An Economist's View of Biological Age

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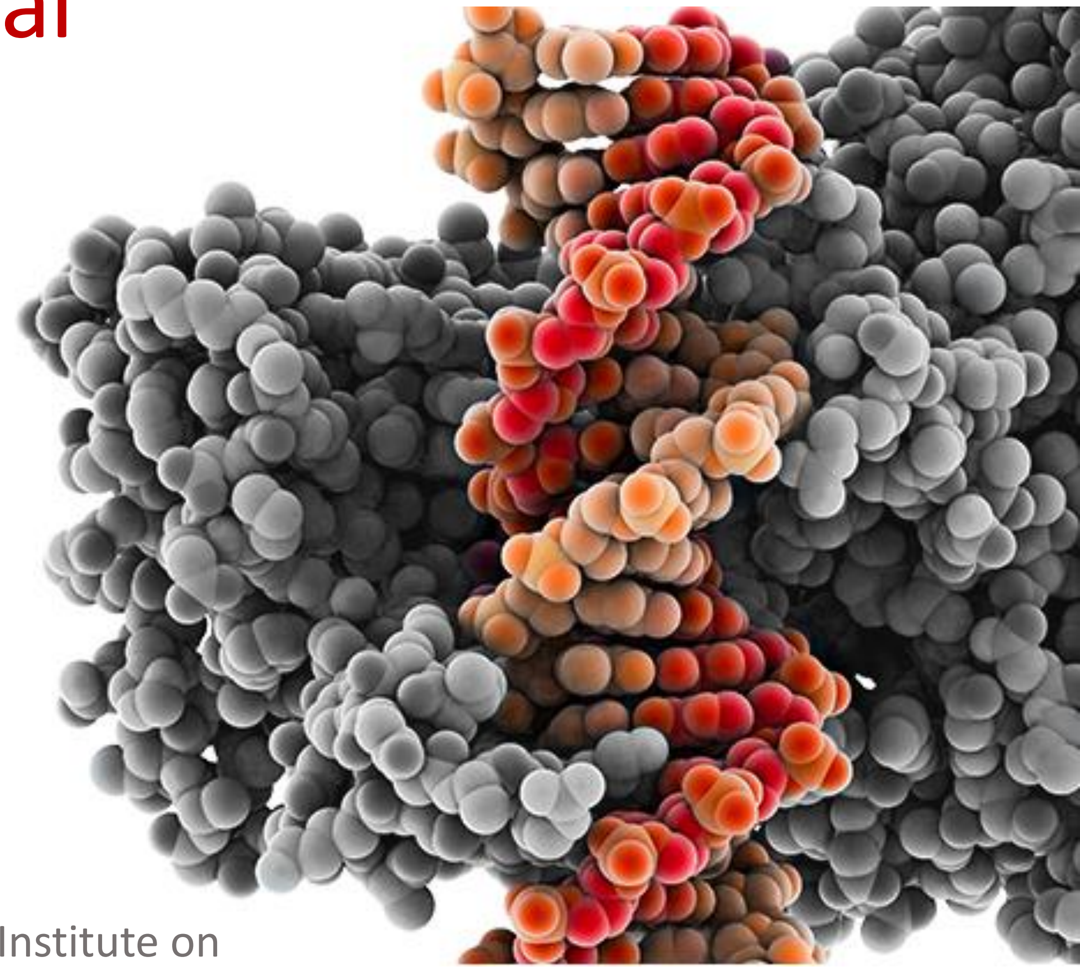

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Why invite an economist to the party?

- Specialize in using quasi-experimental techniques to isolate causality in population-level data
  - Tools: instrumental variables, differences-in-differences, regression discontinuity designs, etc.

