

Quantification of Biological Aging for Resilience Research

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Disclosures

DunedinPACE is a Duke University & University of Otago invention licensed to a private company, TruDiagnostic, from which I receive royalties

I am consulting CSO and SAB Chair of BellSant and SAB member of the the Hooke Clinic

DunedinPACE is freely available to researchers: <https://github.com/danbelsky/DunedinPACE>

Outline

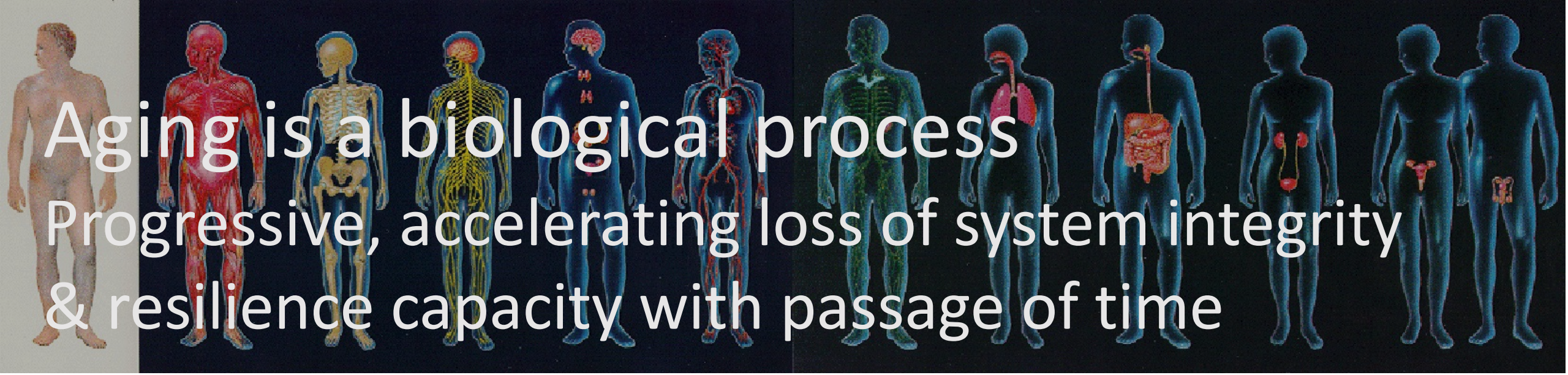
1. Geroscience

Translating the biology of aging to prevent disease

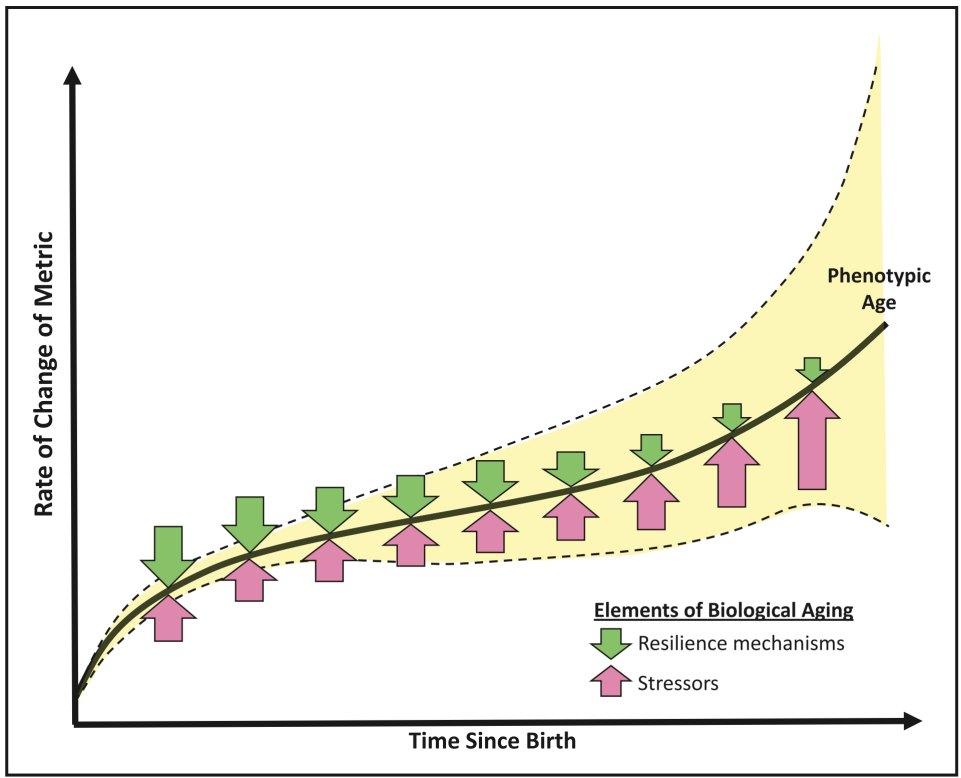
2. Quantification of Biological Aging

From RCT surrogate endpoints to readouts on resilience

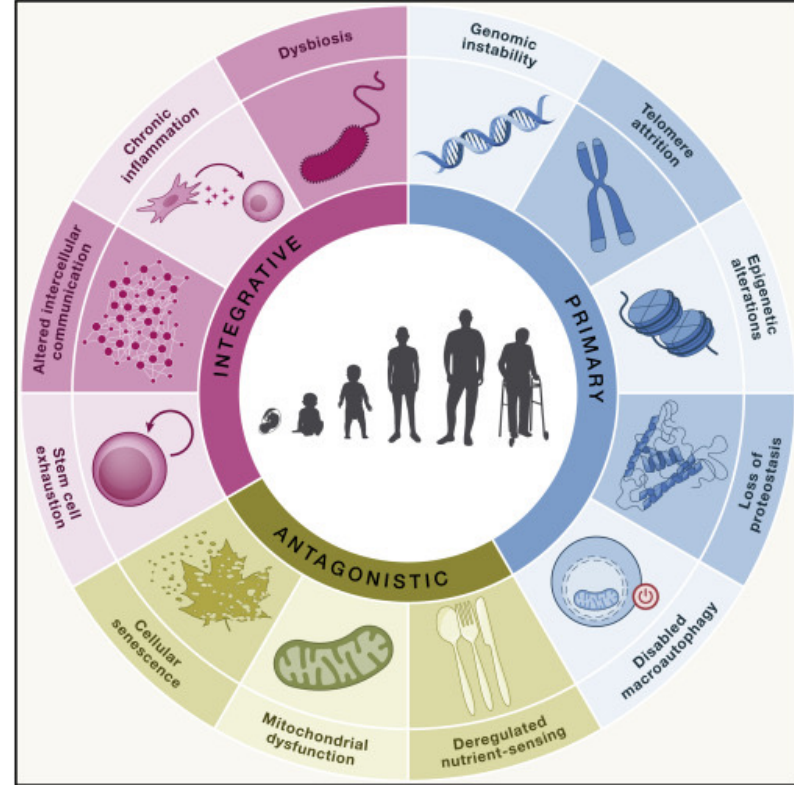
3. Opportunities and next steps



Aging is a biological process
 Progressive, accelerating loss of system integrity
 & resilience capacity with passage of time



Ferrucci et al.
 2018 Circ



Lopez-Otin et al.
 2023 Cell

The Geroscience Hypothesis

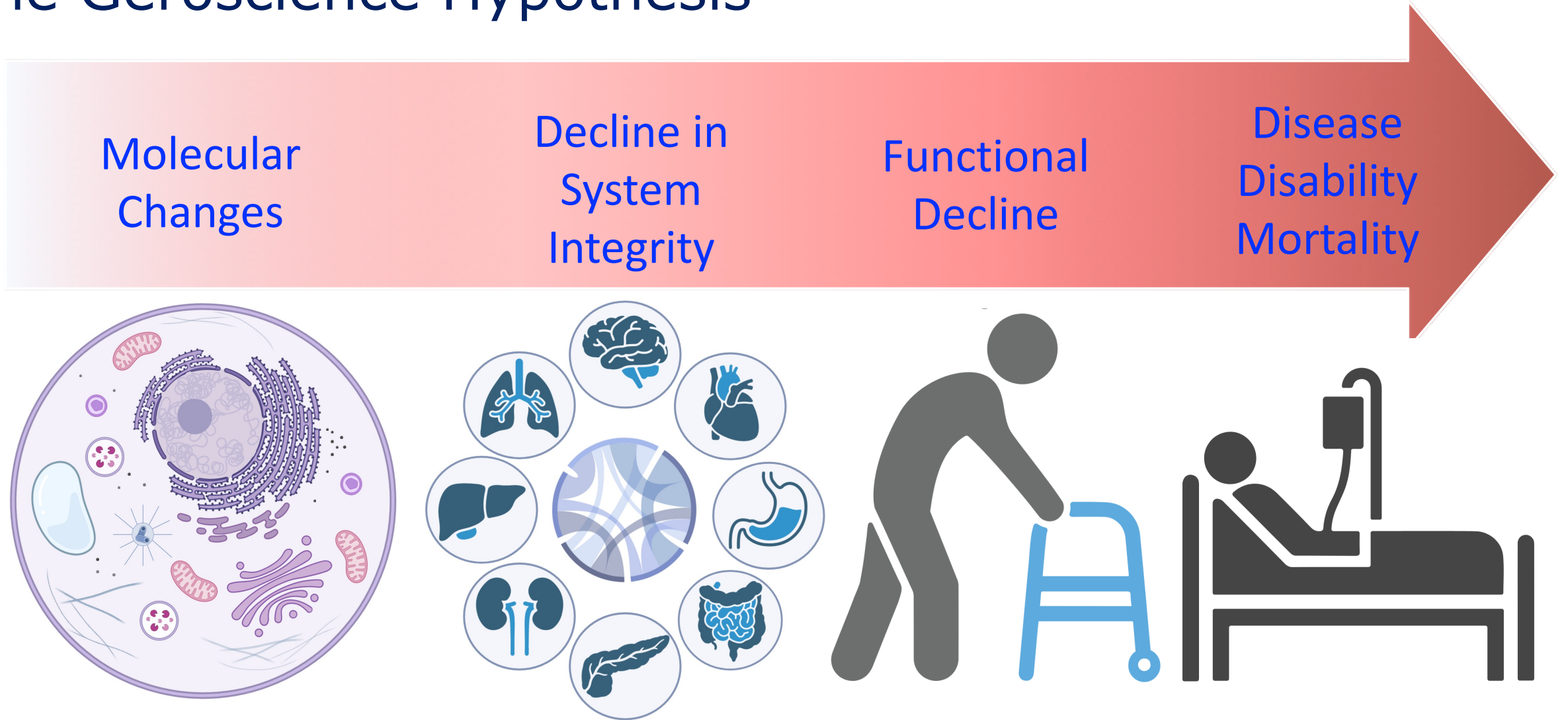
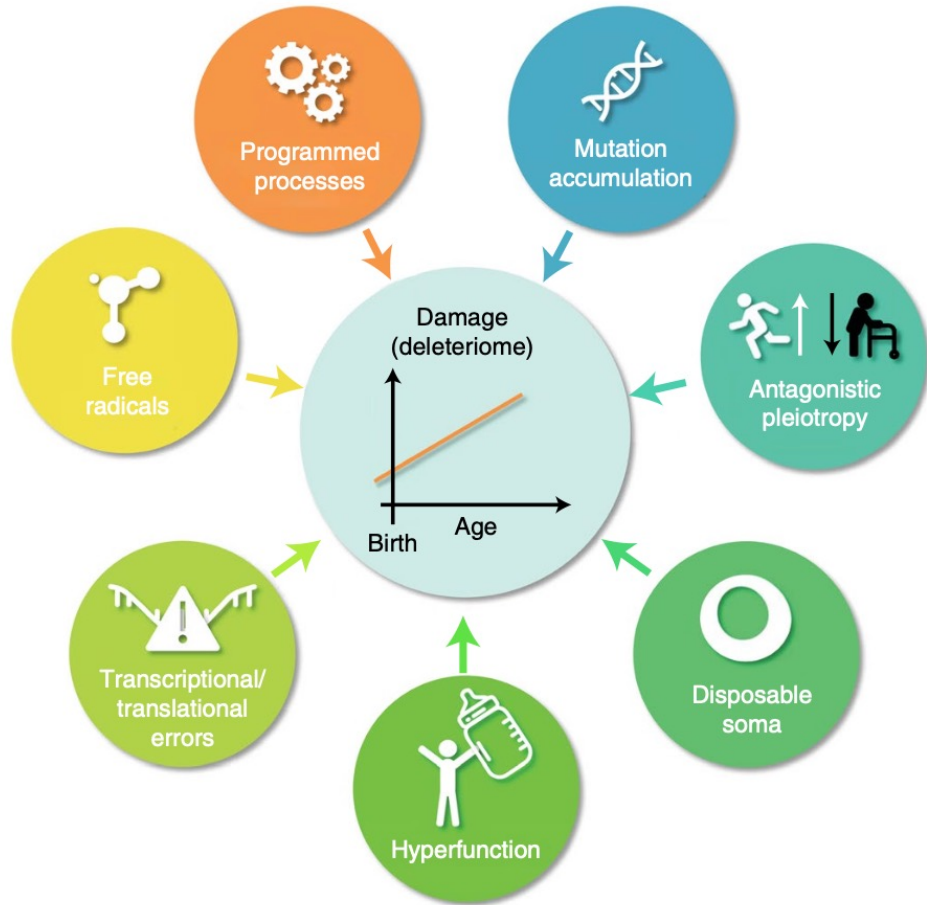
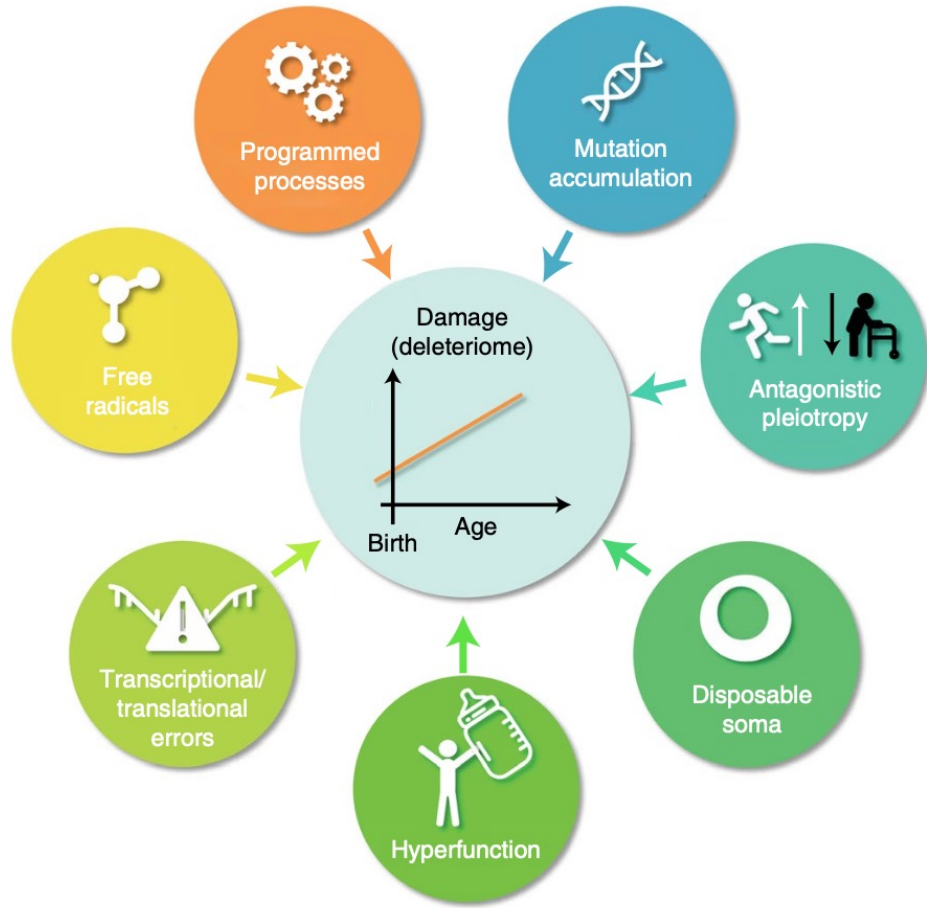


