Early-life determinants of midlife function & health

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Our Promise to Youth

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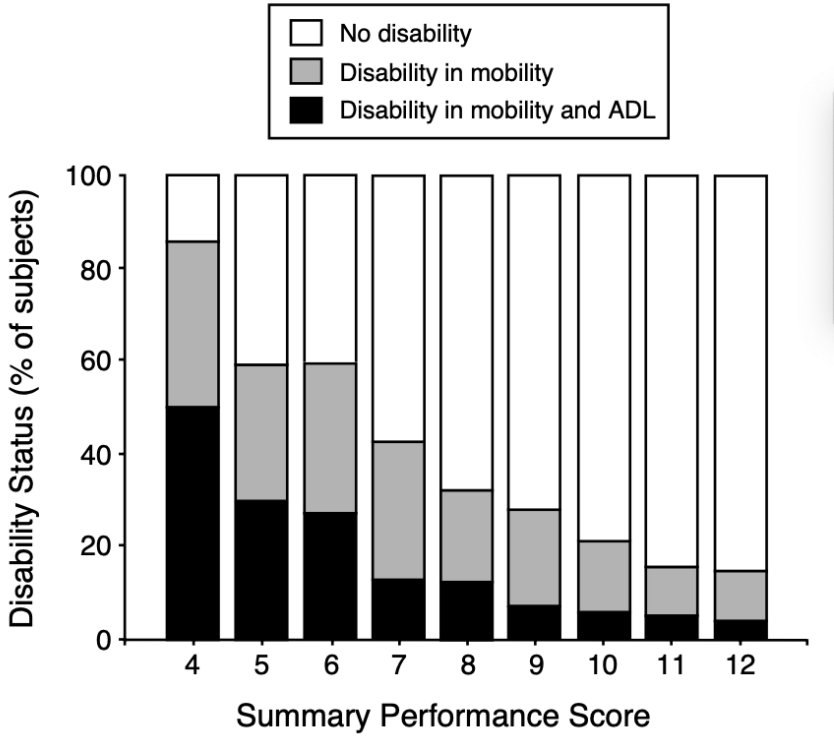
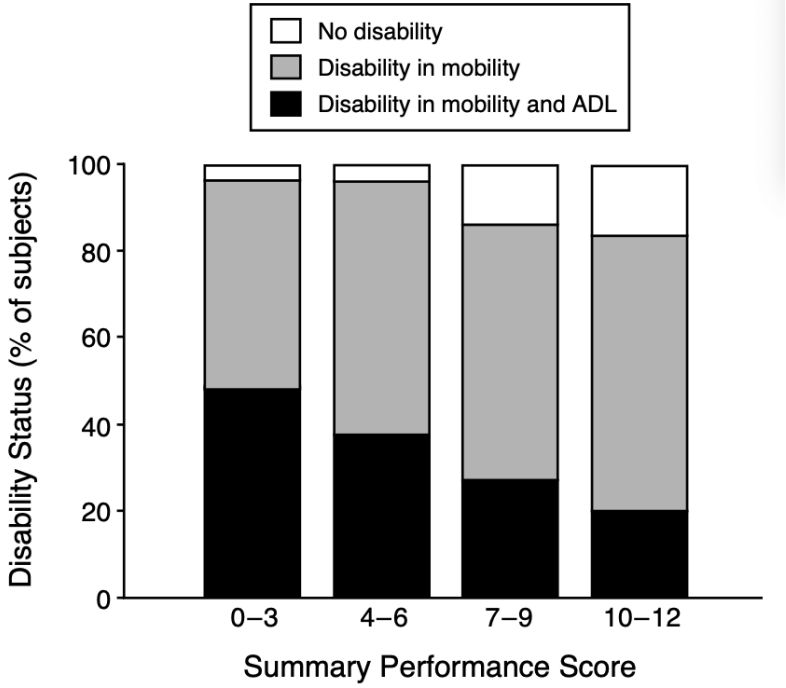
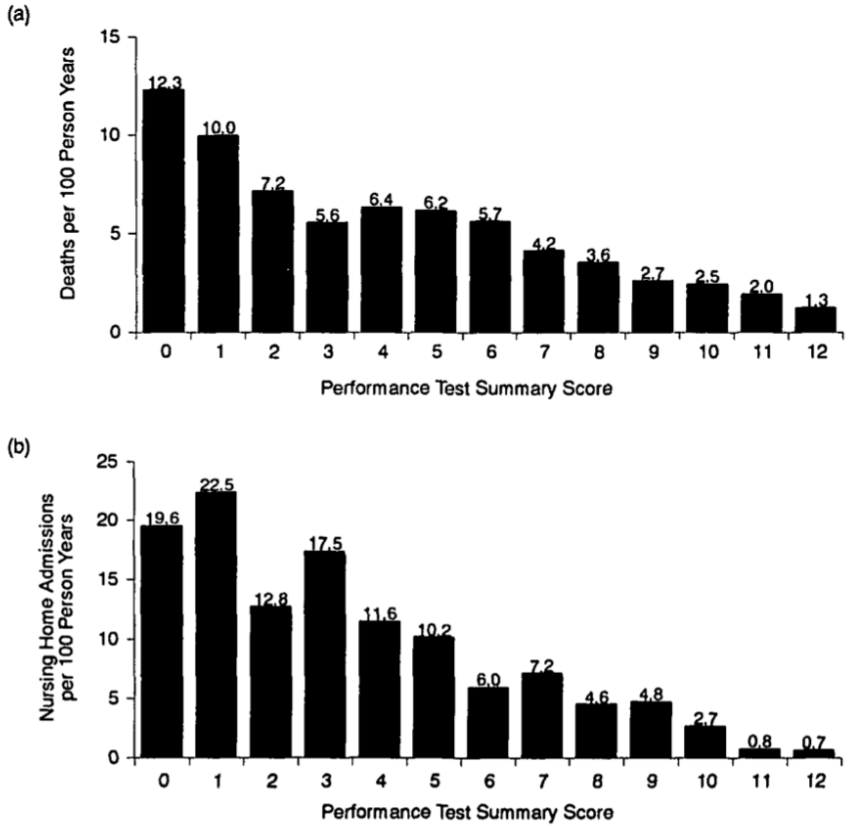
Functional performance predicts disability