- Useful given increasing availability of biomarker/molecular data in large population aging studies (e.g., HRS)

- Expands the range of policy-relevant questions we can ask regarding social determinants of molecular aging

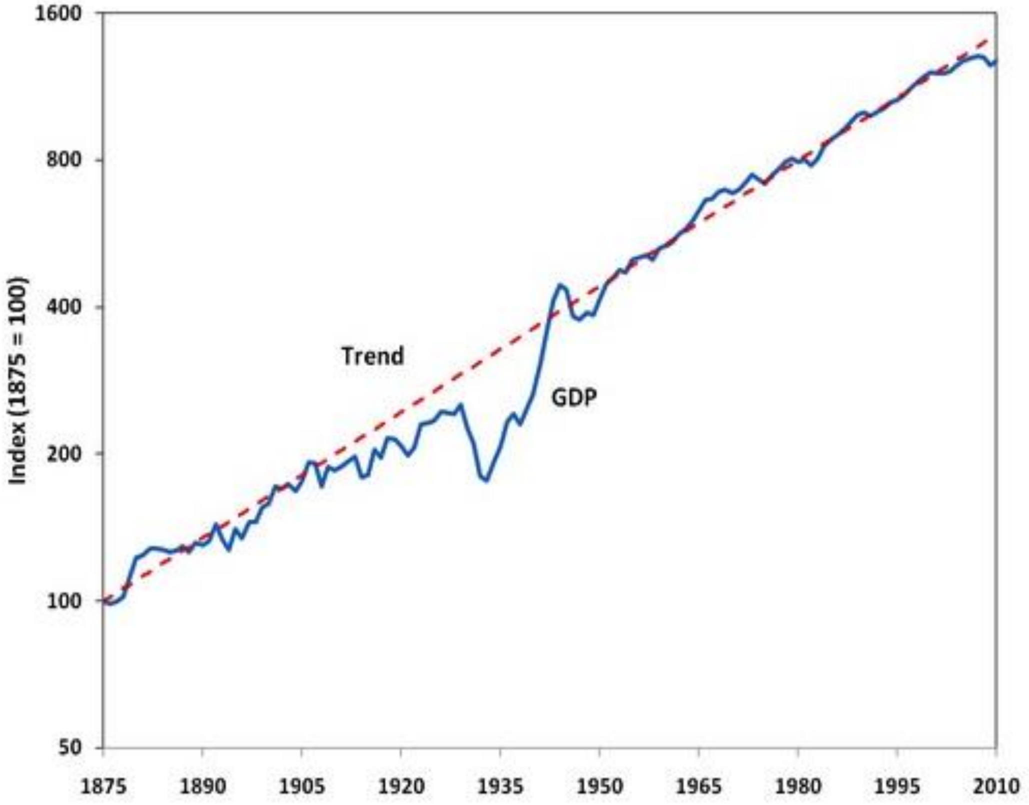
Example: Early-life shocks and late life epigenetic aging

- Challenging to study the causal effect of early-life shocks on epigenetic modifications in humans

- Lack of epidemiological studies with epigenetic and socioeconomic measures across the life course
  - Some exceptions: Dutch Hunger Winter (Heijmans et al., 2008) and Project Ice Storm studies (Cao-Lei et al., 2014)

Research question

- Does exposure to economic fluctuations in utero impact late-life epigenetic aging?
  - Focus on the most severe and prolonged economic downturn in American history → the Great Depression



Real GDP per working-age person in the U.S., 1875-2010

Sources: Kehoe and Prescott (2007) and Timothy Kehoe's website: http://users.econ.umn.edu/~tkehoe/

Why focus on the Great Depression?