Image credit: Calen Ryan

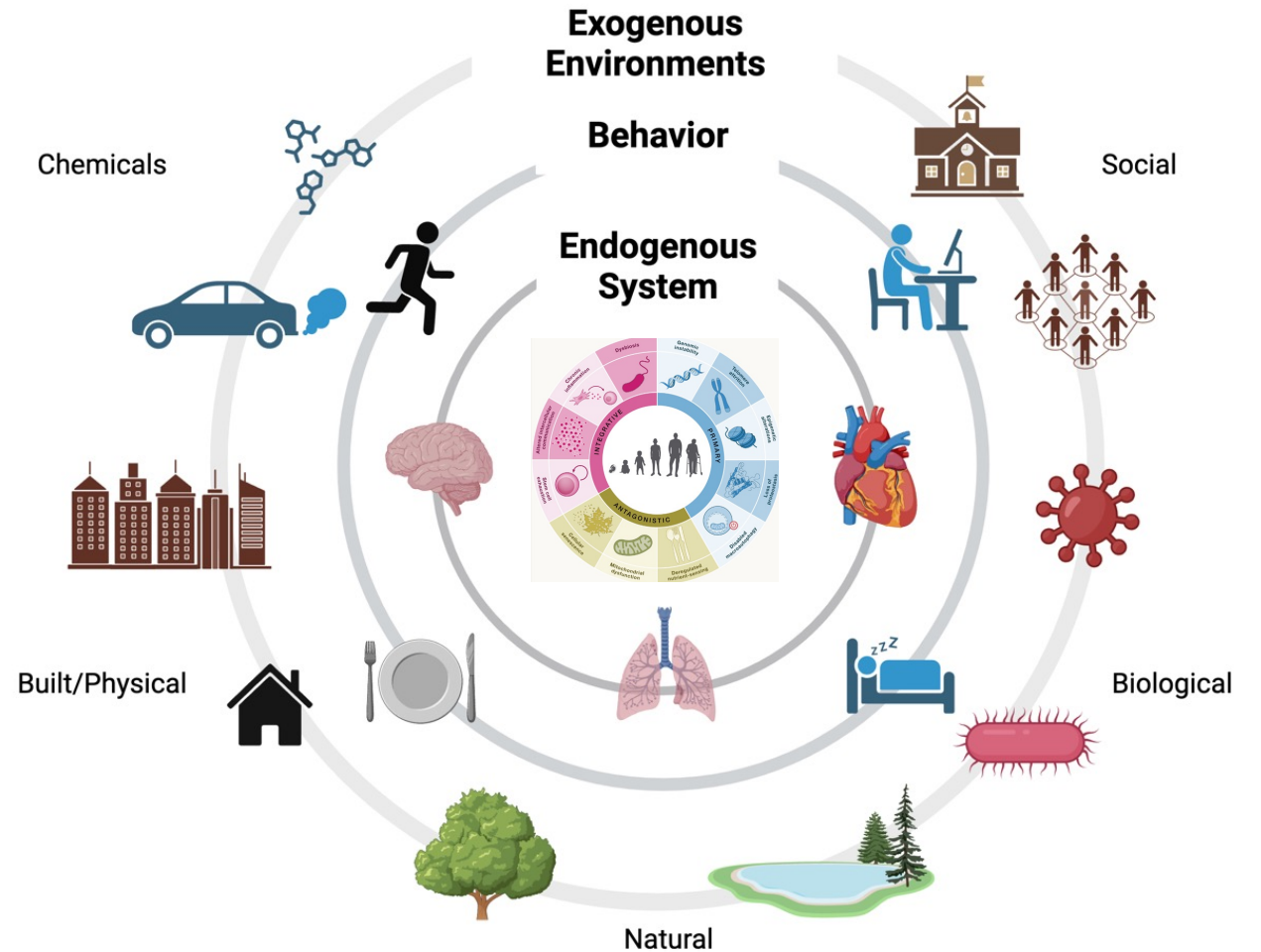
Living ages us...

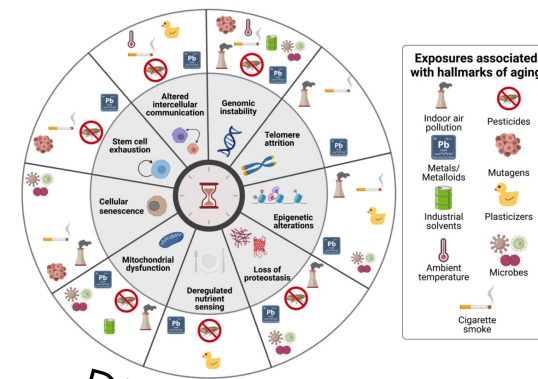


Living ages us...



