model fitting

- Three parameterizations

Timescale	LMM model with a random intercept and slope
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Age + adjustment	$E[Y_{ij}] = (\gamma_{00} + u_{i0}) + (\gamma_{10} + u_{i1})age_{ij} + \boxed{\gamma_2}baseline\_age_i$ $+\gamma_{02}educ_i + \gamma_{03}pe_{ij} + \gamma_{11}age_{ij} \times educ_i$

Sanity check 1: under the data generation rules, the coefficient for time on study and baseline age should be approximately the same

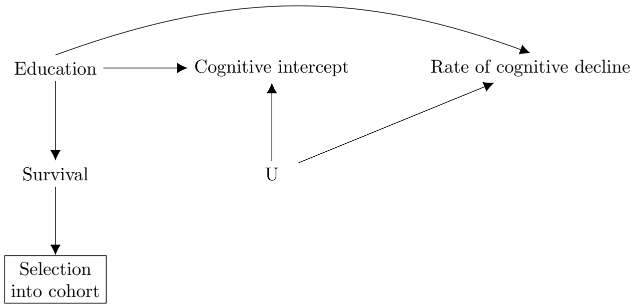
Sanity check 2: the coefficient for baseline age should be approximately zero

Simulation- Model fitting

- Three parameterizations

Timescale	LMM model with a random intercept and slope	Within-person age effect	Between-person age effect
Time on study	$E[Y_{ij}] = (\beta_{00} + b_{i0}) + (\beta_{10} + b_{i1})time_{ij} + \beta_2 baseline\_age_i$ $+\beta_{02}educ_i + \beta_{03}pe_{ij} + \beta_{11}time_{ij}\times educ_i$	β_{10}	β_2
Age	$E[Y_{ij}] = (\alpha_{00} + v_{i0}) + (\alpha_{10} + v_{i1})age_{ij}$ $+\alpha_{02}educ_i + \alpha_{03}pe_{ij} + \alpha_{11}age_{ij}\times educ_i$	α_{10}	α_{10}
Age + adjustment	$E[Y_{ij}] = (\gamma_{00} + u_{i0}) + (\gamma_{10} + u_{i1})age_{ij} + \gamma_2 baseline\_age_i$ $+\gamma_{02}educ_i + \gamma_{03}pe_{ij} + \gamma_{11}age_{ij}\times educ_i$	γ_{10}	$\gamma_{10} + \gamma_2$

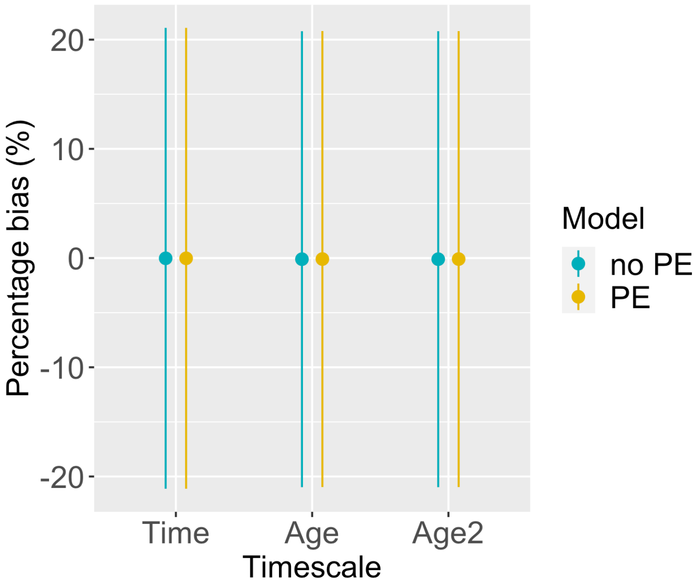
Simulation- Results



- Causal structure 1 (no bias anticipated)

