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# The Epigenetic Index of Accelerated **Pubertal Development** is Associated with **Aging Outcomes** among Older Adults

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# Acknowledgement

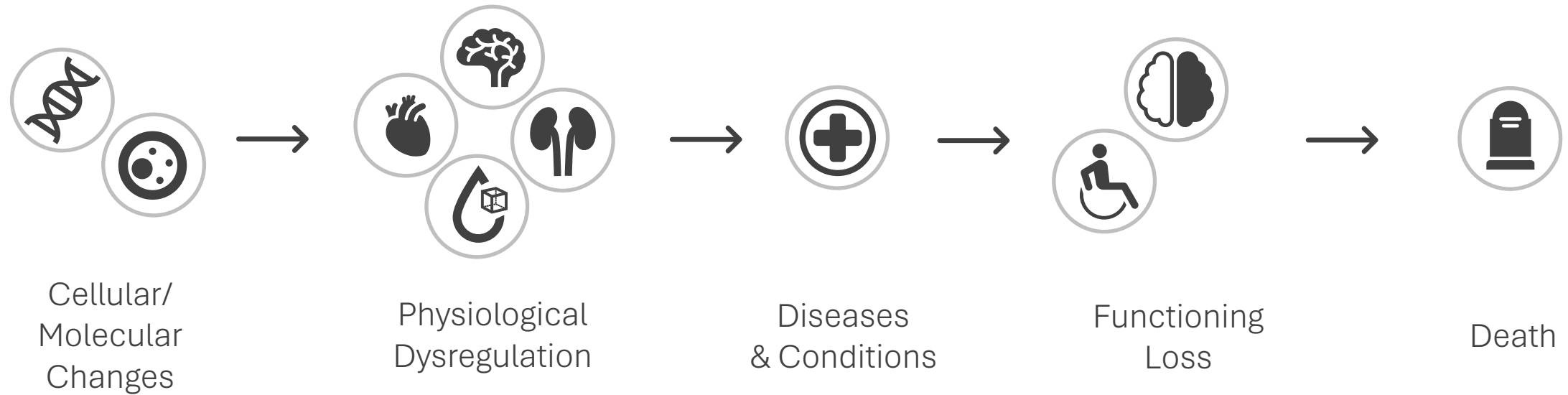
## Coauthors:

Abby de Steiguer, Sepideh Zarandooz, Yayouk Willems, Trey Smith, Joshua Goode, Colter Mitchell, K. Paige Harden, Laurel Raffington

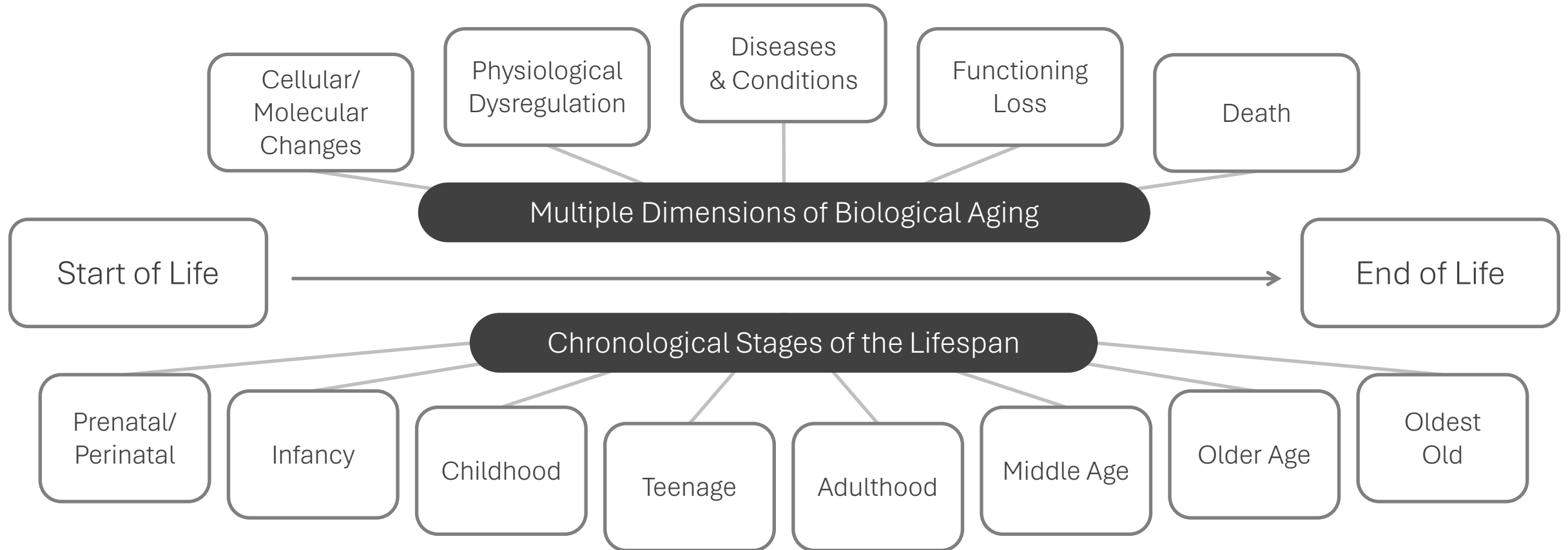
## Funding Sources:

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# Multiple Sequential Dimensions of Biological Aging



# Aging as a lifelong process



# Pubertal Development and Biological Aging

Theoretically:

Evolutionary models posit molecular connections between reproductive development and later-life aging

(J. Belsky, 2019; Ellis et al., 2017; Ellis & Giudice, 2019; Horvath & Raj, 2018; Raffington, 2024)



Threatening/Impoverished  
Environment

Accelerated Reproductive  
Maturation

Adverse environments trigger adaptive mechanisms to accelerate sexual maturity to increase the likelihood of mating and reproduction - Reproduce before potential early death!