1. **Massive economic shock**
   - A quarter of the U.S. labor force was unemployed, fortunes were destroyed, no social safety net
   - Huge unexpected financial and psychological shock for many households (Elder Jr. 1974; Terkel 1970, 2010)

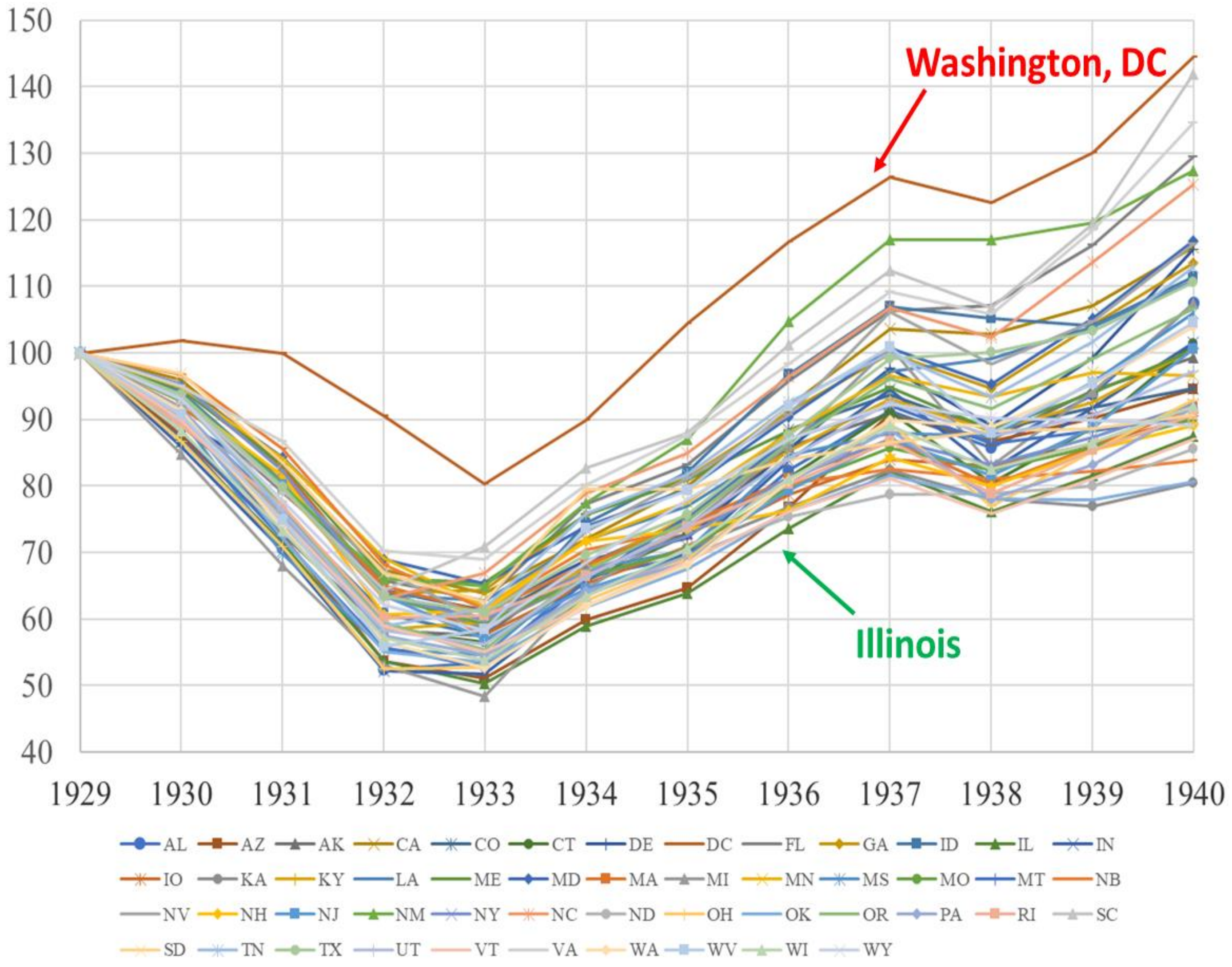
2. **Dramatic geographic and temporal variation in economic** conditions in the 1930s due to the GD and the subsequent government relief programs from the New Deal
   - Exploit state- and year-level variation in macroeconomic conditions during the 1930s to identify the impact of the GD on epigenetic age acceleration