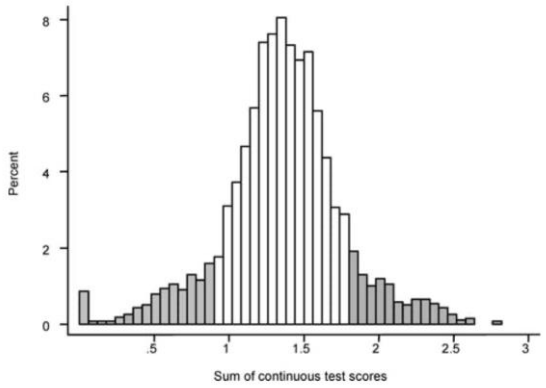
Guralnik et al. 1995 NEJM

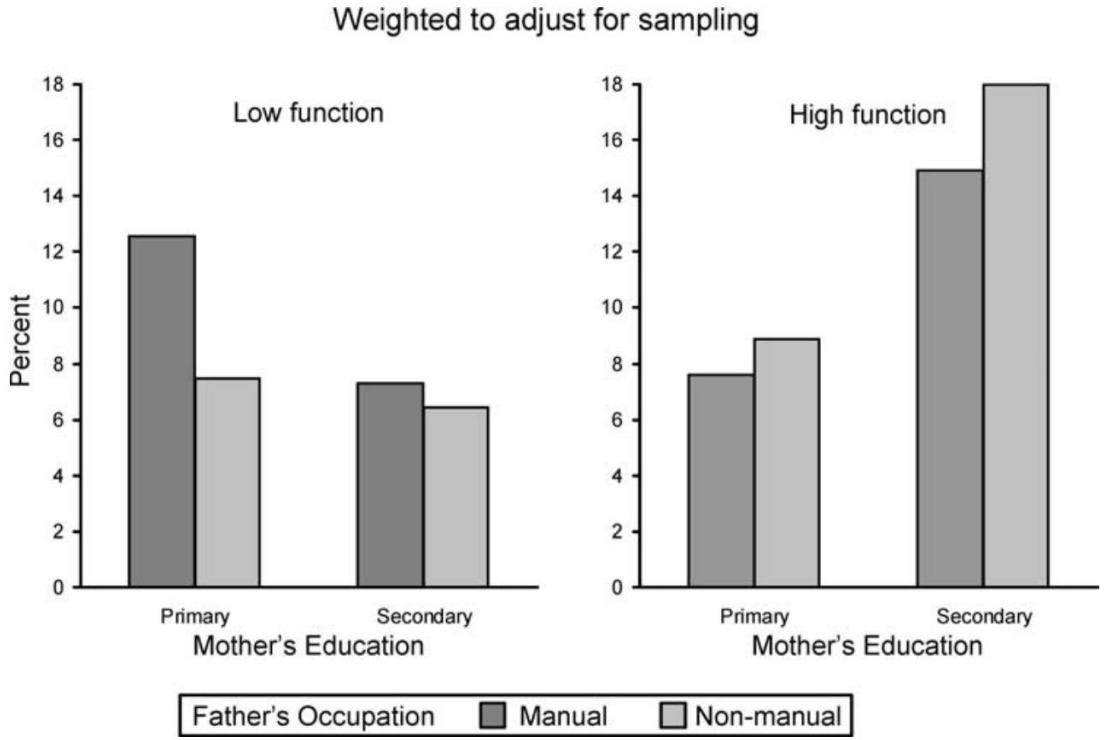
… and mortality



Guralnik et al. 1994 JGMS

Childhood social class predicts midlife function





Guralnik et al. 2006 JGMS

Outline

1. Geroscience & the life course

2. Early-life origins of individual differences in the pace of aging in midlife adults

3. Molecular measurement of pace of aging from DNA methylation

4. Implications & Opportunities

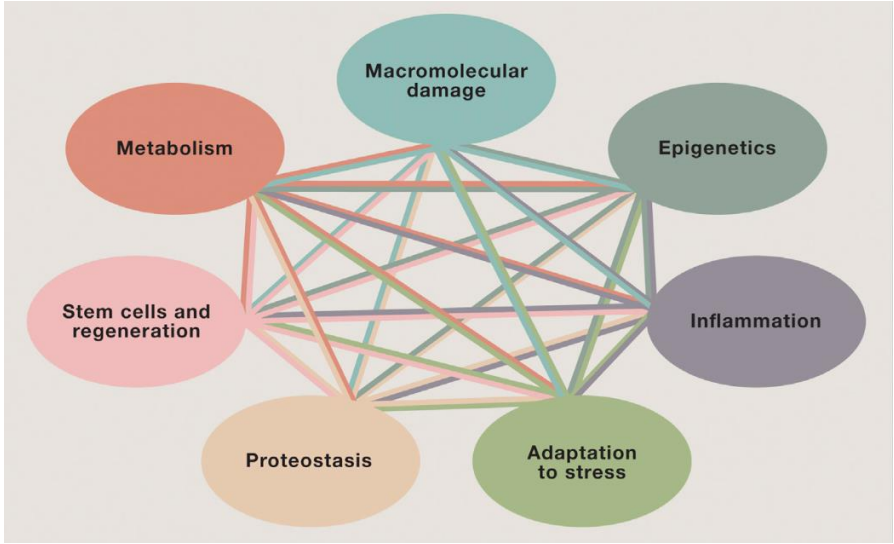
Aging is a biological process