...Though at a potential **long-term cost to health and lifespan**

# Challenge Due to Long Temporal Lag in Human Lifespan



## Among adolescent samples:

Earlier pubertal timing (measured) ~ Faster pace of epigenetic aging

! Do not have the full spectrum of aging phenotypes

(Binder et al., 2018; Hamlat et al., 2023; Raffington et al., 2021; Simpkin et al., 2017; Suarez et al., 2018)



## Among adult samples:

Earlier pubertal timing (recalled) ~ Some specific end-point health outcomes

! Puberty measures are crude, single-item, and subject to recall bias

(Elks et al., 2013; Lakshman et al., 2009; Ohlsson et al., 2020; Daredia et al., 2025; Hamlat et al., 2021, 2023)

# Linking Epigenetic Puberty to Aging Outcomes

deSteiguer et al. 2025

N~3000 US Adolescents  
Texas Twin Project &  
Future of Families and Child  
Well-Being Study



Epigenome-Wide  
Association Study  
+  
Elastic Net



## Phenotypes of Pubertal Development

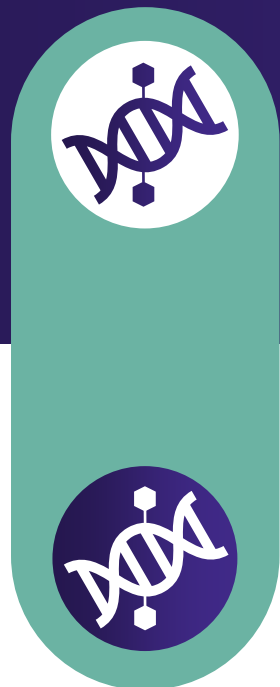
Pubertal Age: Rescaled age norm of the changes in skin, height, body hair, facial hair (boys), voice (boys), breasts (girls), and menstruation (girls).

The Current Study

Sex-Specific  
Epigenetic Puberty Index:

**DNAmPubertalAge**

*The DNA Methylation Pattern  
of Pubertal Development*



*Molecular & Phenotypic  
Aging Outcomes*

N=3642 US Middle-Aged & Older Adults  
Health and Retirement Study



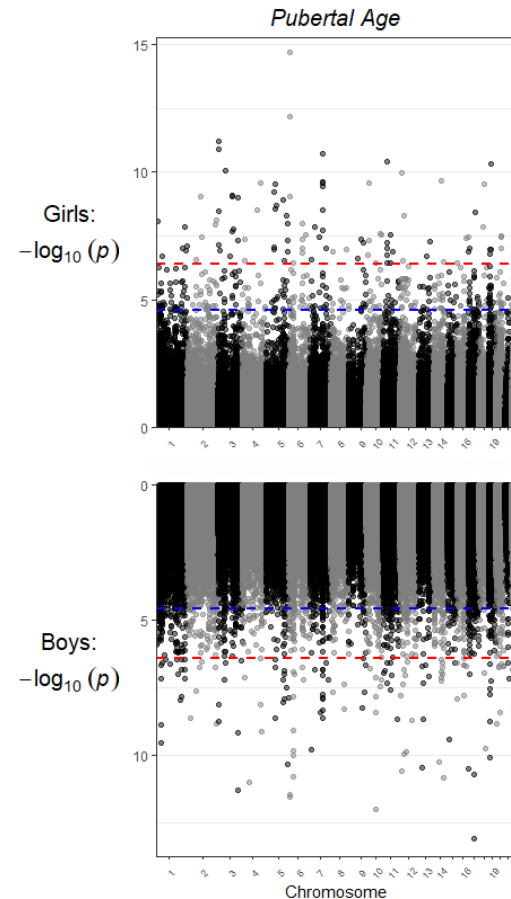
How does the **underlying epigenetic pattern of accelerated pubertal maturation** relate to multiple dimensions of aging outcomes among older adults?

# The Epigenetic Index of Pubertal Development

## Pubertal Development Scale

Self-rated physical changes in skin, height, body hair, facial hair (boys), voice (boys), and breasts (girls). Girls also reported on the onset of menstruation.

**Pubertal Age** – Comparing self-reported physical development to sex-specific age norms. An adolescent's pubertal age is the age at which their level of physical maturity is typical for their sex. Elastic-net-based.