3. **We can use the Health and Retirement Study (HRS)!**
   - 1st nationally representative study in the U.S. to collect epigenetic data that has necessary state-level geographic variation (N=4,018)

HRS sample and data

- HRS respondents born between 1929-1940
- Had their blood drawn in 2016 (~75-86)
- Link state-level data on wages to individuals' state of birth from in utero period to age 16
- Use 6 publicly-available epigenetic aging clocks/pace of aging measures

Wage index by state (1929=100)



Data source: Bureau of Economic Analysis

Difference-in-differences specification

$$EAA_{isrc} = \beta_0 + \sum_{t=-3}^{T} \beta_t\, Wages_{sc} + X_i'\beta + Z_{s\,1930} * c + \theta_s + \eta_c + u_{(s1930\times c)} + \gamma_r * c + \varepsilon_{isrc}$$

- EAA_{isrc} : epigenetic age acceleration measure for individual *i* born in state *s* in region *r* in year *c* in 2016
- *Wages:* aggregate wage index at the state and year level for the period before conception (pre-trend), in utero, and in early childhood (*t*=-3 to 16)
- *X*: sex, race, and maternal education
- $Z_{s1930} * c$: vector of state-level characteristics around 1930 including maternal and infant mortality rate and the state population interacted with YOB time trends
- $u(_{s1930\times c})$: state's share of wage earners in manufacturing in 1930 interacted with YOB FE's
- θ_s and η_c : state and year of birth fixed effects
- $\gamma_r * c$: region of birth*YOB time trends
- ε_{isrc}: random error term clustered at the state of birth and individual level
- All models are estimated using the HRS sample weights for the VBS sample

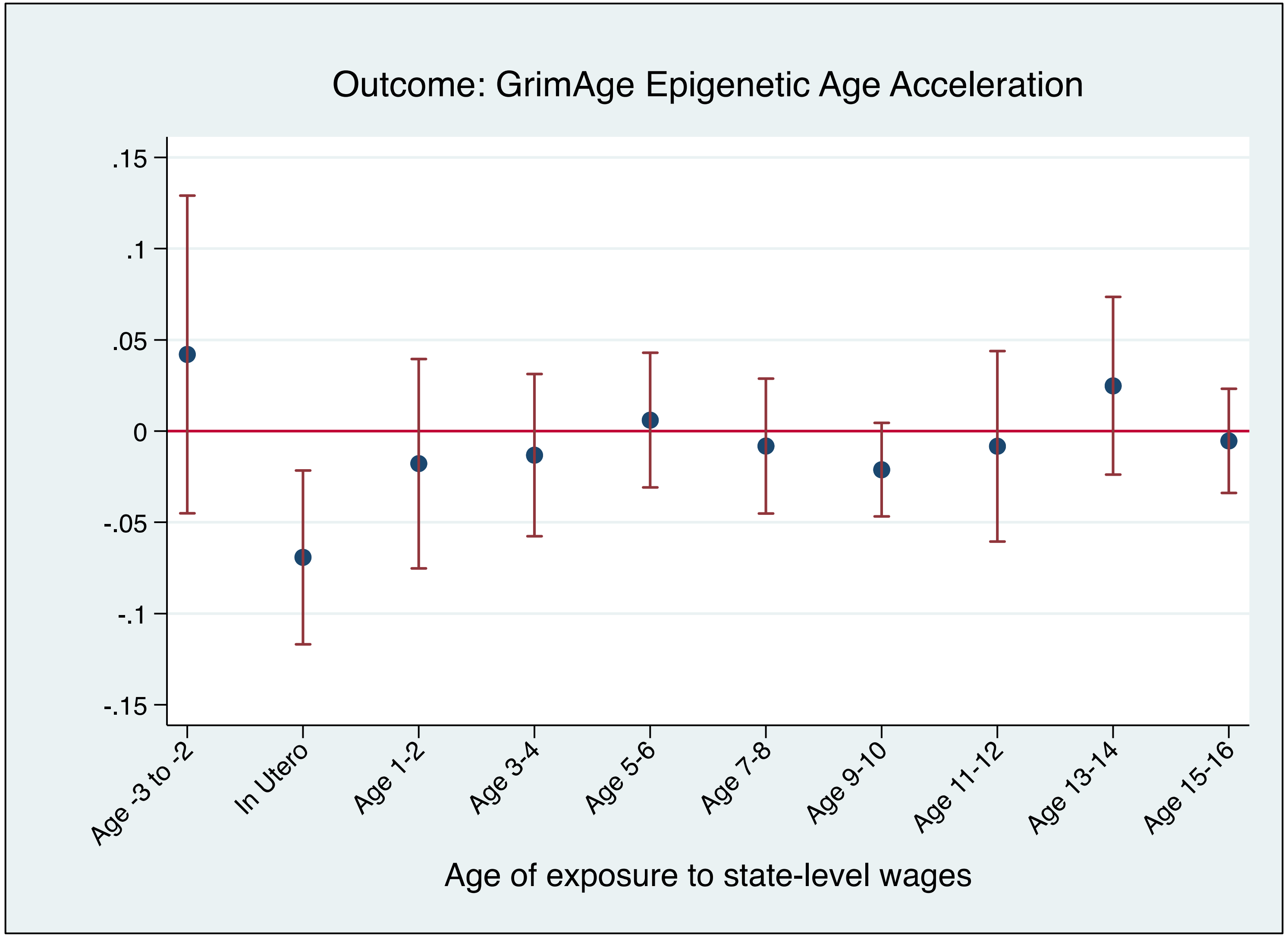
Baseline model: State-level wages in utero on EAA