a gradual and progressive decline in system integrity

Kirkwood 2005

Lopez-Otin et al.
2013 Cell

Kennedy et al.
2014 Cell



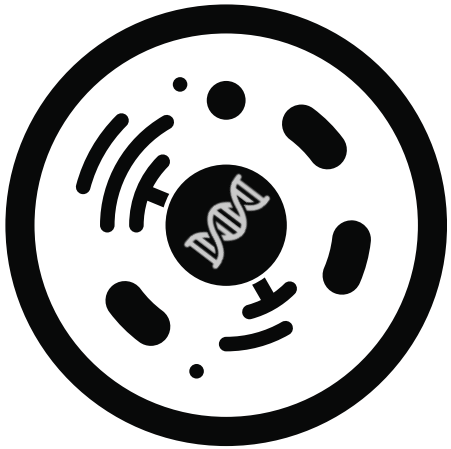
A geroscience model of aging-related burden of disease

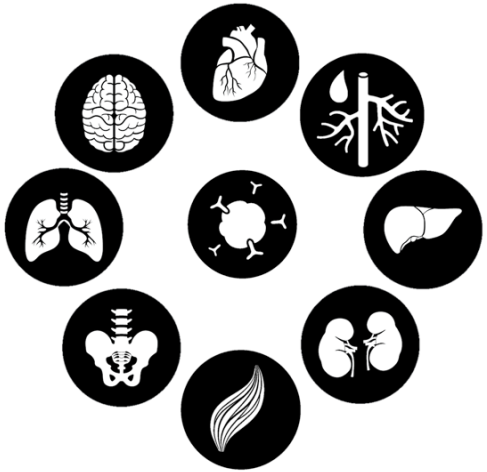
Molecular Changes

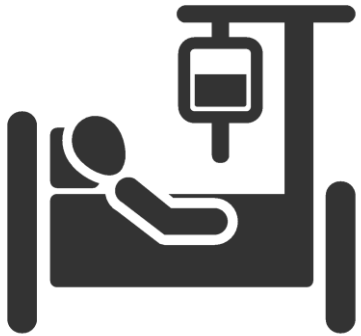
Decline in System Integrity

Functional Decline

Disease
Disability
Mortality







Evolving theoretical models of aging

Disease → Disability/Frailty → Death

Belsky et al. 2015 PNAS
Moffitt, Belsky et al. 2016 J Geron A Med Sci
Belsky et al. 2017 Aging Cell