DNAmPubertalAge

Girls: 195 CpG sites

Boys: 166 CpG sites



Saliva-Blood ICC

=

0.640

(95% CI: 0.309, 0.971)

PCGrimAgeAccel: 0.67

PCPhenoAgeAccel: 0.66

DunedinPACE: 0.68

\*DNAmPoverty: 0.53

\*DNAmSES: 0.65

# Aging Outcomes

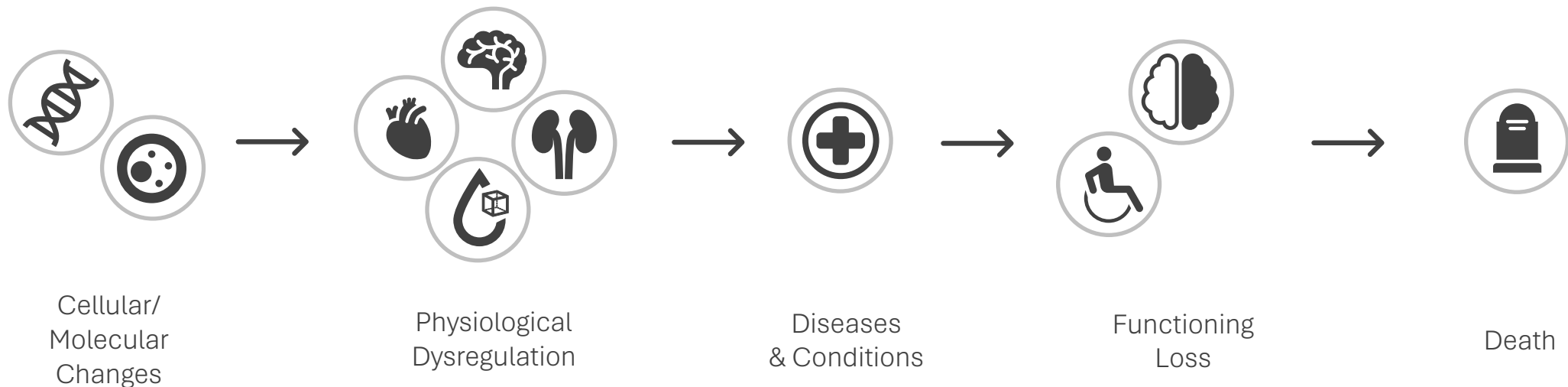
**Cellular/Molecular Changes:** PhenoAge Acceleration, PC GrimAge Acceleration, DunedinPACE

**Physiological Dysregulation:** Expanded Biological Age Acceleration (ExpBioAge)

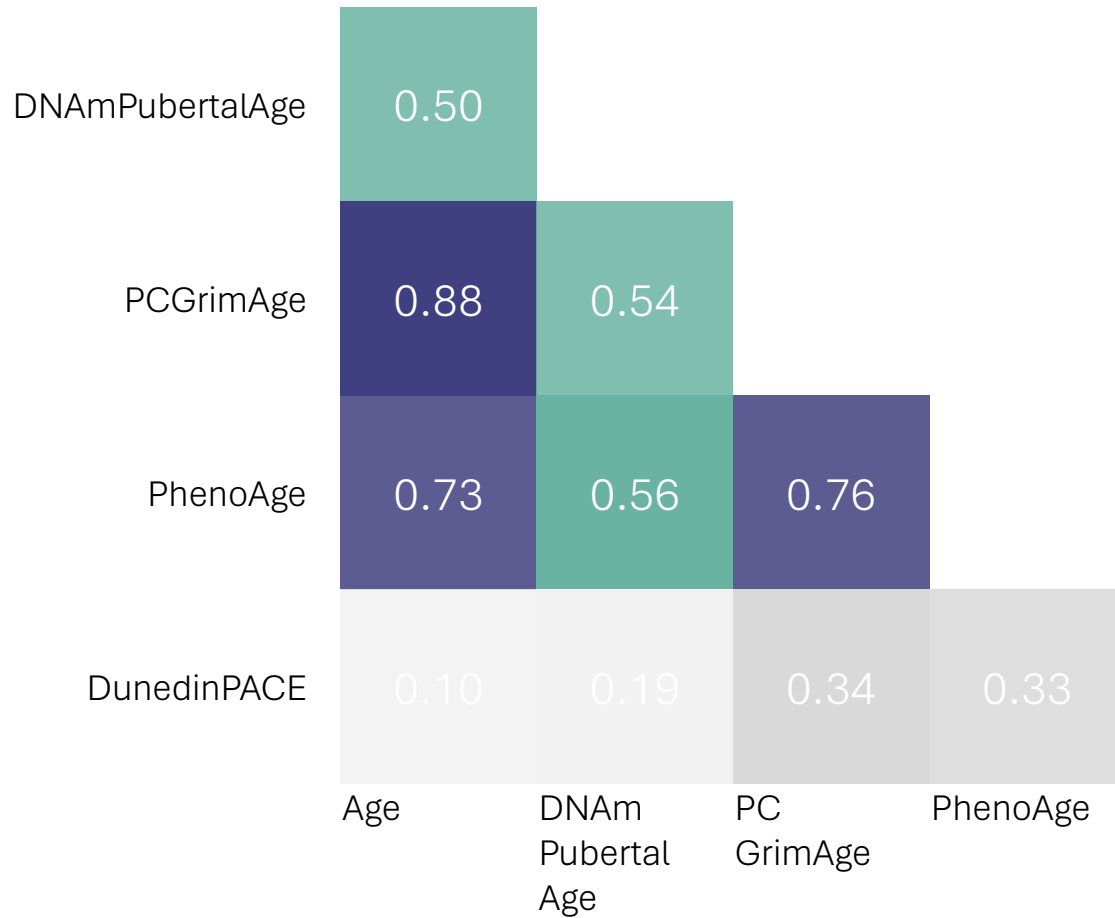
**Diseases & Conditions:** Multimorbidity Count