OUTCOME	Horvath EAA	Horvath 2 EAA	Hannum EAA	Levine EAA	GrimAge EAA	DunedinPoAm EAA
Wage index in utero	0.0523	-0.0157	-0.0299	-0.0055	**-0.0762*** **	**-0.0017*** **
	[0.0462]	[0.0387]	[0.0452]	[0.0446]	**[0.0229]**	**[0.0006]**
Observations	832	832	832	832	832	832
R-squared	0.15	0.142	0.189	0.17	0.273	0.134
YOB FE	X	X	X	X	X	X
SOB FE	X	X	X	X	X	X
Individual Covariates	X	X	X	X	X	X
Mother's Education	X	X	X	X	X	X
Add'l state controls*linear trends	X	X	X	X	X	X
Share of Manufacturing*YOB FE	X	X	X	X	X	X
Region of birth*linear trends	X	X	X	X	X	X

Cluster robust standard errors in brackets. *** p<0.01, ** p<0.05, * p<0.1

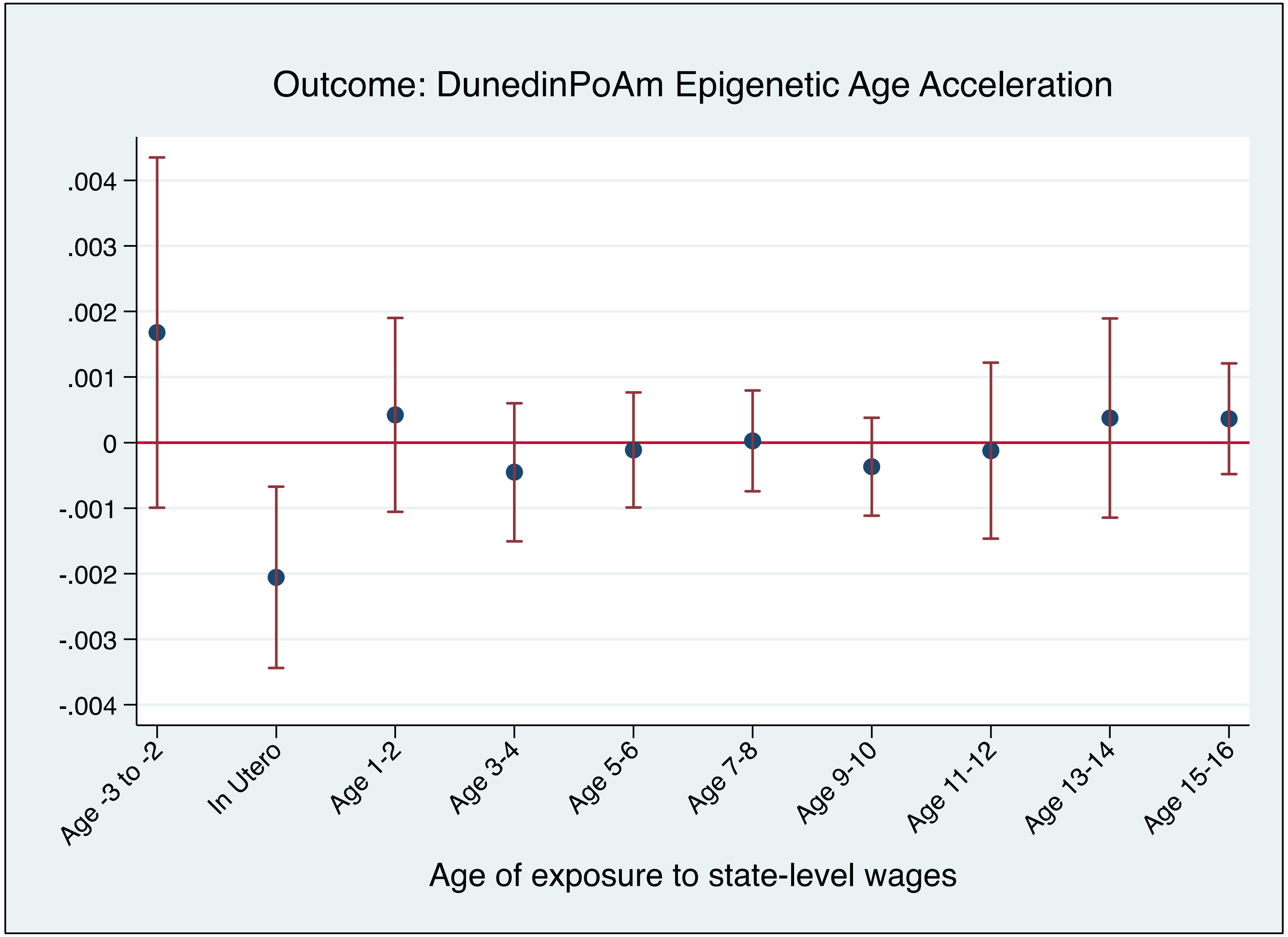
- A 1-SD increase in the wage index in utero led to 0.31 SD & 0.37 SD declines in GrimAge EAA and PoAm EAA
- 1-SD of the wage index is equivalent to ~80% of the overall decline in wages during the GD

State-level wages in childhood on GrimAge EAA



Cluster robust 95% confidence intervals. Coefficients are from the fully specified model.

State-level wages in childhood on PoAm EAA



Cluster robust 95% confidence intervals. Coefficients are from the fully specified model.

Study conclusions (preliminary)

- Economic fluctuations from the GD increased epigenetic age acceleration among individuals who survived until 2016
- Effects of the shock appear to be linked to exposures during the in utero period
- Effects do not appear to be explained by selective responses (mortality or fertility) and are not driven by Dust Bowl states, New Deal spending, or WWII

Gaps and Opportunities

- Need more longitudinal data AND causal research designs to assess whether biological aging processes are affected by the social environment

- Epigenetic aging measures are sensitive and have relatively large effect sizes
  - Effect sizes of quasi-natural experiments tend to be modest
  - Improved identification of treatment effects in smaller samples
  - Identify effects in older (surviving) samples

- Mechanistic insights → WHY do in utero insults result in faster aging?

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