Effect of education on cognitive decline

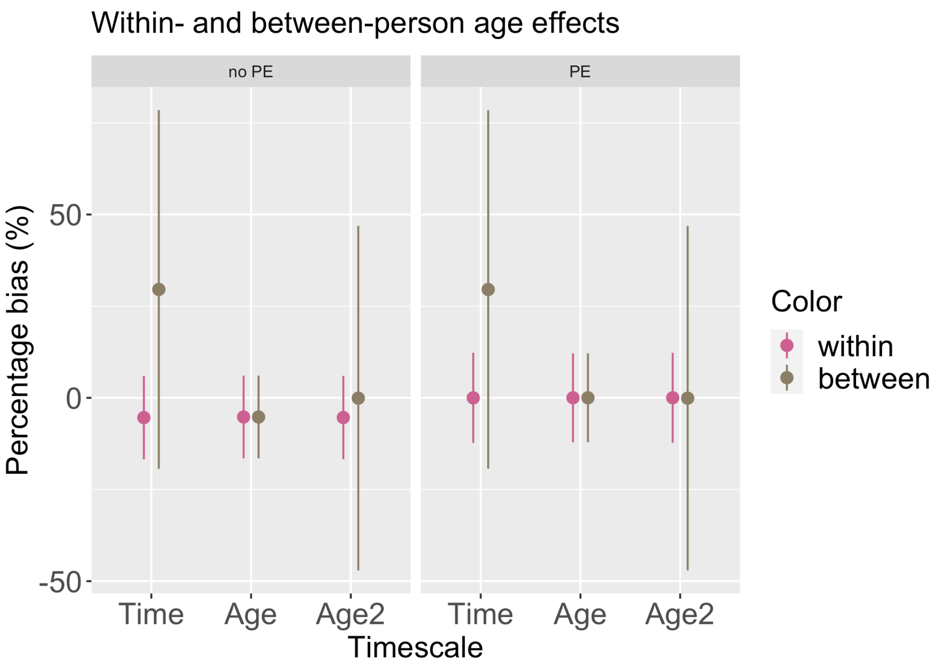
β_{11} / α_{11} / γ_{11}

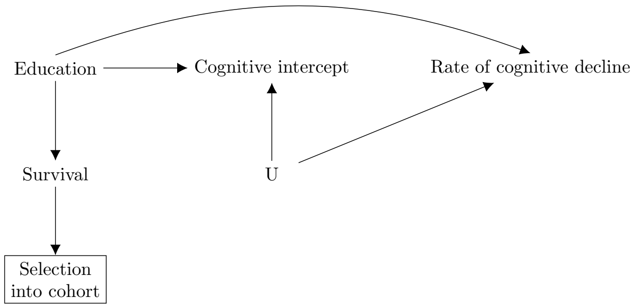


- Takeaway:
  - In causal structure 1, the estimated effect of education on rate of cognitive change was unbiased, independent of timescale

Simulation- Results

- Causal structure 1 (no bias anticipated)





Time scale	LMM model with a random intercept and slope	Within	Between
Time	$E[Y_{ij}] = \beta_{10} time_{ij} + \beta_2 baseline\_age_i + \cdots$	β_{10}	β_2
Age	$E[Y_{ij}] = \alpha_{10} age_{ij} + \cdots$	α_{10}	α_{10}
Age2	$E[Y_{ij}] = \gamma_{10} age_{ij} + \gamma_2 baseline\_age_i + \cdots$	γ_{10}	$\gamma_{10} + \gamma_2$

- Takeaway:
  - In causal structure 1, all timescales gave unbiased estimates for within-person age effect. Time as timescale overestimated between-person age effect

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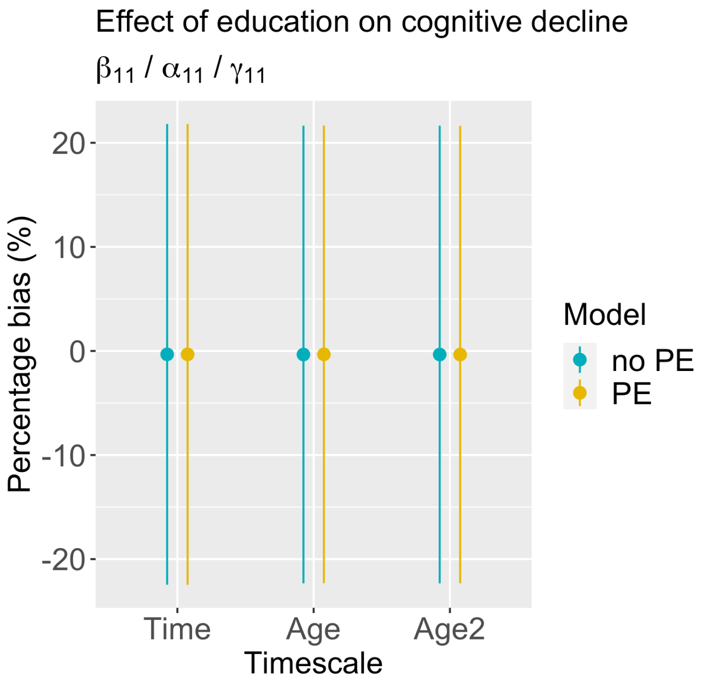
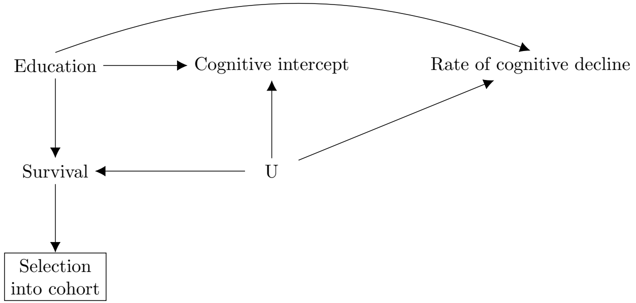
Simulation- Results