**Functioning Loss:** ADL/IADL Count, Cognitive Function (Reverse Coded), Cognitive Decline

**Death:** 6-Year Mortality



# The epigenetic pubertal age is correlated with chronological age

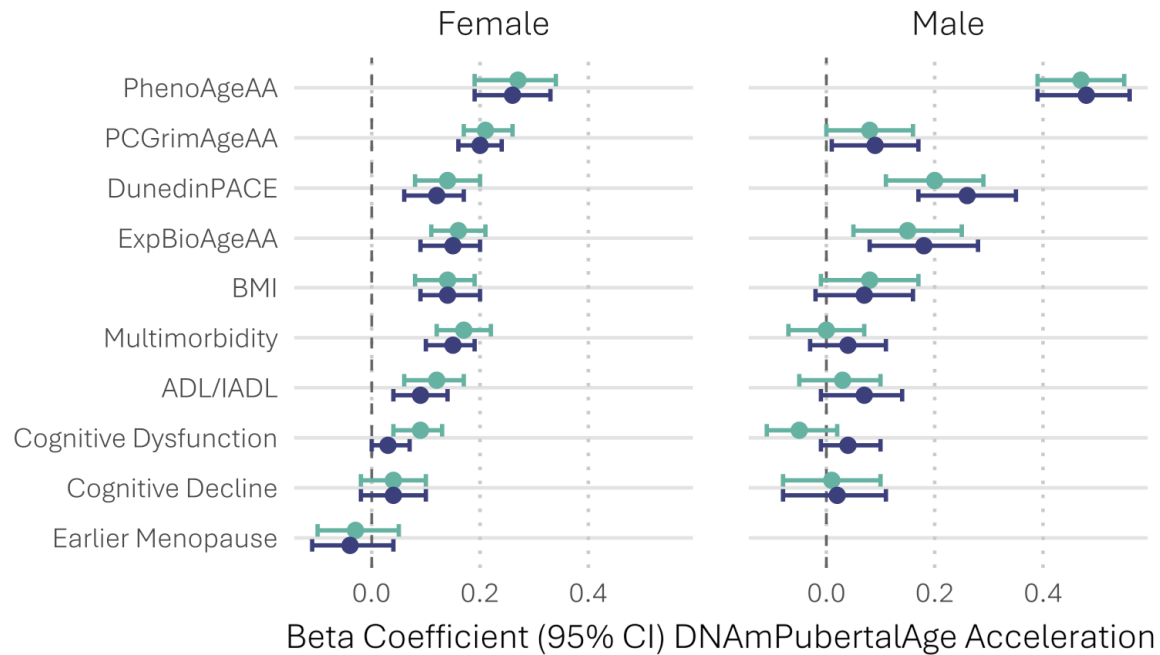


The association with chronological age was more moderate for DNAmPubertalAge compared with PCGrimAge and PhenoAge

DNAmPubertalAge: **0.50** (0.48 - 0.53)  
PCGrimAge: **0.88** (0.87 - 0.88)  
PhenoAge: **0.73** (0.71 - 0.74)

All subsequent analyses residualized epigenetic puberty index, PhenoAge, and PCGrimAge for chronological age to indicate age-acceleration.

The **DNA methylation pattern** of accelerated pubertal maturation is associated with molecular and clinical aging biomarkers and mortality for both sexes.



### For both females and males

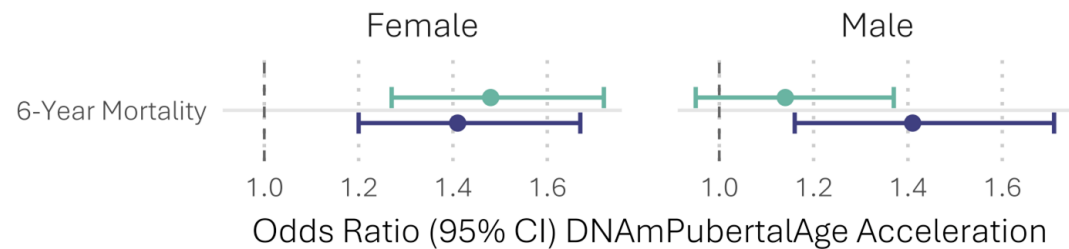
More advanced DNAmPubertalAge Acceleration is associated with