So does where and how we live



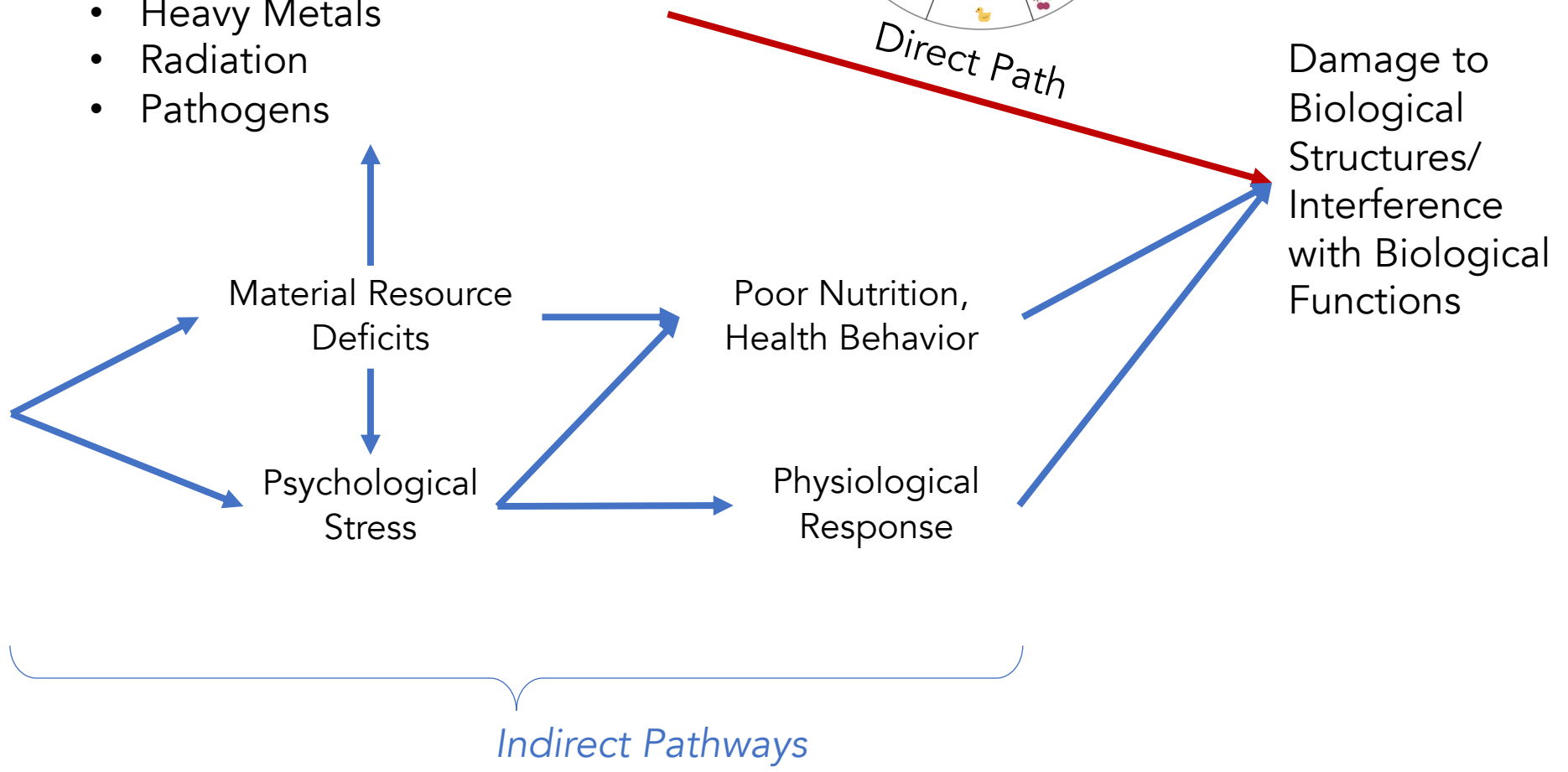


Chemical and Biological Toxins

- Air Pollution
- Heavy Metals
- Radiation
- Pathogens

Social Toxins

- Poverty
- Violence
- Discrimination
- Social Isolation

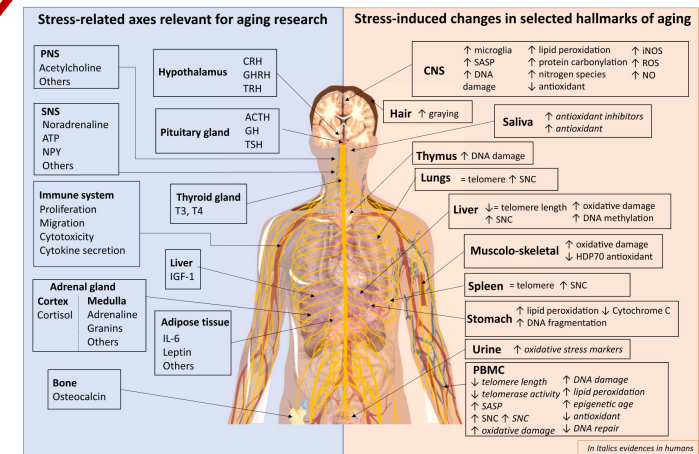
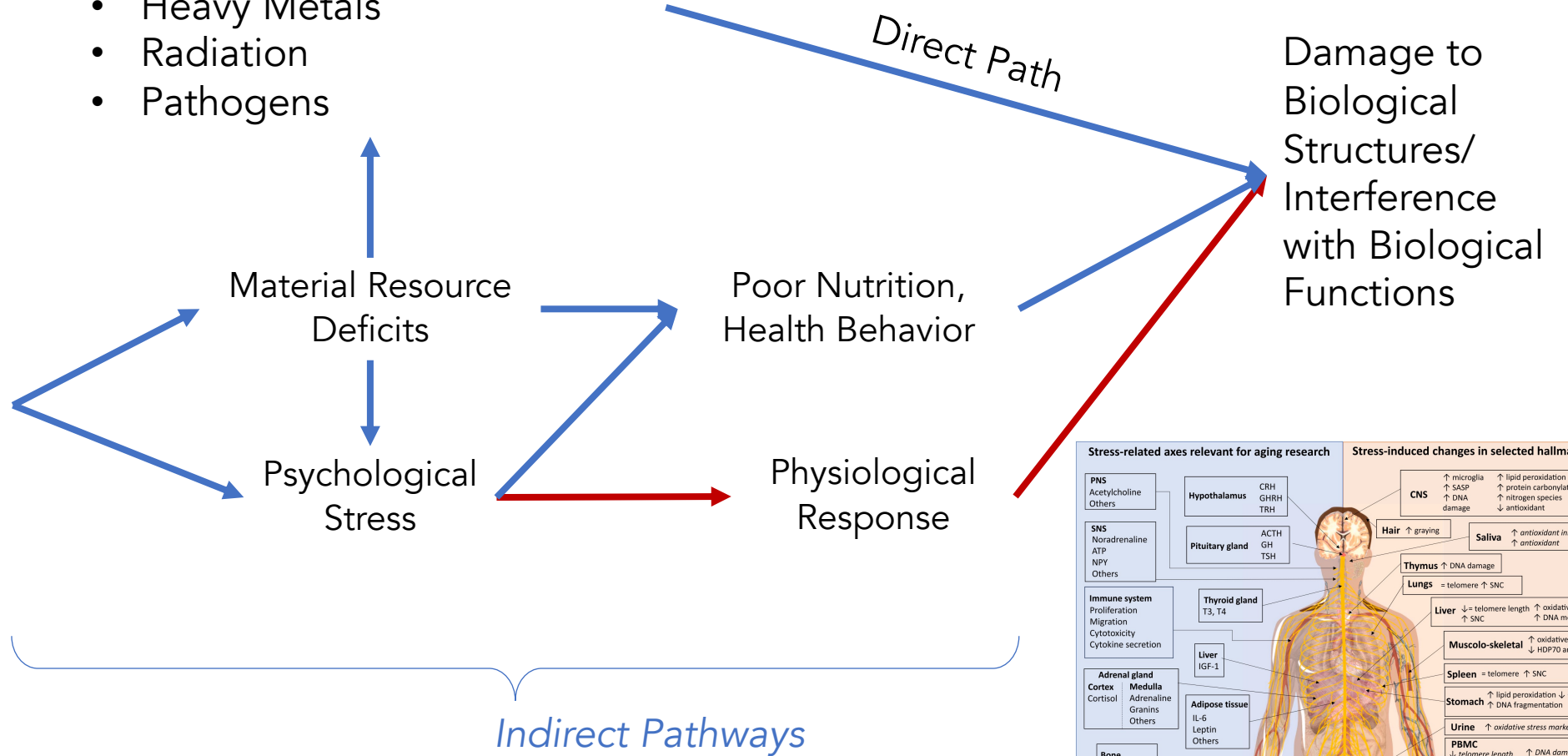


Chemical and Biological Toxins

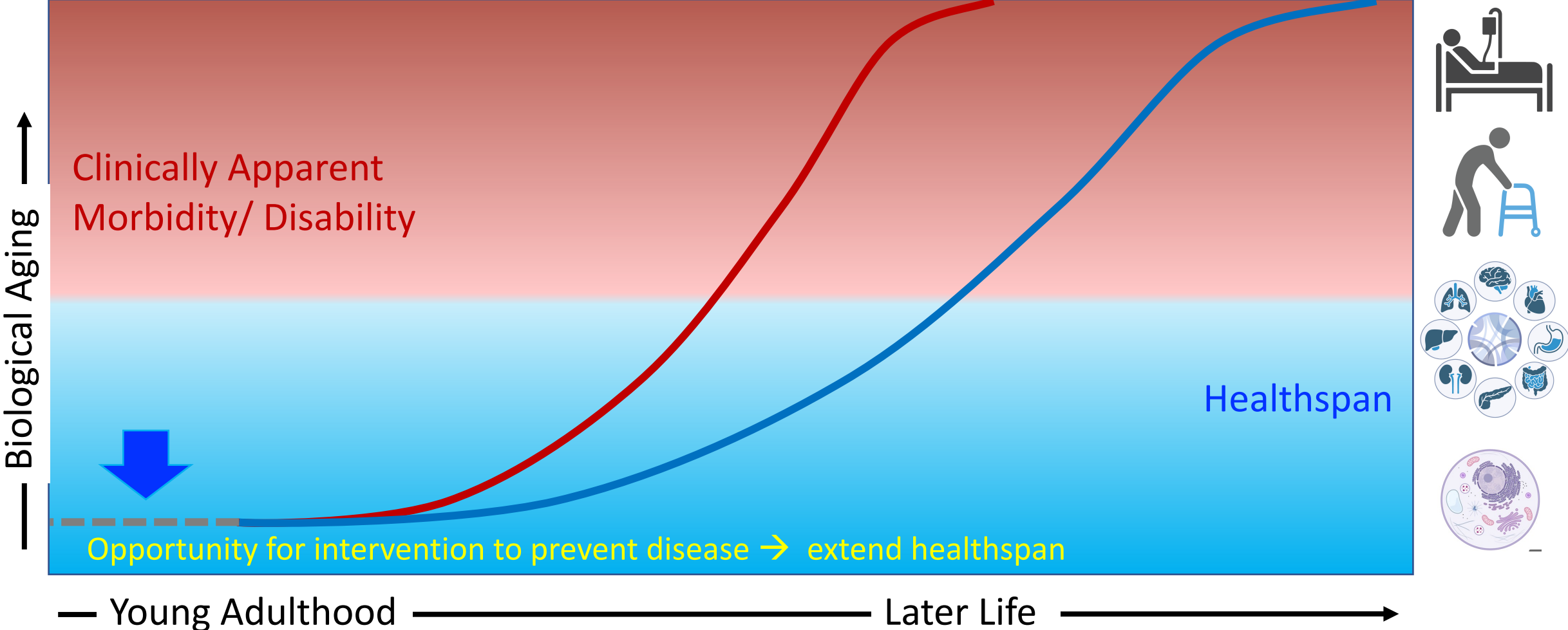
- Air Pollution
- Heavy Metals
- Radiation
- Pathogens

Social Toxins

- Poverty
- Violence
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- Social Isolation



Trajectories of biological aging diverge in advance of the onset of morbidity and disability



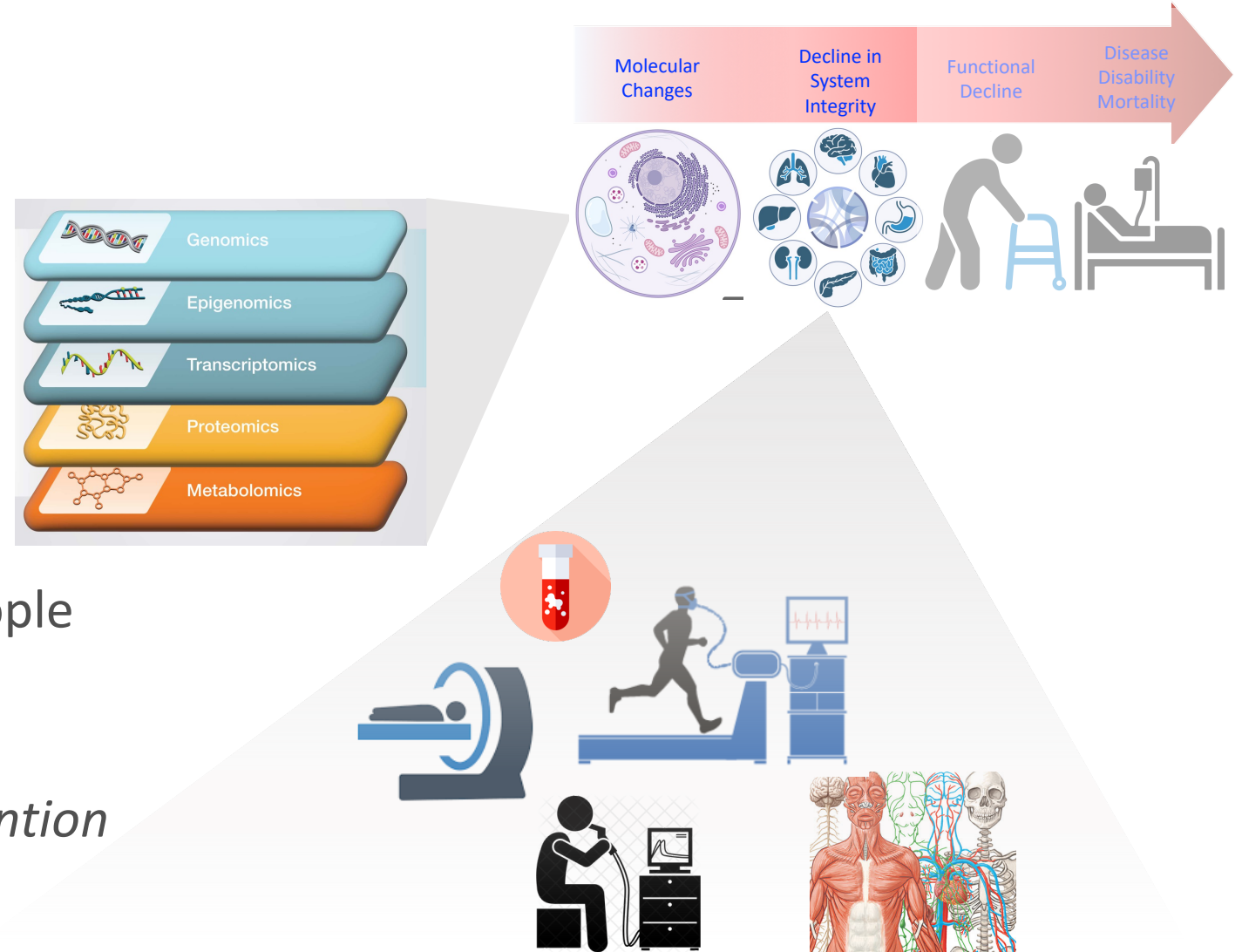
Belsky et al. 2015 PNAS
Moffitt et al. 2016 J Geron A
Belsky & Ferrucci In Press

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Quantification of biological aging