Evolving theoretical models of aging

Disease → Disability/Frailty → Death

Early-life Adversity

Belsky et al. 2015 PNAS
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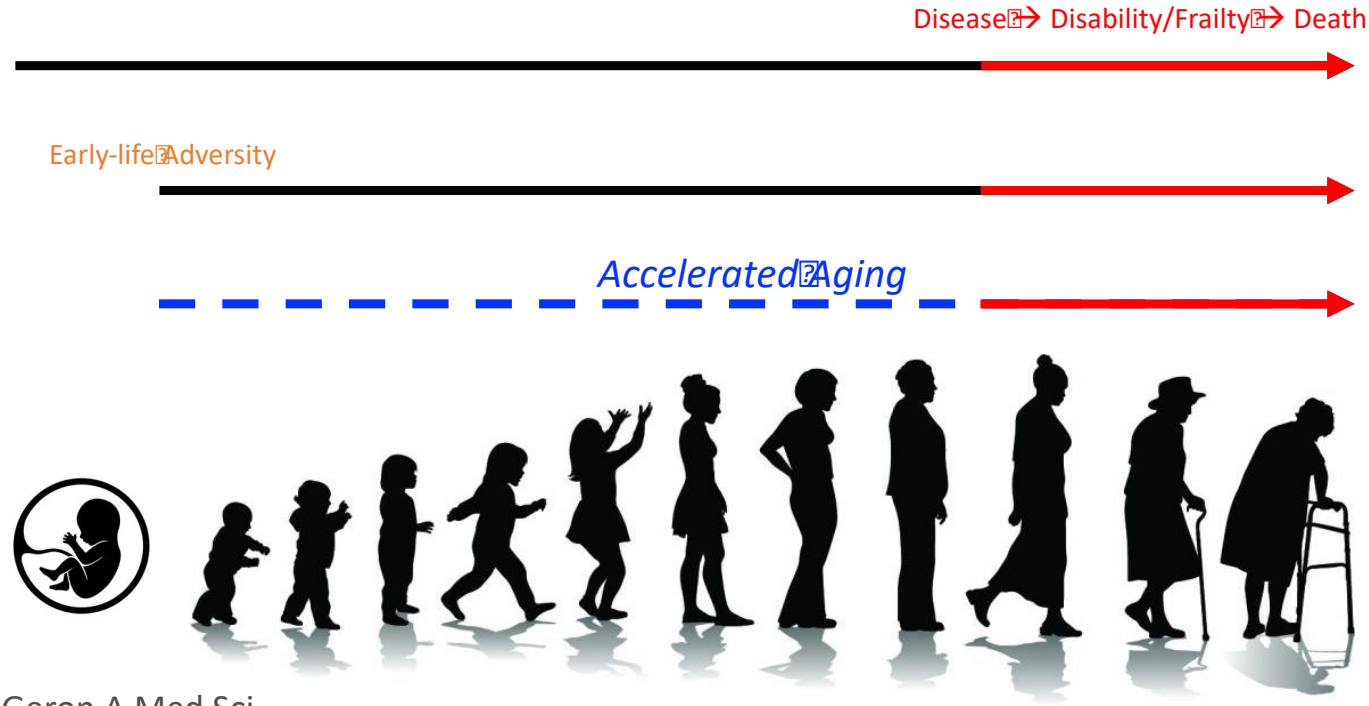
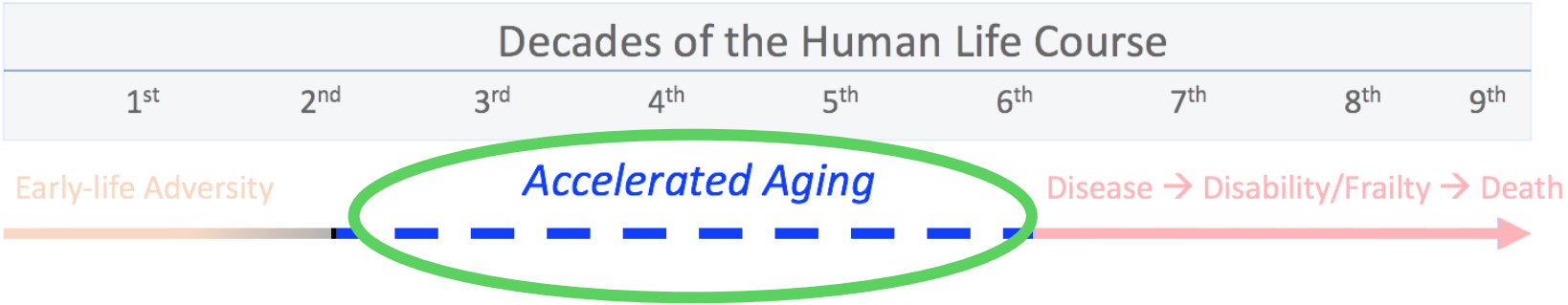
Belsky et al. 2017 Aging Cell

Evolving theoretical models of aging



Belsky et al. 2015 PNAS
Moffitt, Belsky et al. 2016 J Geron A Med Sci
Belsky et al. 2017 Aging Cell

Can we observe the process of aging in young, healthy humans?