- PhenoAge AA, PC GrimAge AA, DunedinPACE
- Expanded BioAge AA
- 6-yr Mortality

### Among females

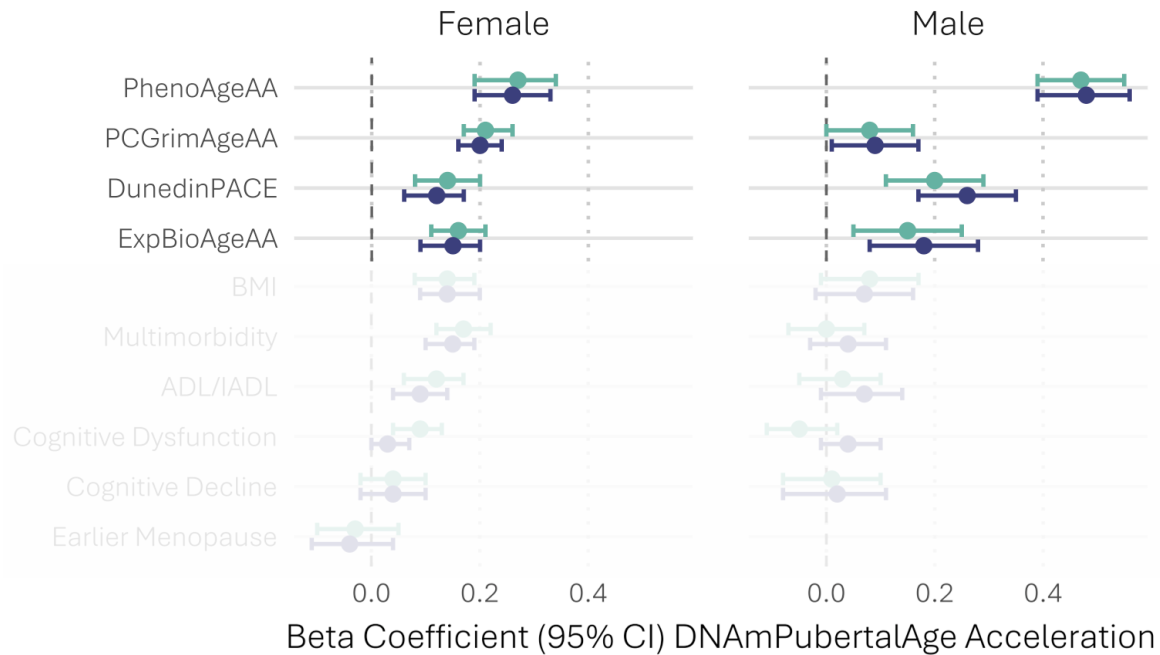
More advanced DNAmPubertalAge Acceleration is additionally associated with

- Higher BMI
- Multimorbidity
- ADL/IADL



Model    ● Adjusted    ● Unadjusted  
*(Adj: Age groups, race/ethnicity, and education)*