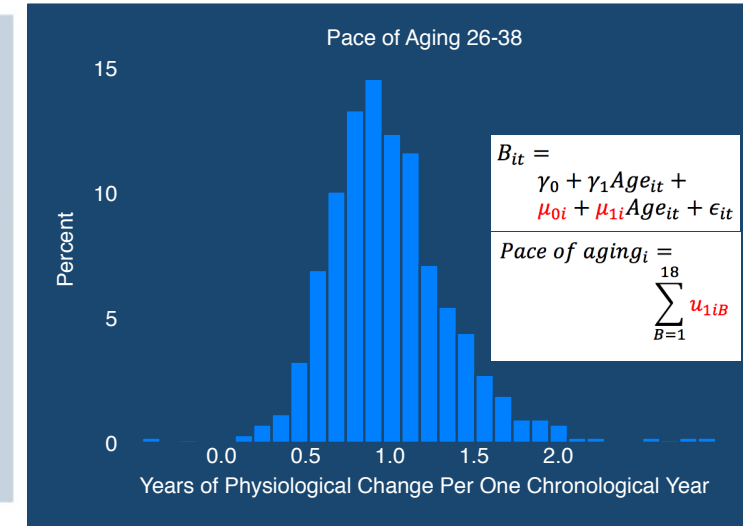
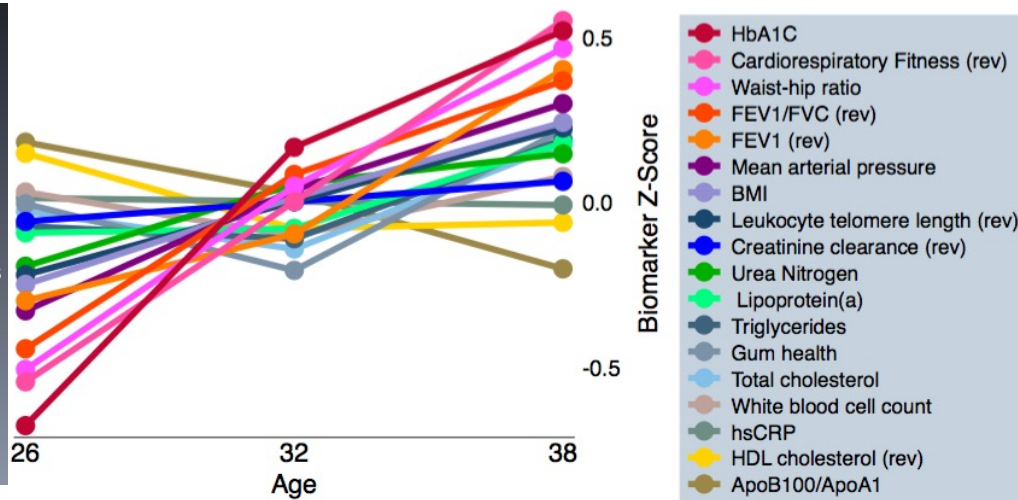
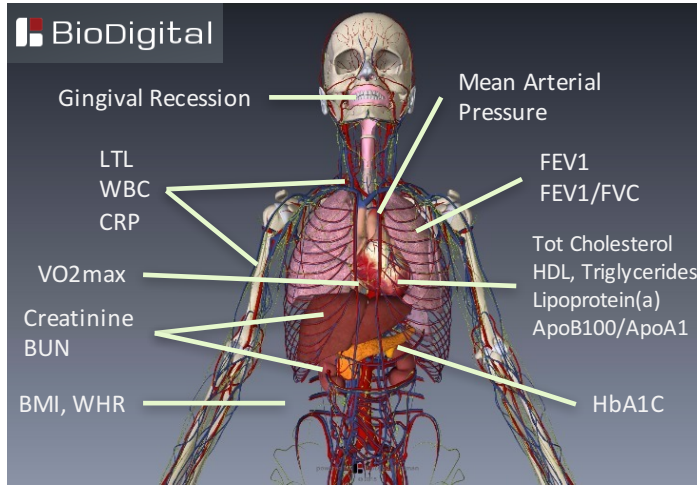
Data-driven approaches



Opportunities

- High variability in younger people
- Pre-clinical assessment of risk
- *Sensitive to preventive intervention*

People age at different rates – *from young adulthood*



Belsky et al. [2015 PNAS](#)

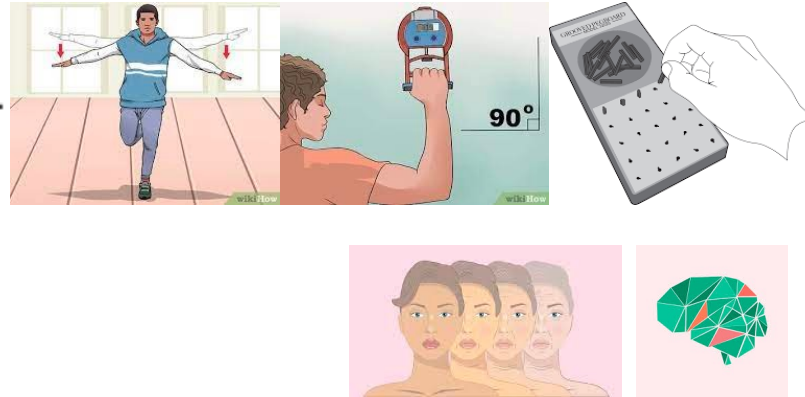
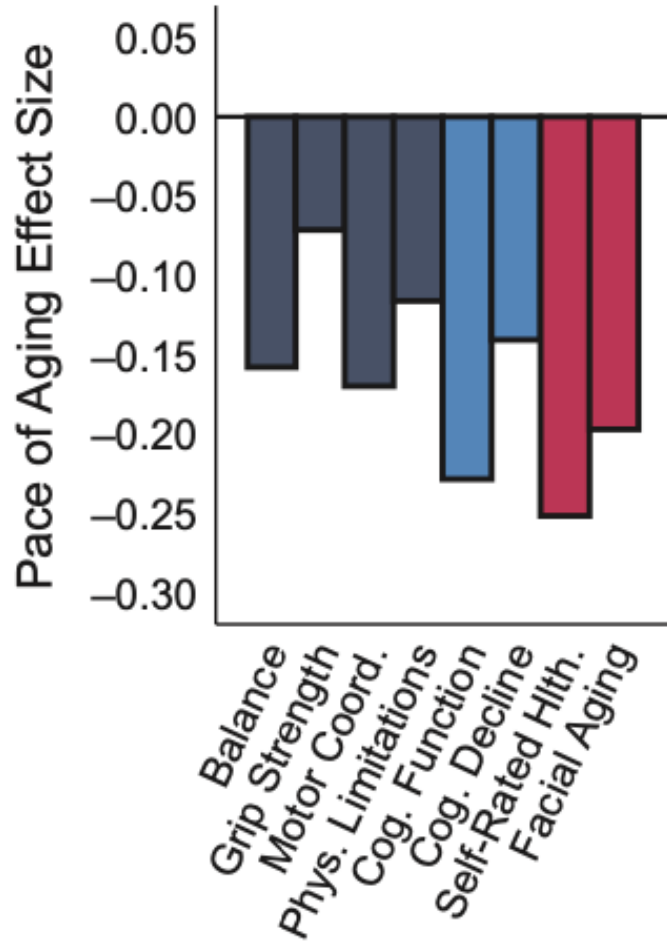
Aging is characterized by a gradual and progressive decline in system integrity

The rate of aging can be inferred from the rate of decline in integrity across multiple organ systems

This decline should be observable already by young adulthood



Young adulthood differences in Pace of Aging are associated with functional deficits & brain aging



[Belsky et al. 2015 PNAS](#)
[Belsky et al. 2018 Am J Epid](#)

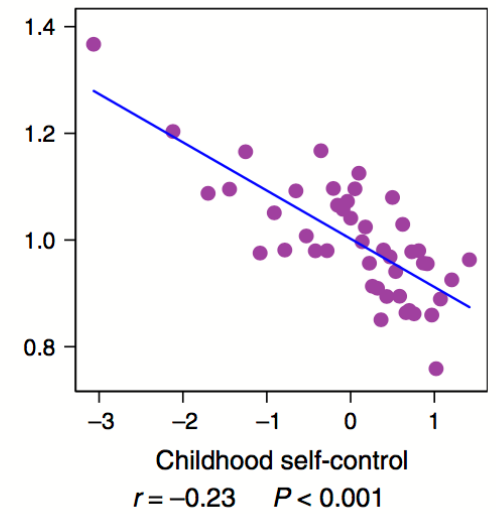
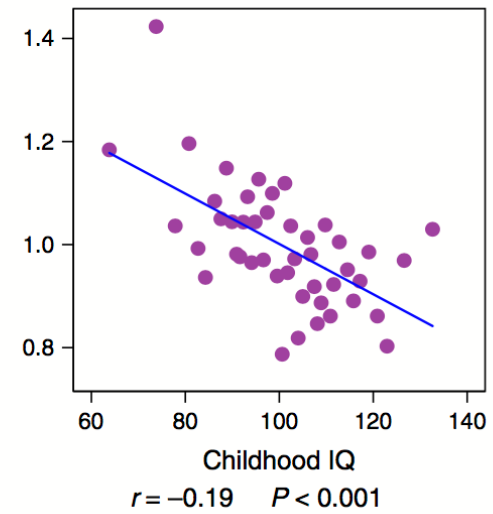
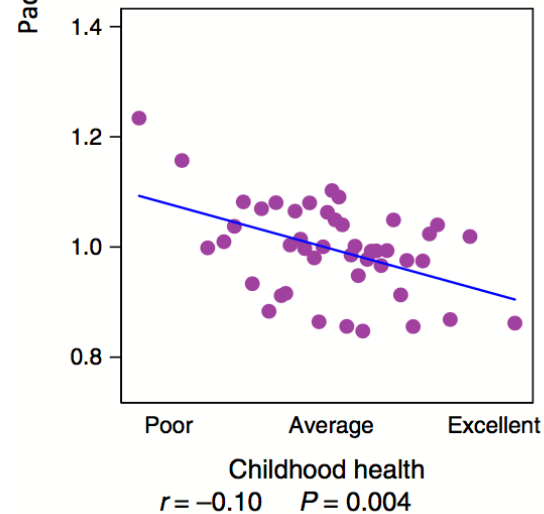
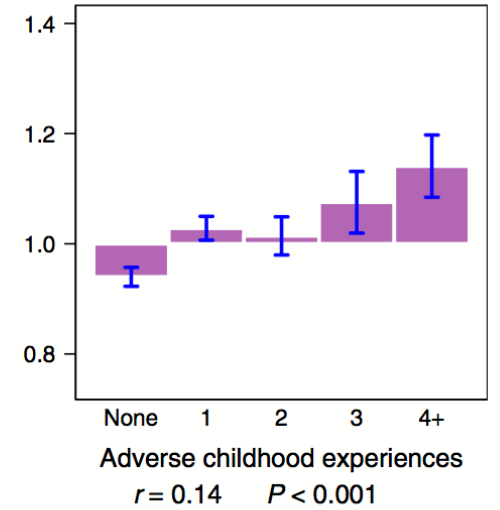
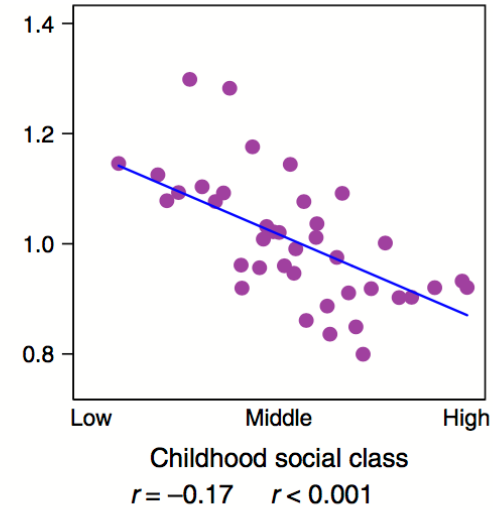
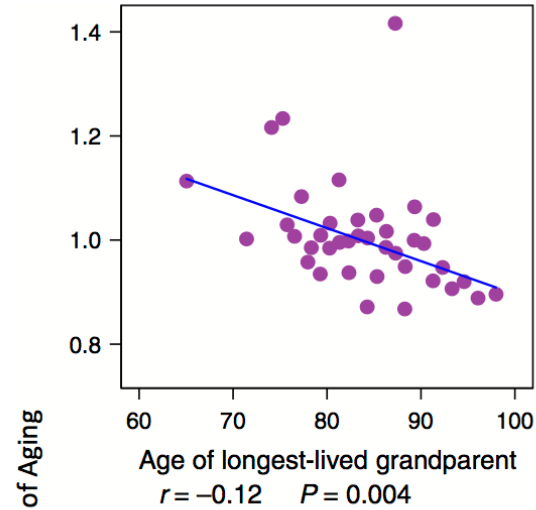
+ aging-related brain characteristics