The Pace of Aging

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

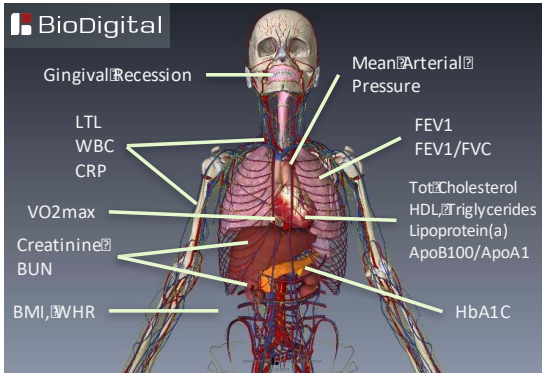
The rate of aging can be inferred from the rate of decline in integrity across multiple organ systems

Belsky et al. 2015 PNAS

The Pace of Aging

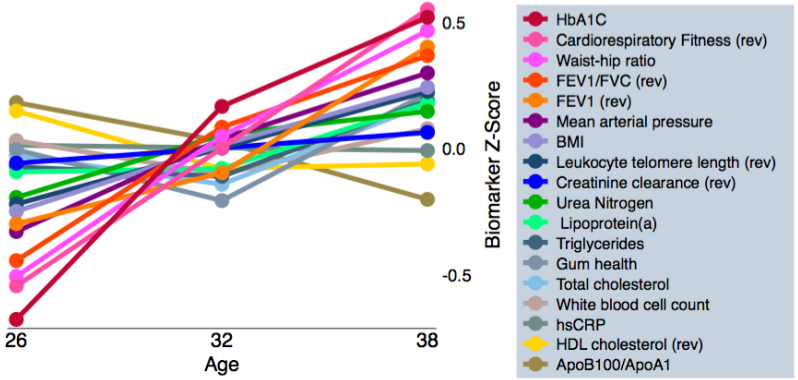
1

Measure 18 organ-system-integrity indicators at 3 time points



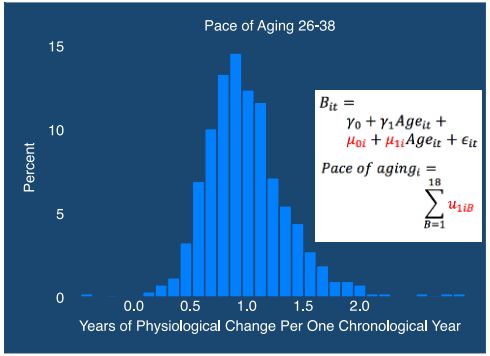
2

Model change over time: Do young, healthy bodies show signs of aging?



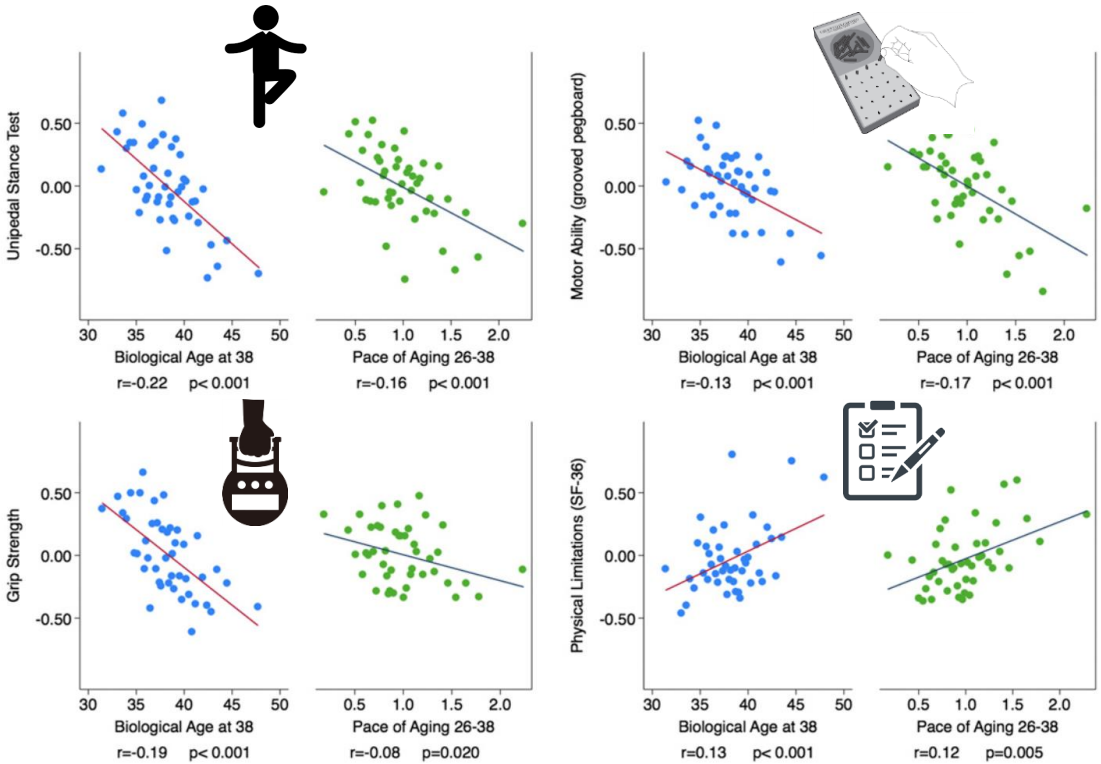
3

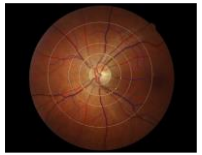
Build composite of slopes of change across 18 indicators: "The Pace of Aging"