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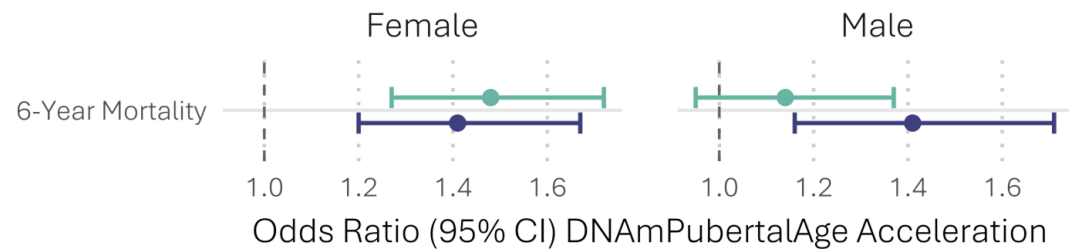
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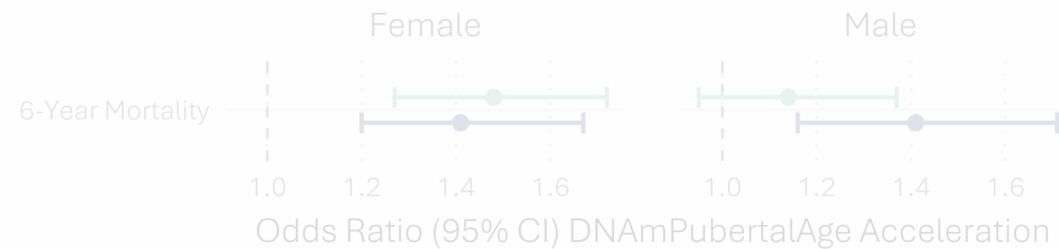
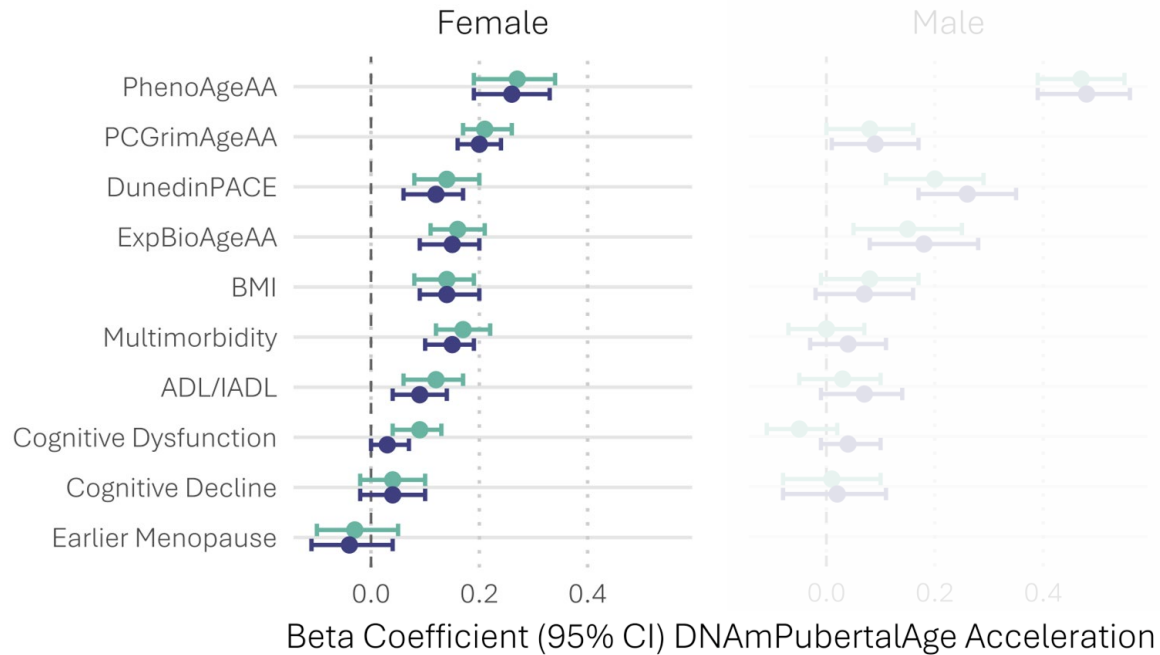
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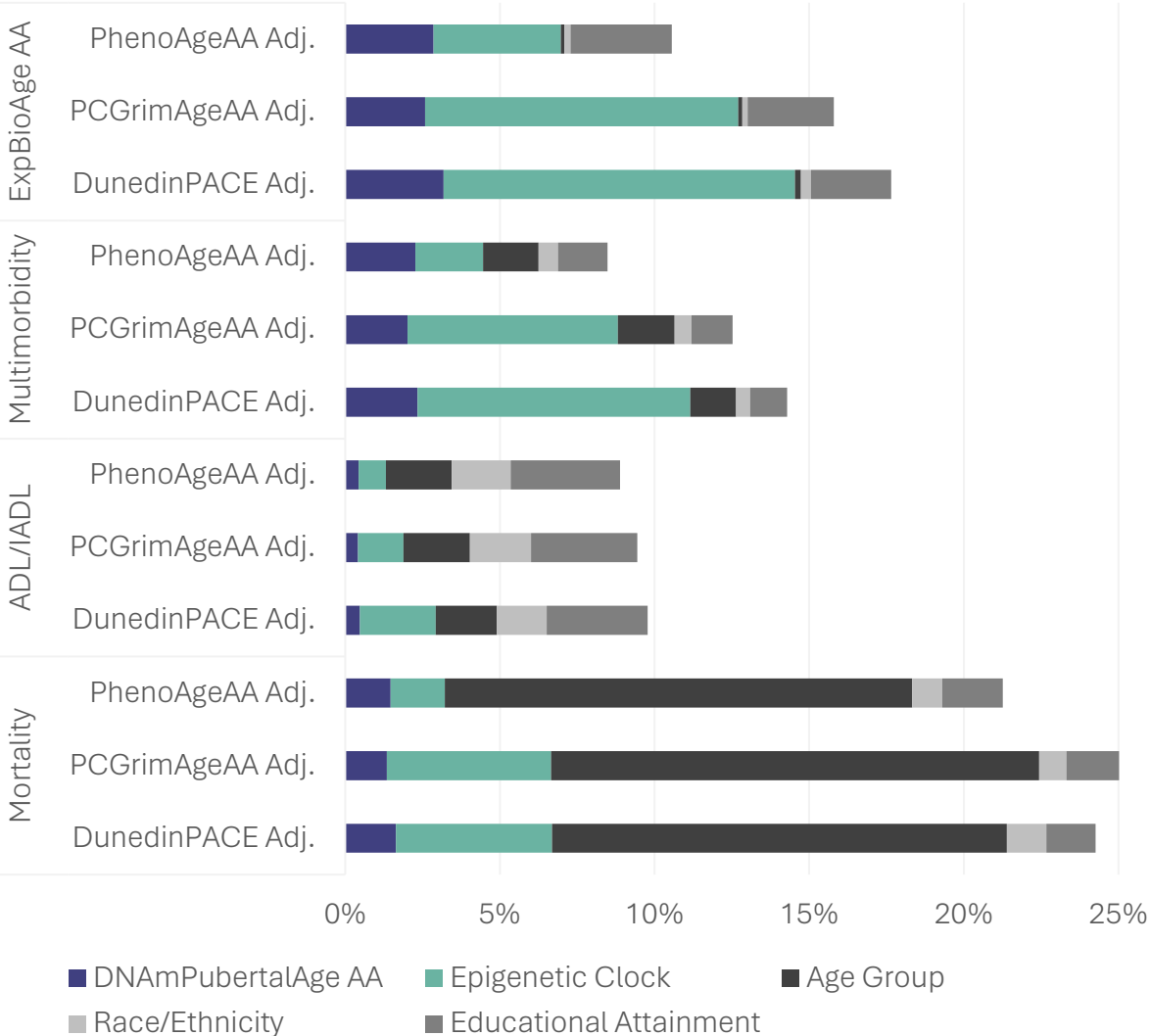
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The **DNA methylation pattern** of accelerated pubertal maturation further links to downstream aging outcomes in females, accounting for unique variance beyond clocks.