- White matter hyperintensities
- Cortical thinning
- Hippocampal atrophy

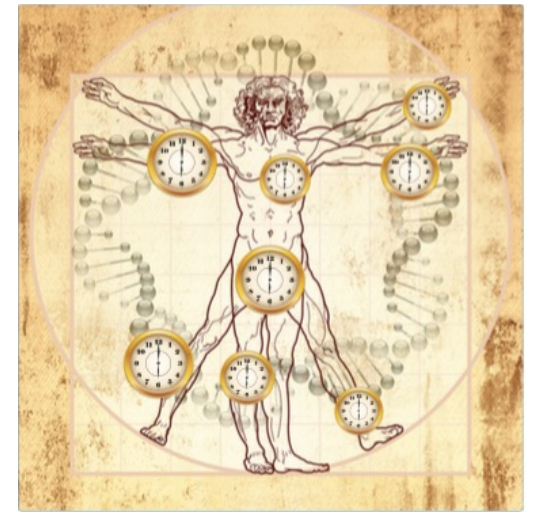
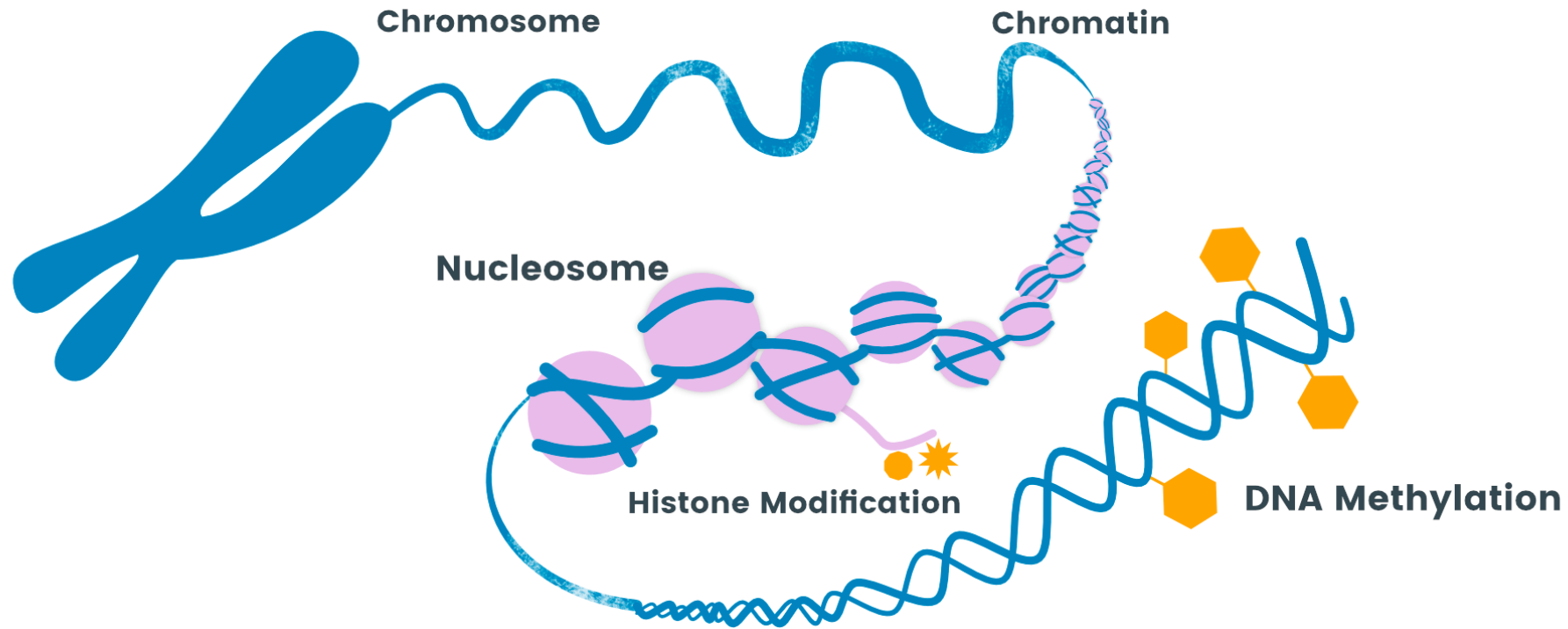
Elliott et al. [2019 Mol Psych](#)

Elliott et al. [2021 Nat Aging](#)

Childhood risk factors forecast faster young adulthood pace of aging



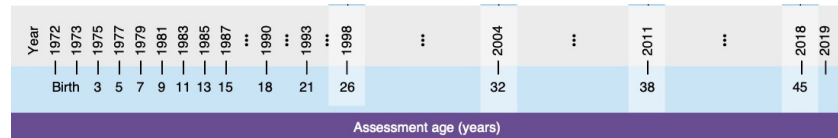
Epigenetic “clocks” estimate biological aging from DNA methylation



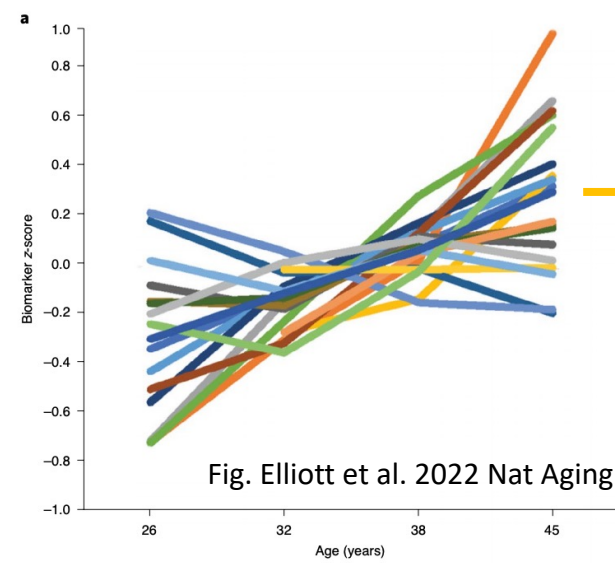
Horvath 2013 Genom Biol
Horvath & Raj 2018 Nat Rev Genet

A DNAm biomarker of Pace of Aging: DunedinPACE

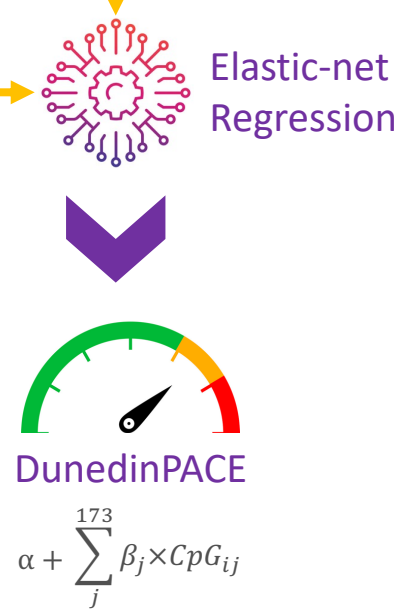
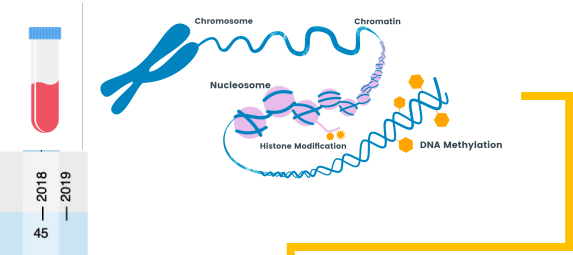
Dunedin Birth Cohort Follow-up



- BMI
- Waist-hip ratio
- Hemoglobin A1c
- Leptin
- Mean arterial pressure
- VO₂Max (rev)
- FEV₁/FVC (rev)
- FEV₁ (rev)
- Total cholesterol
- Triglycerides
- HDL cholesterol (rev)
- Lipoprotein(a)
- ApoB100/ApoA1
- eGFR (rev)
- Blood urea nitrogen
- hsCRP
- White blood cell count
- Mean periodontal attachmer
- Dental caries experience



Blood DNAm at age 45



- Developed from analysis of Dunedin Study birth cohort
- Within-person change in 19 biomarkers
- Follow-up from age 26-45 across 4 measurements
- DunedinPACE epigenetic clock trained to predict composite slope of change
- Result is a “speedometer” for the Pace of Aging

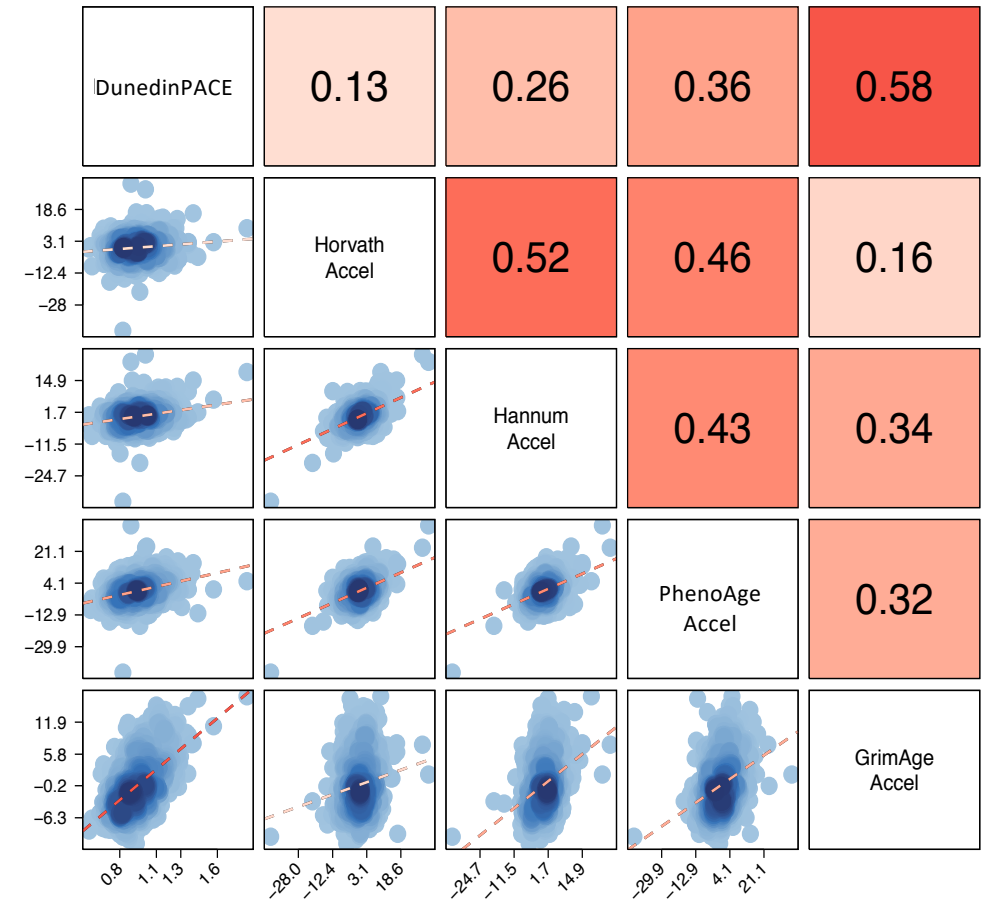
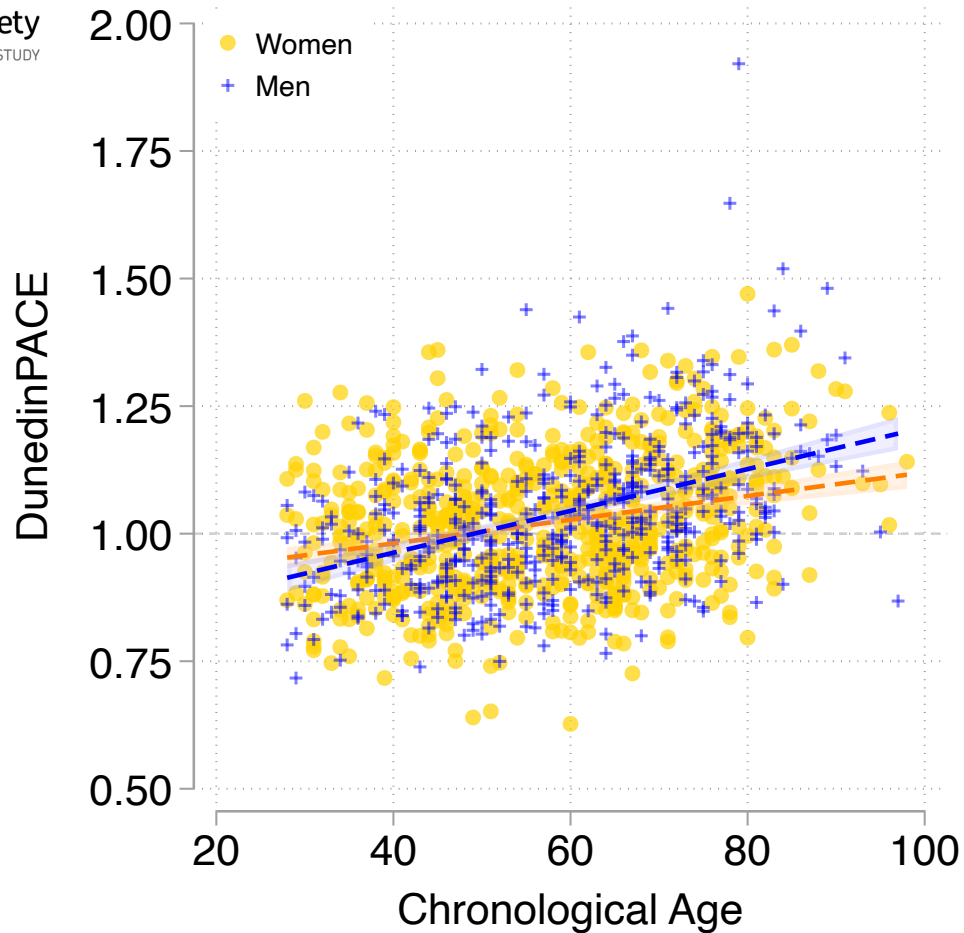
AG032282 (Moffitt)