- Causal structure 2 (selection bias)

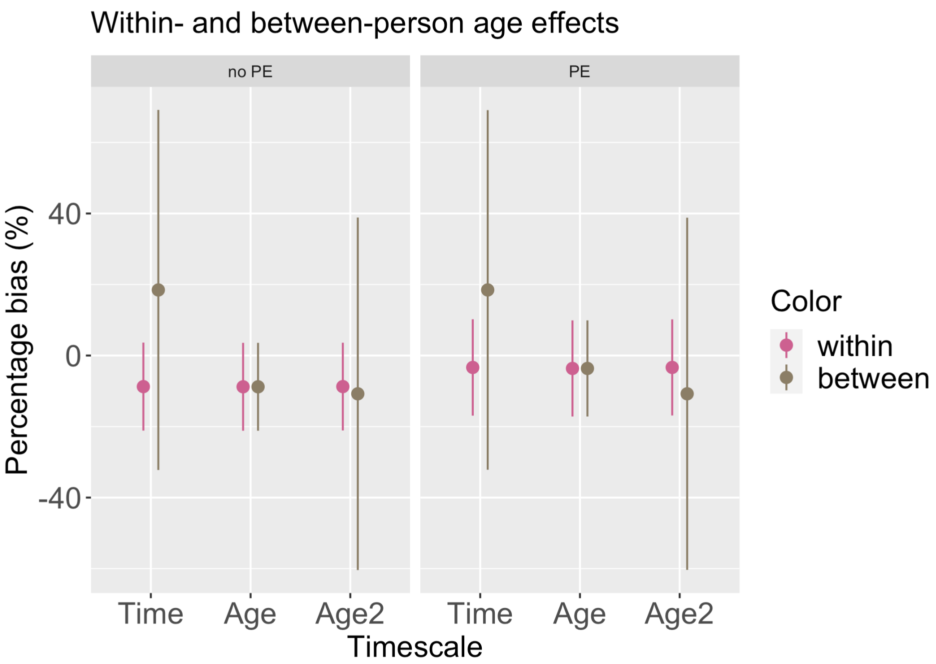


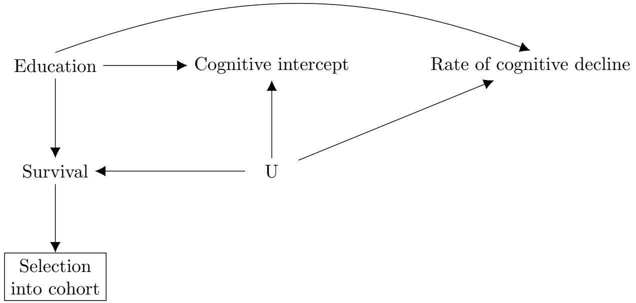


- Takeaway:
  - In causal structure 2, the magnitude of bias with moderate input parameters was relatively small, but independent of timescale

Simulation- Results

- Causal structure 2 (selection bias)





Time scale	LMM model with a random intercept and slope	Within	Between
Time	$E[Y_{ij}] = \beta_{10} time_{ij} + \beta_2 baseline\_age_i + \cdots$	β_{10}	β_2
Age	$E[Y_{ij}] = \alpha_{10} age_{ij} + \cdots$	α_{10}	α_{10}
Age2	$E[Y_{ij}] = \gamma_{10} age_{ij} + \gamma_2 baseline\_age_i + \cdots$	γ_{10}	$\gamma_{10} + \gamma_2$

- Takeaway:
  - In causal structure 2, all timescales underestimated within-person age effect and the magnitude of bias was independent of timescale

Summary

- Under current data generating structures (true within- and between-person age effects are the the same), analytical timescale did not affect the magnitude of bias in within-person age effect
  - “Wrong” analytical timescale may give biased between-person age effect
- Analytical timescale did not affect the magnitude of bias in estimated effect of education on rate of cognitive decline
  - In the absence of bias, time on study and current age resulted in almost identical unbiased results
  - In the presence of selection bias, the magnitudes of bias were similar (and small)

Next steps- simulation

- Nonlinear age effect
- Cohort effect
- Healthy participation effect
  - A 75-year-old person who enrolls in a study may be healthier (higher cognitive level, lower rate of decline) than an otherwise comparable person who turns 75 after several years of follow-up
- Loss to follow-up

Weuve et al. (2015). Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. Alzheimer's & dementia, 11(9), 1098-1109.

Next steps

- Assess and compare the associations between education and cognitive decline in the Health and Retirement Study and the Life After 90 Study under the following three scenarios:
  - Using time as the timescale
  - Using current age as the timescale
  - Using current age as the timescale and adjust for baseline age

Comments or suggestions?

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