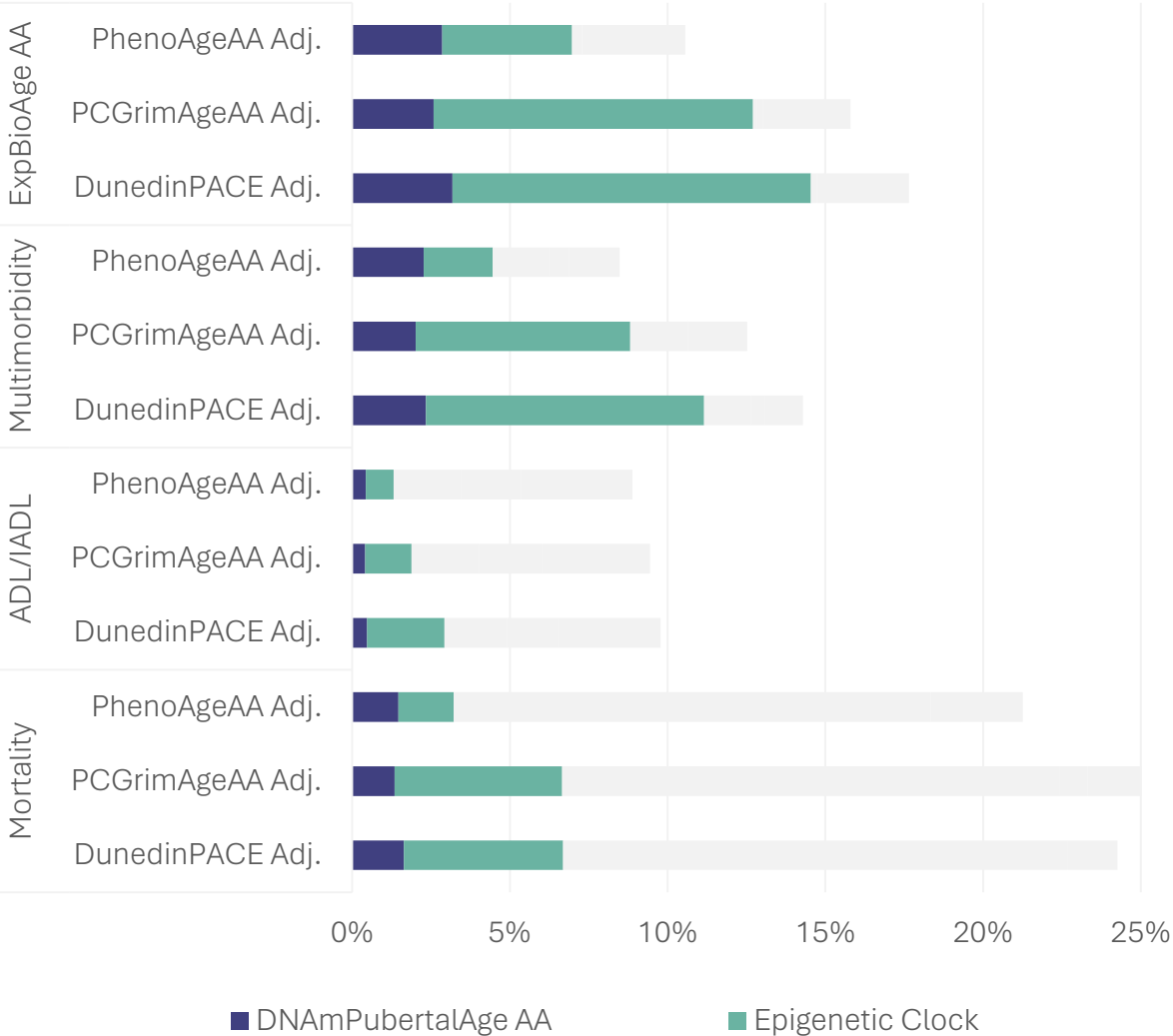


R-Square Decomposition:  
(Shorrocks-Shapely approach)

Among females, DNAmPubertalAge Acceleration accounts for a unique portion of the variation in:

- Clinical biological age (2.6%–3.2%)
- Multimorbidity (2.0%–2.3%)
- ADL/IADL (0.4%–0.5%)
- 6-year mortality (1.3%–1.6%)