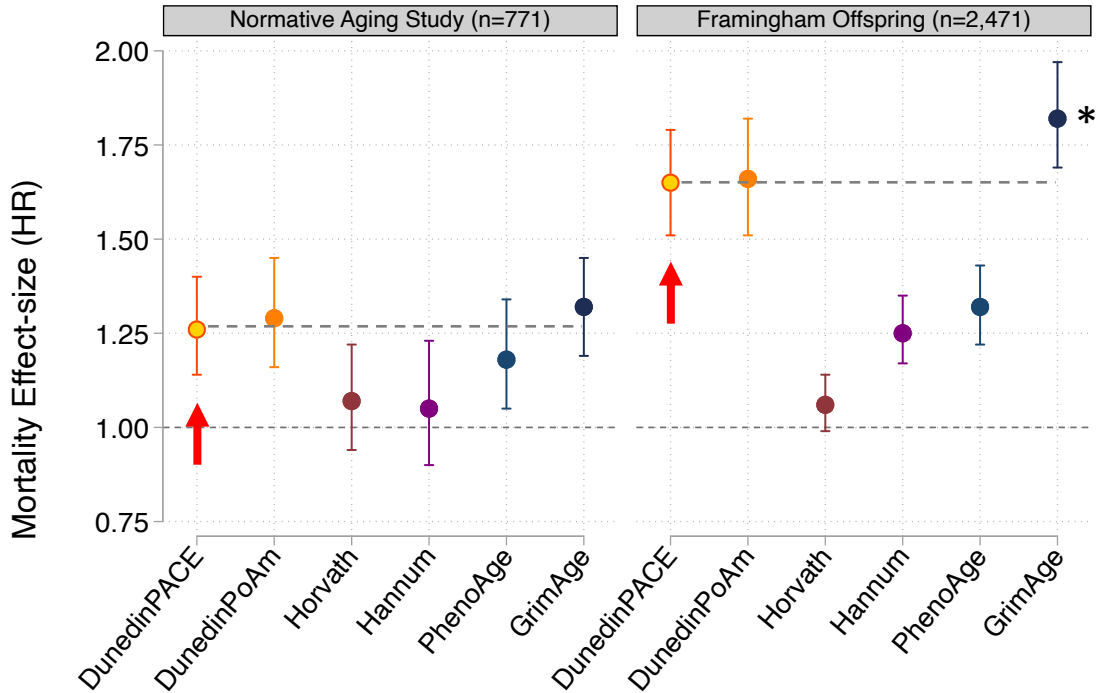
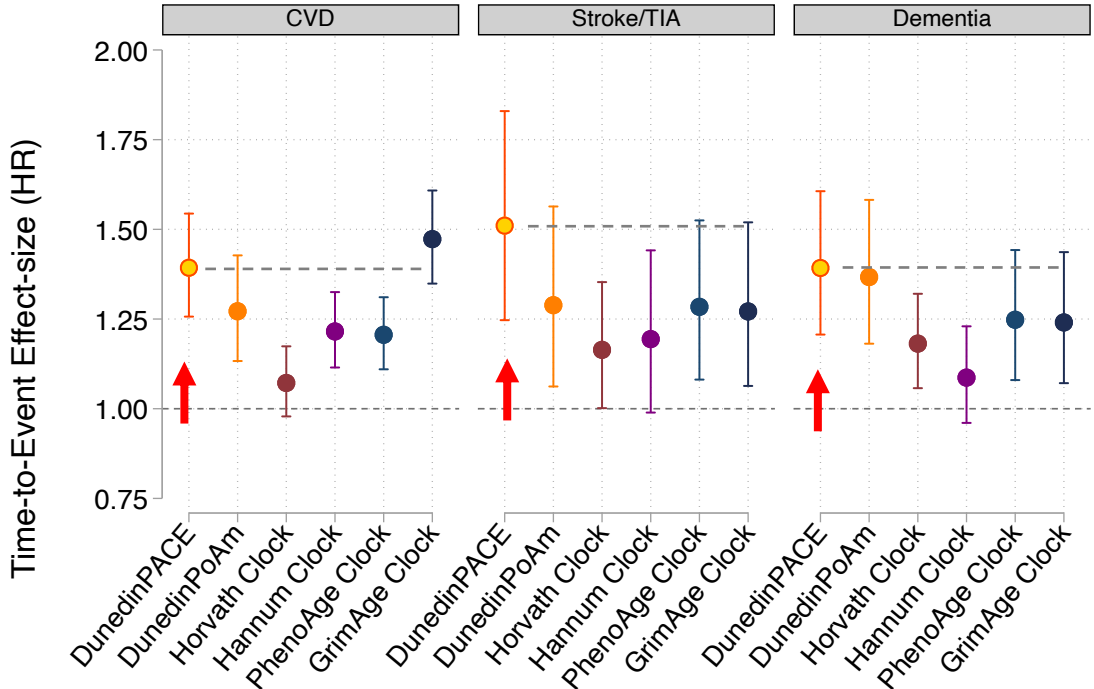
DunedinPACE indicates faster Pace of Aging in individuals with older chronological and biological age



N=1,175



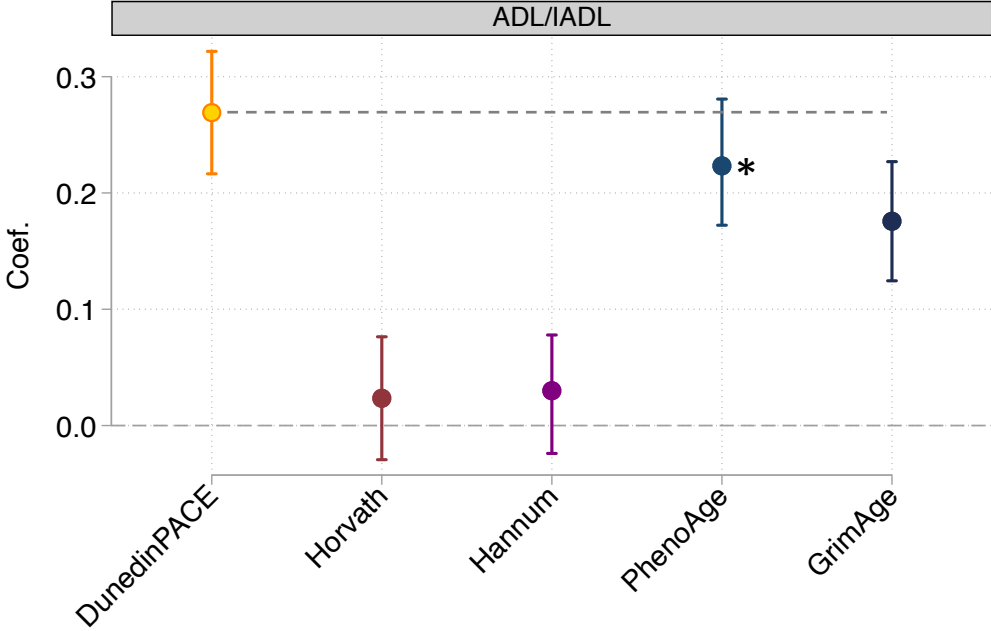
Faster DunedinPACE → incident morbidity & mortality



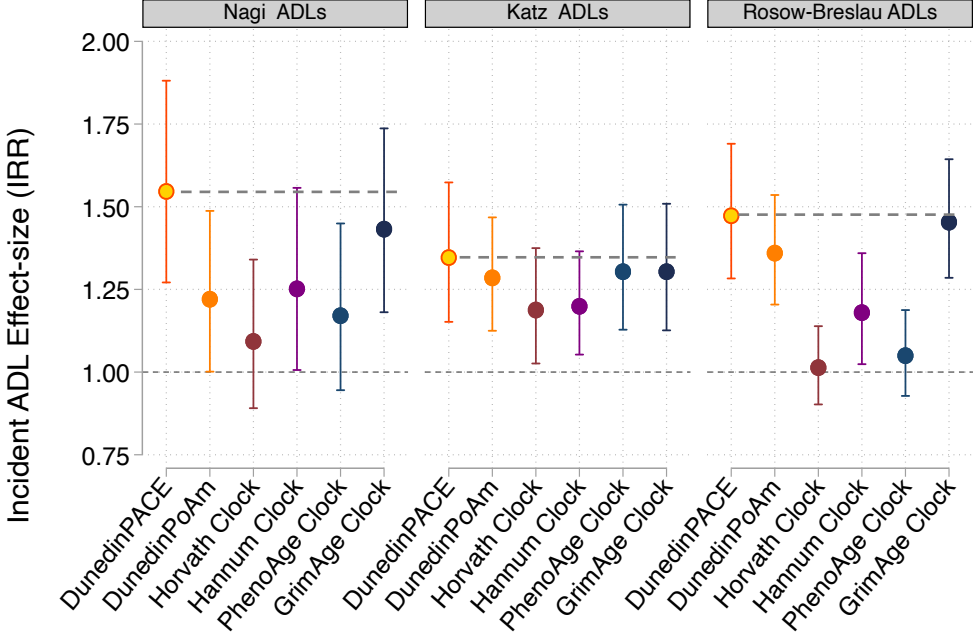
See also
 Hypertension, Sisters Study (Kresovich et al. 2023 Hypertension)
 Morbidity & Mortality, HRS (Faul et al. 2023 PNAS)
 Mortality, FITSA (Fohr et al. 2023 J Geron A)
 Health and Function, Taiwan Biobank (Lin 2023 Front Genet)

Many more

Faster DunedinPACE → incident disability



Prevalent Disability
in the HRS



Incident Disability
in the Framingham Heart Study



DunedinPACE is slowed by calorie restriction

R01AG061378

n=220 non-obese adults randomized 2:1 to 25% CR for 24mo (avg adherence ~12%)

DNAm analysis included

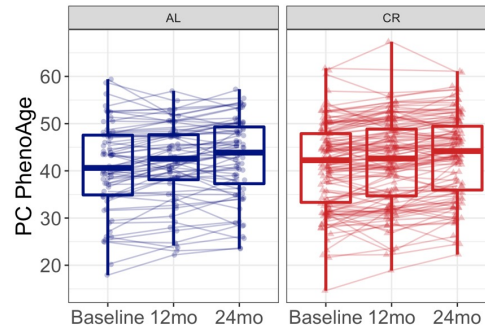
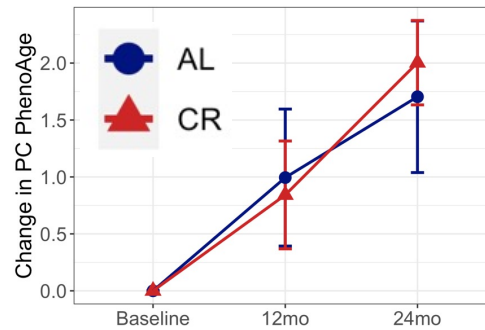
n=128 CR Treatment

n=69 AL Control



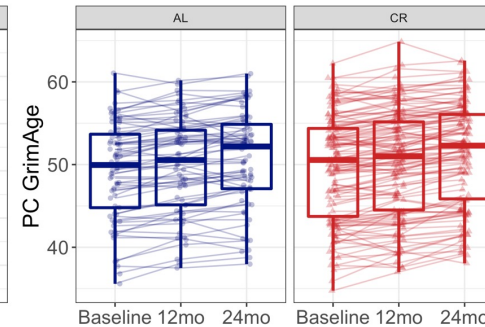
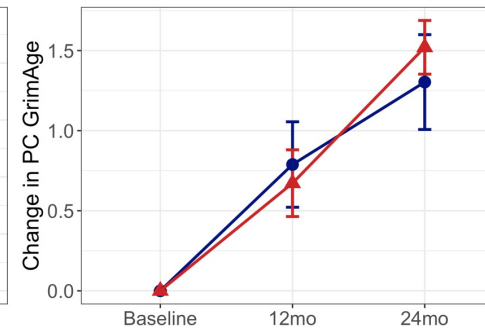
PC PhenoAge