Belsky et al. 2015 PNAS

Faster Pace of Aging associated with poor physical function, cognitive decline, facial aging





Belsky et al. 2015 PNAS

Early-life risks predict accelerated Pace of Aging

Family History

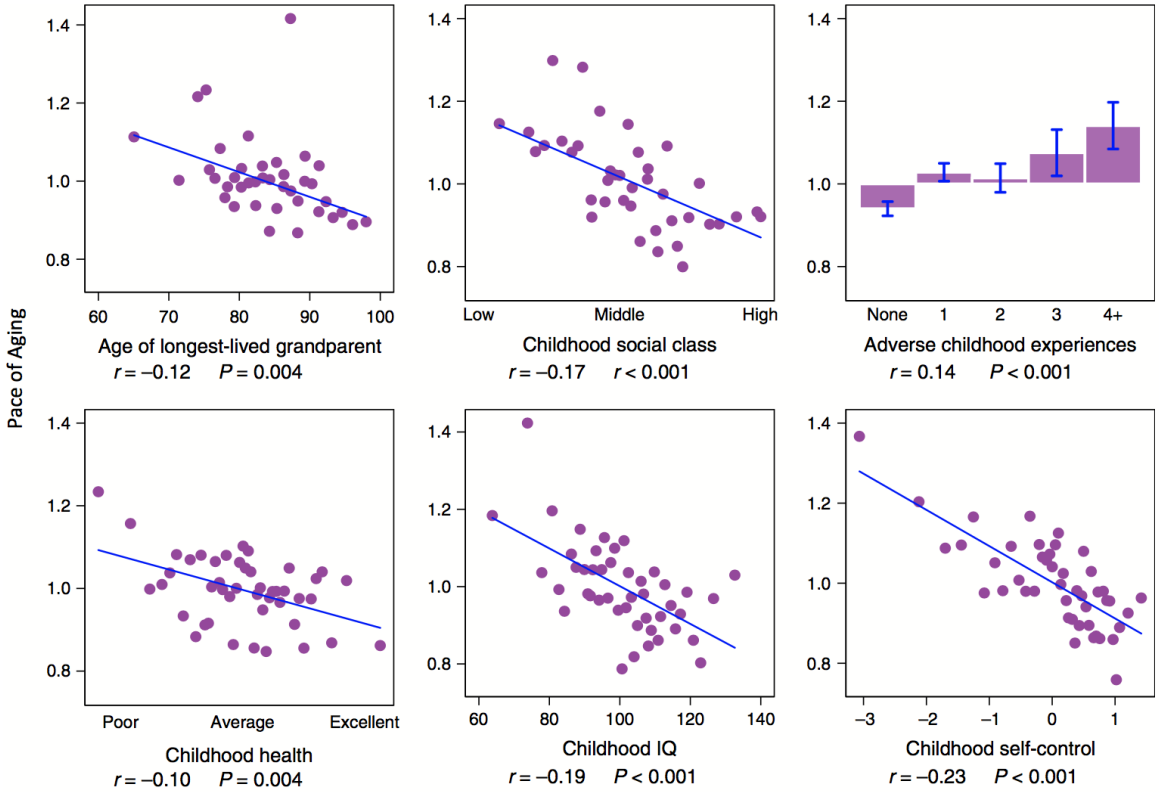
Family SES

ACEs

Physical Health

Childhood IQ

Childhood Self-control

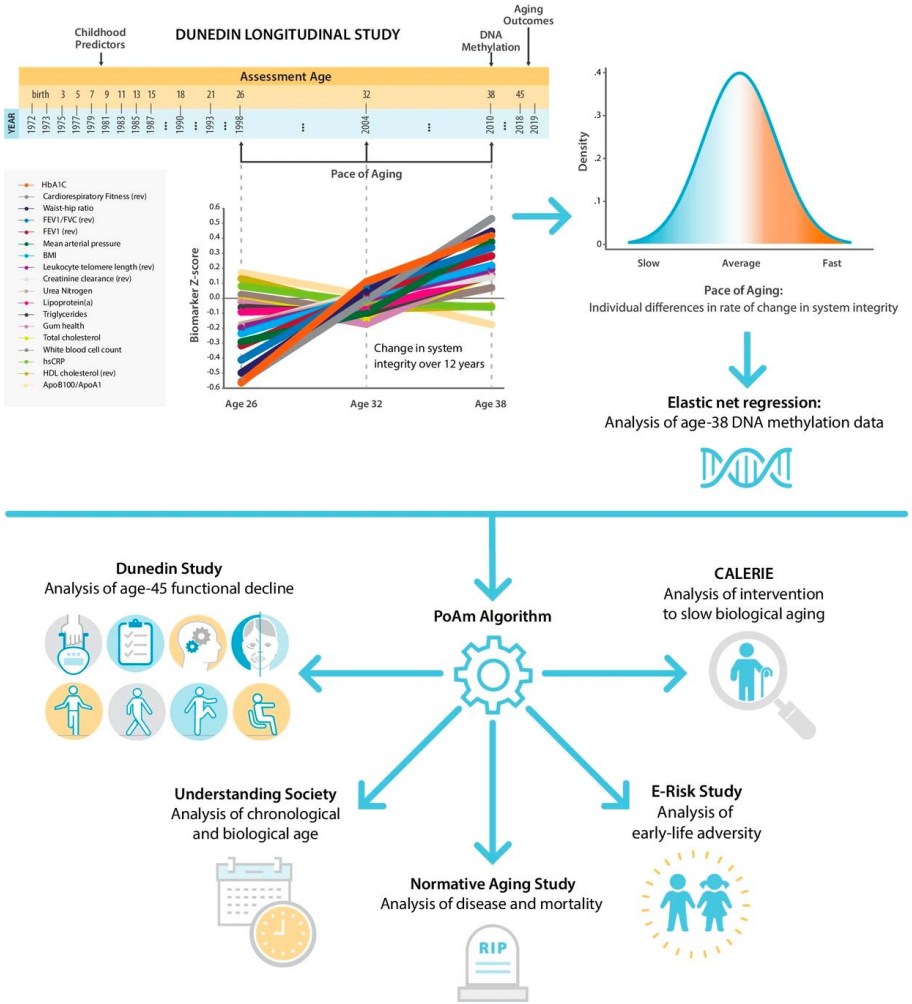


Belsky et al. 2017 Aging Cell

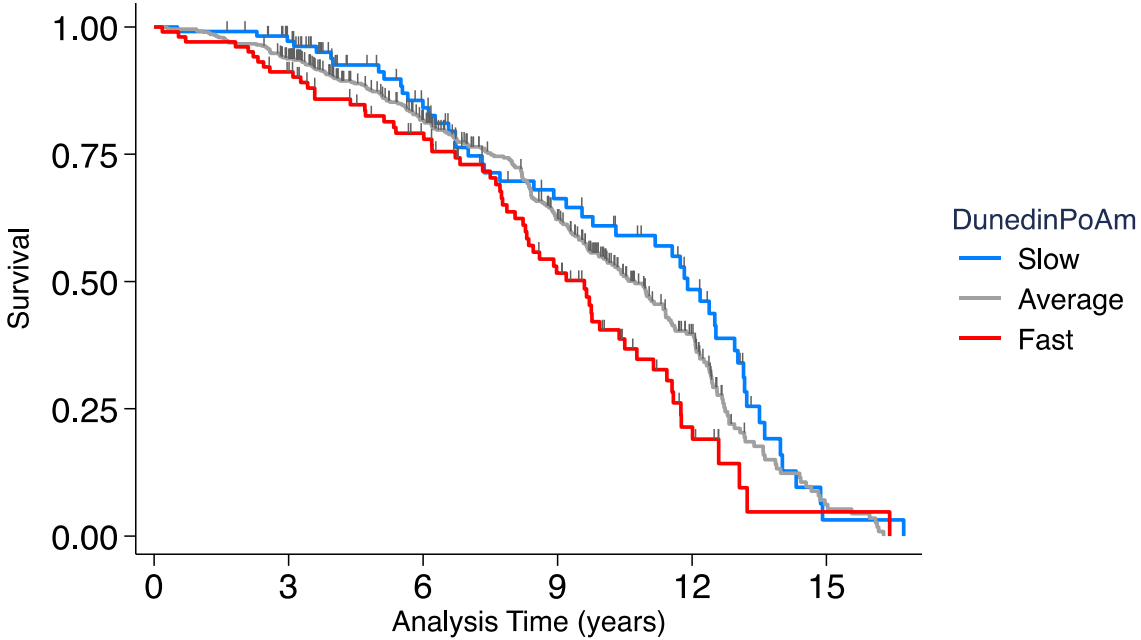
RESEARCH ARTICLE

Quantification of the pace of biological aging in humans through a blood test, the DunedinPoAm DNA methylation algorithm

Daniel W Belsky[1,2]*, Avshalom Caspi[3,4,5,6], Louise Arseneault[3], Andrea Baccarelli[7], David L Corcoran[6], Xu Gao[7], Eiliss Hannon[8], Hona Lee Harrington[4], Line JH Rasmussen[4,9], Renate Houts[4], Kim Huffman[10,11], William E Kraus[10,11], Dayoon Kwon[2], Jonathan Mill[8], Carl F Pieper[11,12], Joseph A Prinz[6], Richie Poulton[13], Joel Schwartz[14], Karen Sugden[4], Pantel Vokonas[15], Benjamin S Williams[4], Terrie E Moffitt[3,4,5,6]



DunedinPoAm predicts morbidity & mortality in older adults



Number At Risk (Deaths)