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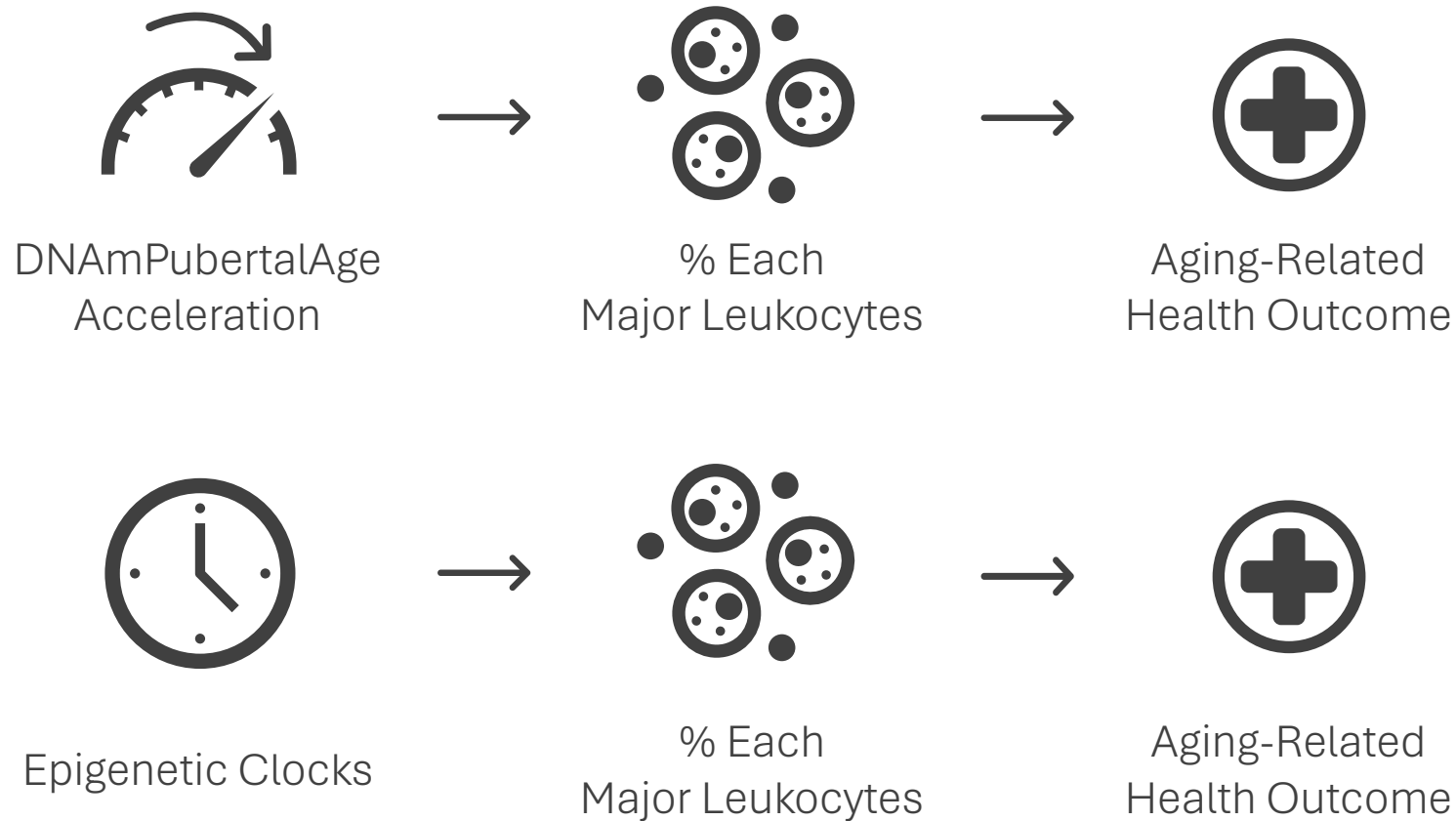
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DNAmPubertalAge acceleration explained substantially less unique variance (57% on average) than the clocks.

Adding six major immune cell types as additional covariates attenuates the associations between epigenetic puberty and aging outcomes



*Average coefficients attenuation after adding covariates:*

↓ 34%

↓ 13%

*Identify whether links exist  
vs  
Decompose causal pathways*

# Takeaways

**The underlying biology of pubertal maturation might be a pro-aging mechanism.**



Why? Because pubertal maturation is energetically costly and generates oxidative and inflammatory stress through rapid biosynthetic and endocrine activation, it may heighten the physiological stress and reduce the body's capacity for long-term maintenance.

**The underlying biology of pubertal development may be important for understanding and measuring biological aging, yet has been overlooked in the development of aging algorithms in adults.**



Implication: When measuring aging, every phenotype that reflects aging across the lifespan should be considered a valuable potential data input. Developmental processes could be important sources to improve aging biomarker generation.



## Portal Gate

*Train biomarkers on time-sensitive underlying biology, either of a developmental process or certain exposures, and then apply to richly phenotyped cohorts to understand what the biology means.*

### Early-life Development and Epigenetic & Brain Aging

- Generation R cohort
- n=2500 cord blood DNAm + n=1200 age 10 blood DNAm
- n=3000 age 10 MRI
- Physical, adaptive, language, cognitive, and socioemotional developmental hallmarks

### Epigenetic Index of Pubertal Development

- Trained & Validated in TTP+FFCWS (n~3000 youths)
- Applied to HRS (n=3600)

### Epigenetic Indices of Childhood SES & Poverty

- Trained in TTP+FFCWS (n~3000 youths)
- Validated in TwinLife (n~1000)
- Applied to FHS, HRS, and SOEP linking to childhood and adult SES

### Epigenetic Index of Cognitive Development

- Trained in TTP (n=1800) and Validated in TwinLife (n~1000)
- Applied to HRS HCAP (n=4000), maybe Add Health, ALSPAC