No difference in change



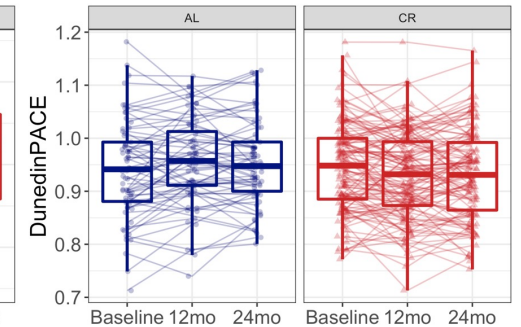
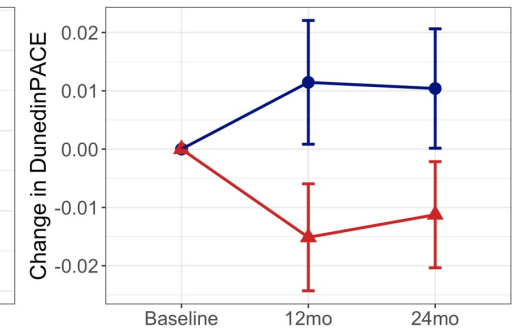
PC GrimAge

No difference in change



DunedinPACE

Slowed PACE in CR vs. AL



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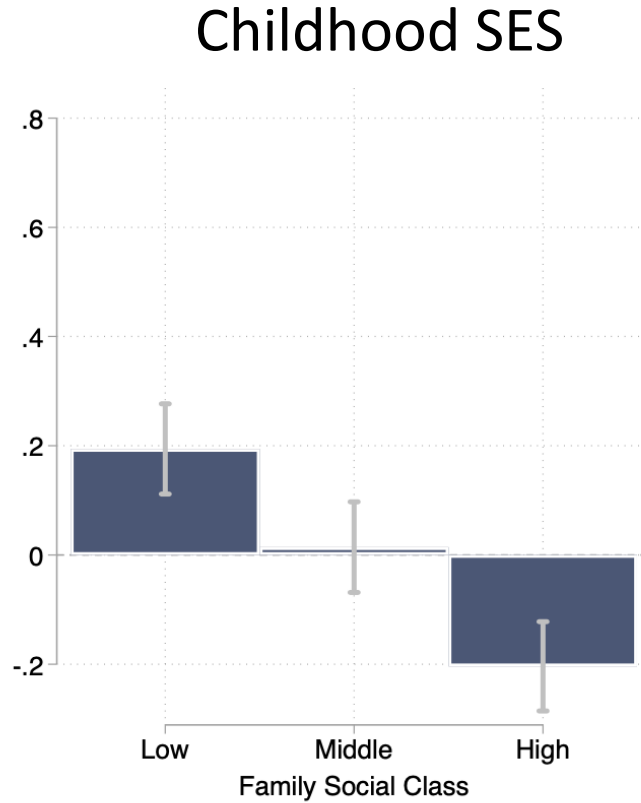
Opportunities to apply biological aging metrics to identify resilient individuals

Childhood social adversity

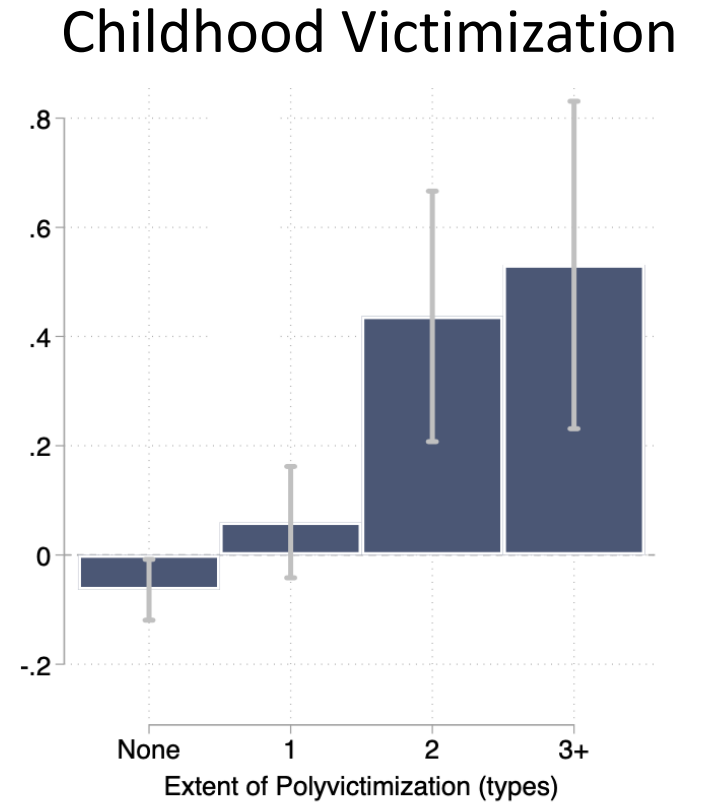
E-RiSK
Study

N=1,116

A.
Age 18 DunedinPACE



B.
DunedinPACE z-score, Age 18



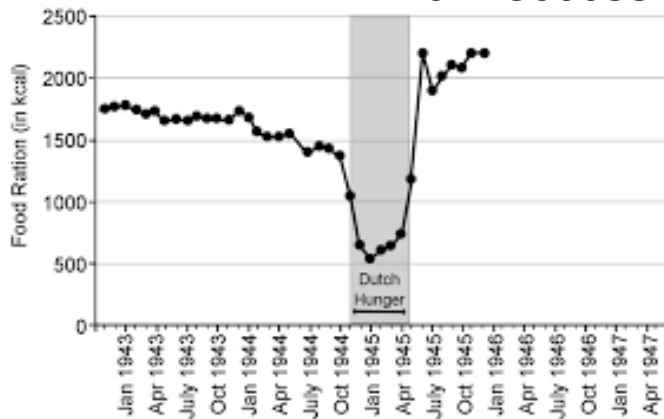
See also

Social mobility Graf et al. 2022 PNAS Nexus, 2024 JAMA NO (education) Multi Cohort, Sugden et al. 2023 J Geron A (neighborhood) HANDLS, Shen et al. 2023 JAMA Net Open (early-life poverty) HRS, Schmitz & Duque 2022 PNAS (ACEs) CARDIA, Kim et al. 2023 JAMA Net Open
Many more

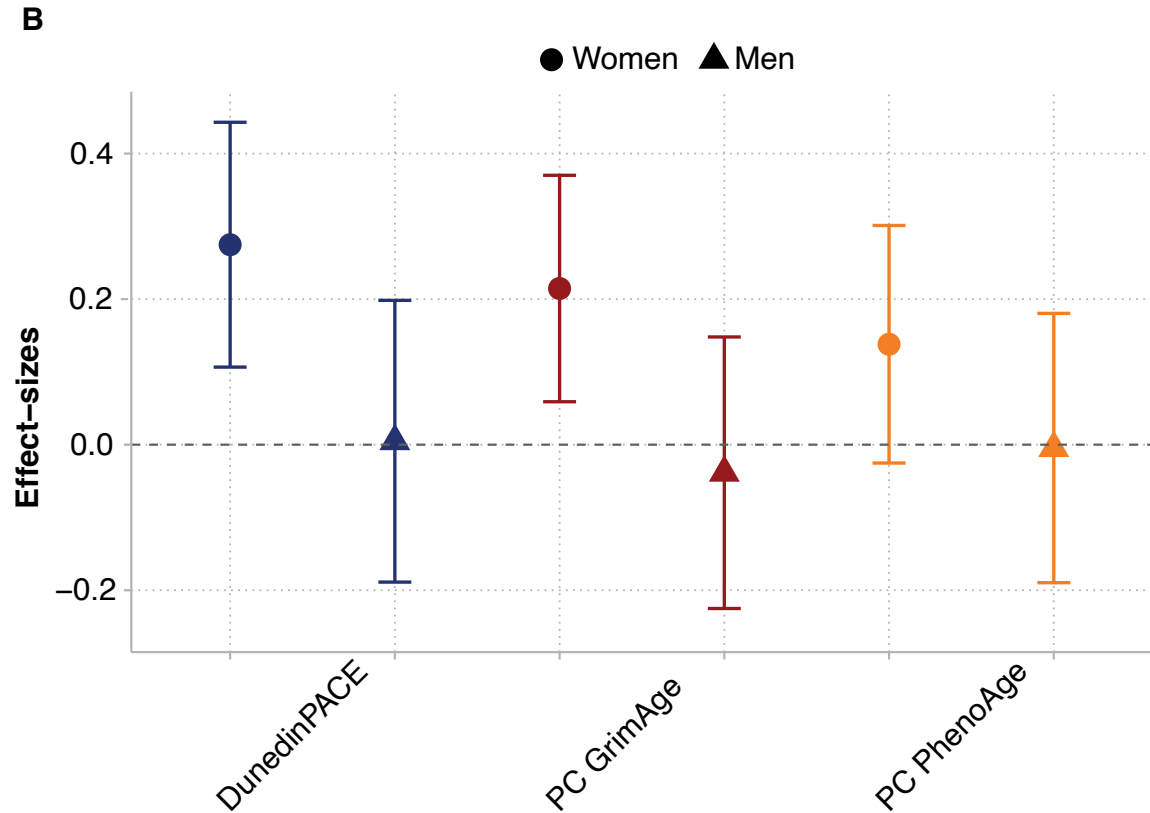
Opportunities to apply biological aging metrics to identify resilient individuals



R01AG066887



In-utero famine exposure



Models adjusted for sex, age, DNAm est. cell counts

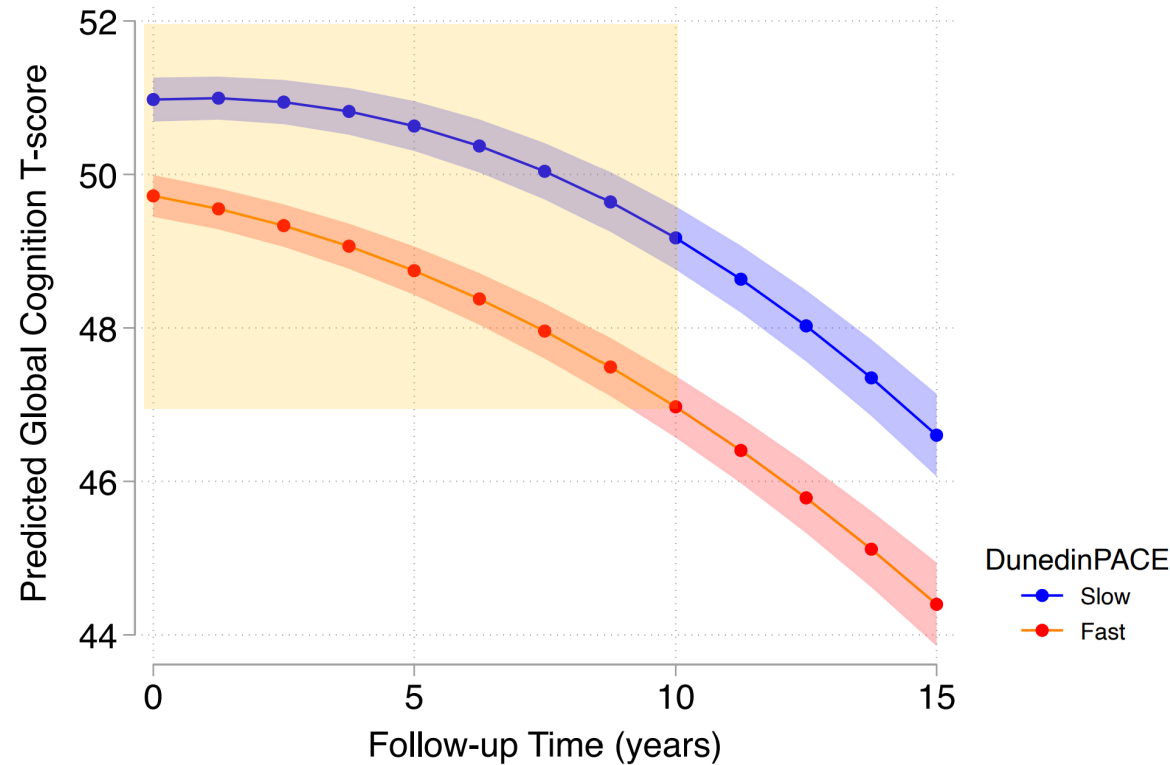
Cheng et al. [MedRxiv 2023](#)

See also Schmitz & Duque [2022 PNAS](#)

Opportunities to apply biological aging metrics as predictors of resilience

Forecasting cognitive aging

Cognitive Domain	Test Measure
Verbal Memory	Logical Memory – Immediate Recall
	Logical Memory – Delayed Recall
	Logical Memory - % Retained
Visual Memory	Visual Reproductions – Immediate Recall
	Visual Reproductions – Delayed Recall
	Visual Reproductions - % Retained
Learning	Paired Associated - Total
Attention	Trail Making Test Part A – Time
	Trail Making Test Part B - Time
Abstract Reasoning	Similarities – Total
Language	Boston Naming Test – Total Correct Without cues
Visuospatial	Hooper Visual Organization Test – Total Score
Motor Speed	Finger Tapping – Dominant and Non-Dominant

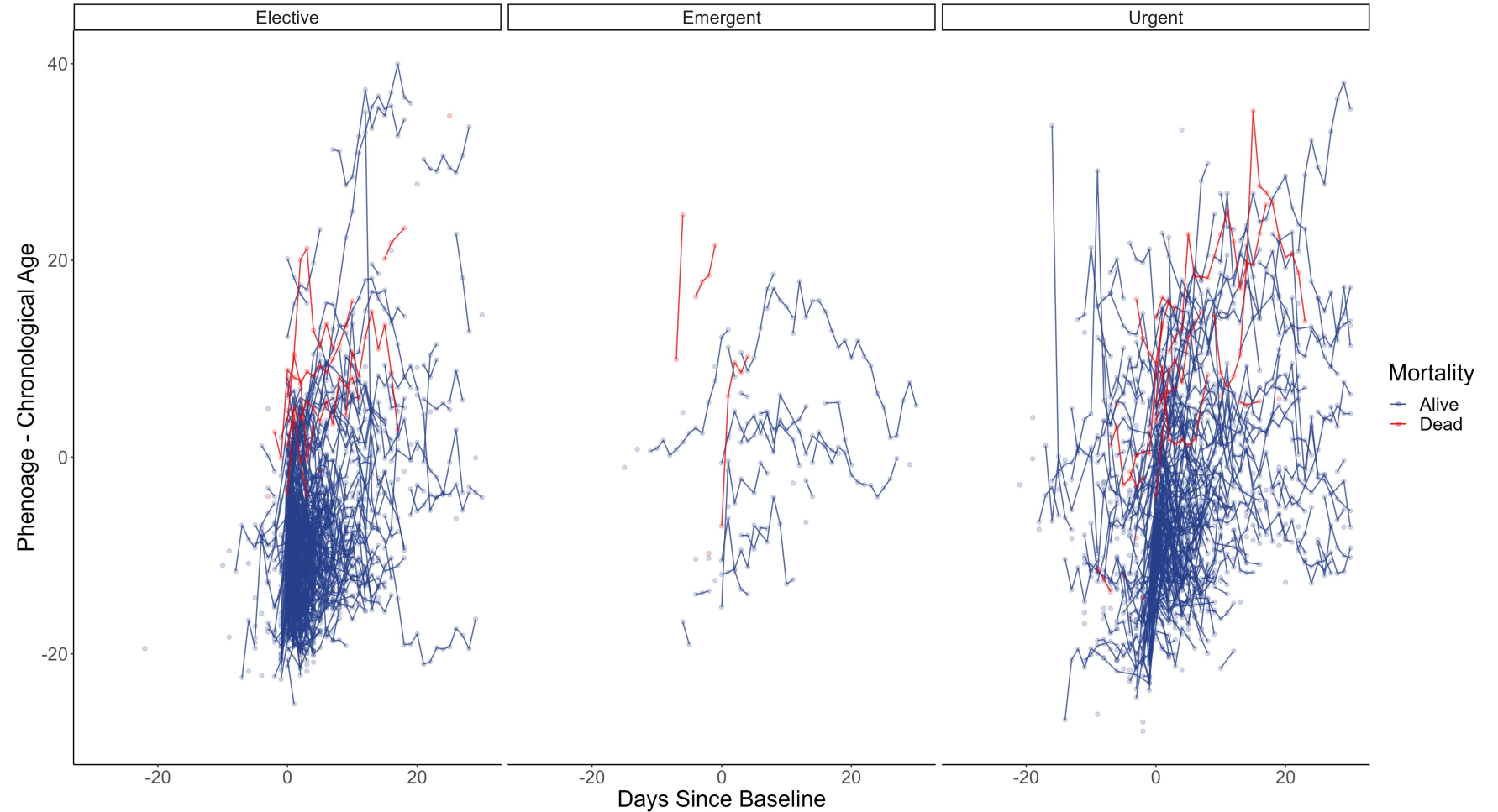


Opportunities to apply biological aging metrics as predictors of resilience

Pre-op stratification



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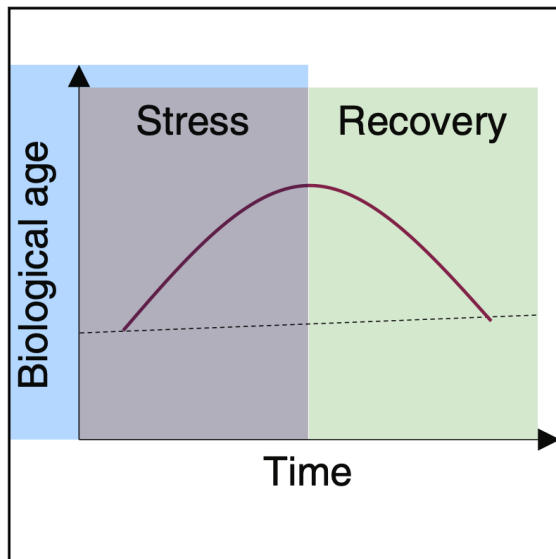


Opportunities to apply biological aging metrics to measure resilience

Cell Metabolism

Biological age is increased by stress and restored upon recovery

Graphical abstract



Authors

Jesse R. Poganik, Bohan Zhang, Gurpreet S. Baht, ..., Steve Horvath, James P. White, Vadim N. Gladyshev

Correspondence

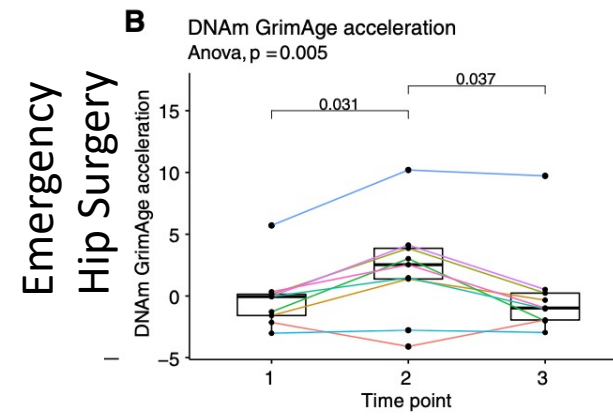
james.white@duke.edu (J.P.W.),
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In brief

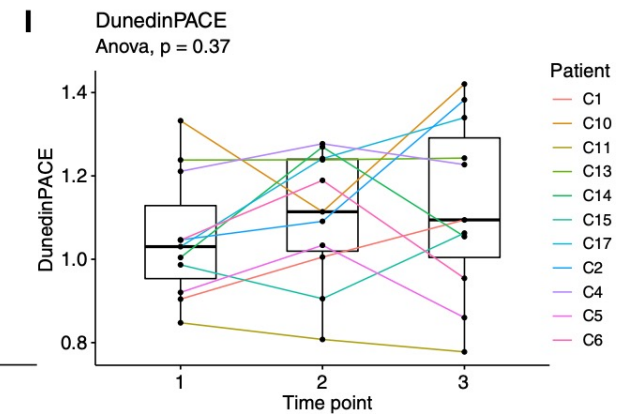
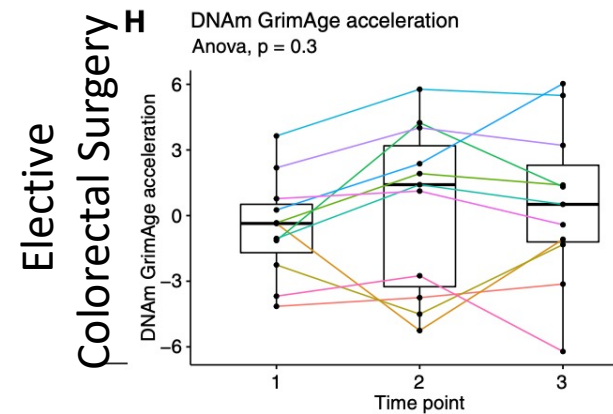
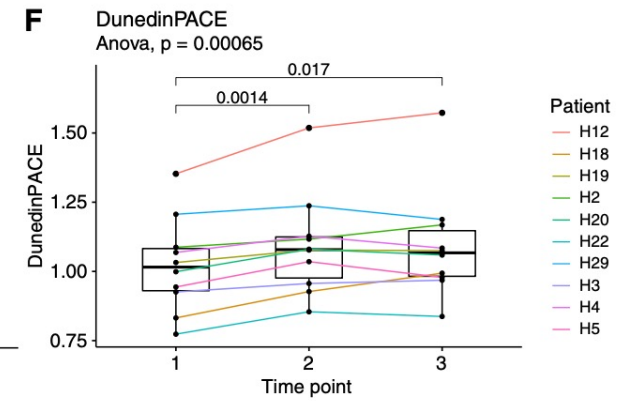
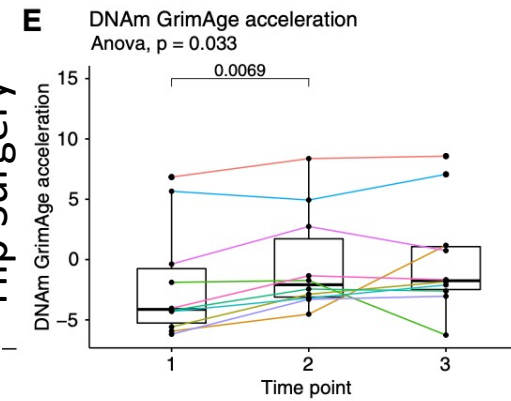
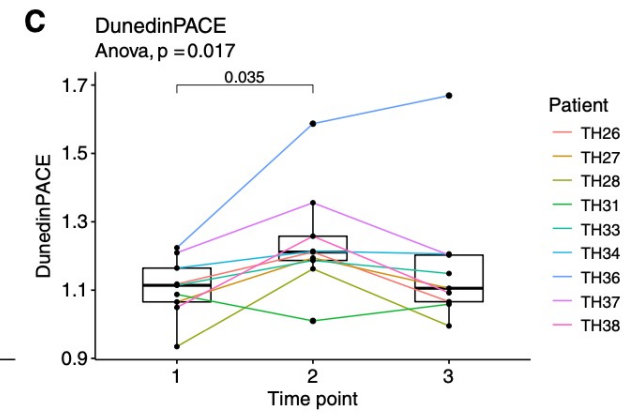
Poganik et al. analyzed various models of severe stress in mice and humans and found that stress transiently elevates biological age as readout by multiple advanced biomarkers of aging. They demonstrate that biological age is not static, but dynamic.

Article

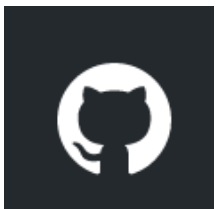
GrimAge



DunedinPACE



Code to compute DunedinPACE from Illumina 450k and EPIC Array data is available on GitHub



Code to implement DunedinPACE in Illumina 450k or EPIC array data at <https://github.com/danbelsky/DunedinPACE>

Code to compute blood-chemistry biological age measures from custom biomarker sets is available on GitHub



Code to implement KDM BA, PhenoAge, and Homeostatic Dysregulation methods
<https://github.com/dayoonkwon/BioAge>

Collaborators & Funders

Columbia

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Allison Aiello
Alan Cohen
Jen Manly
AJ Adkins-Jackson
Yian Gu
Martin Picard
Vivek Moitra
Yousin Suh
Ying Wei

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[R01AG066887](#)

[R01AG061378](#)

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Virginia Kraus
Daniel Parker
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National Institute
on Aging



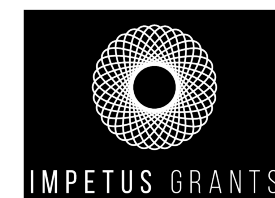
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Our Promise to Youth



Thank You!