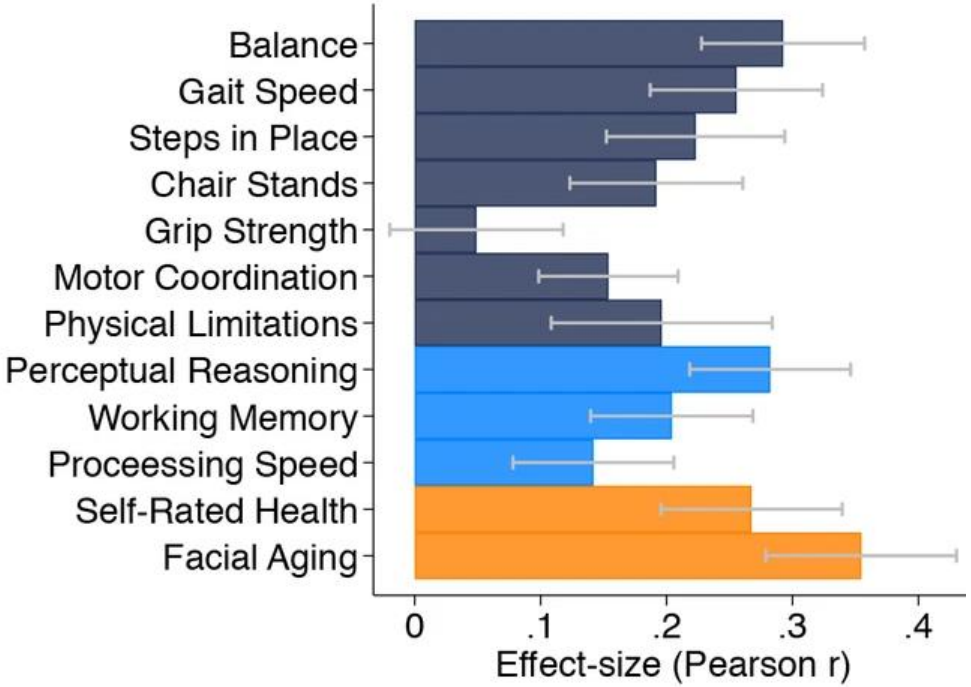
Slow DunedinPoAm	112	(3)	97	(10)	58	(11)	38	(9)	22	(17)	1
Average DunedinPoAm	481	(30)	435	(47)	295	(63)	189	(52)	68	(43)	7
Fast DunedinPoAm	102	(9)	90	(11)	67	(21)	38	(16)	9	(5)	1

VA U.S. Department of Veterans Affairs

Normative Aging Study

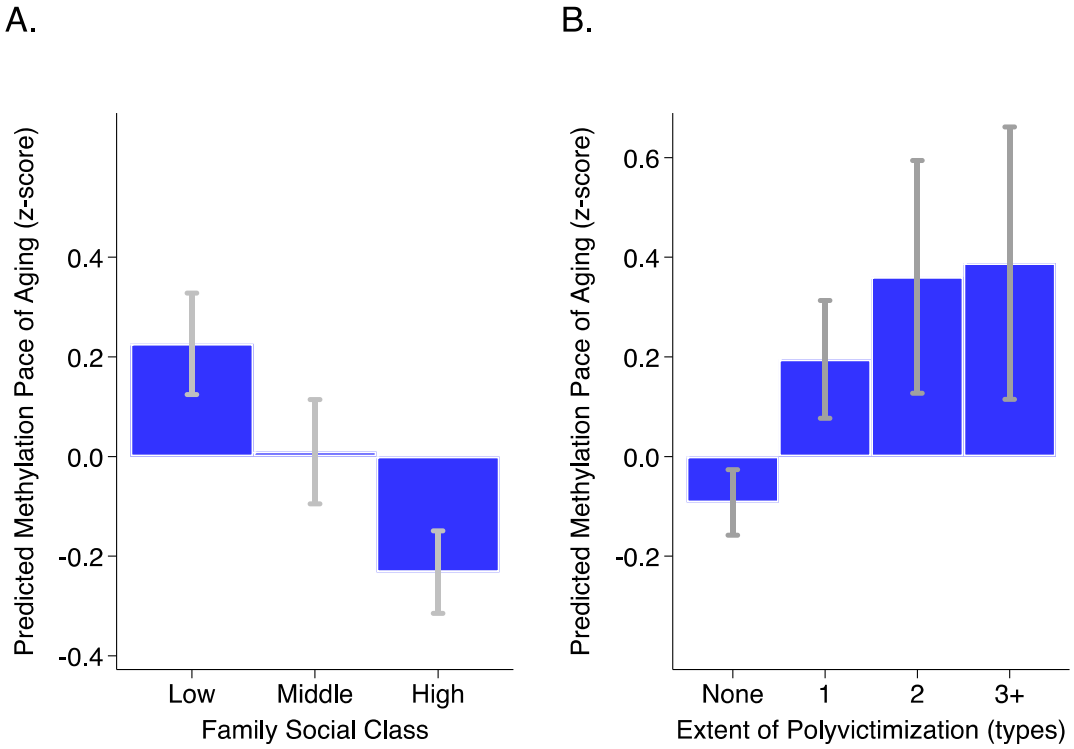
Belsky et al. 2020 eLife

Faster DunedinPoAm predicts deficits in function at age 45 years



Belsky et al. 2020 eLife

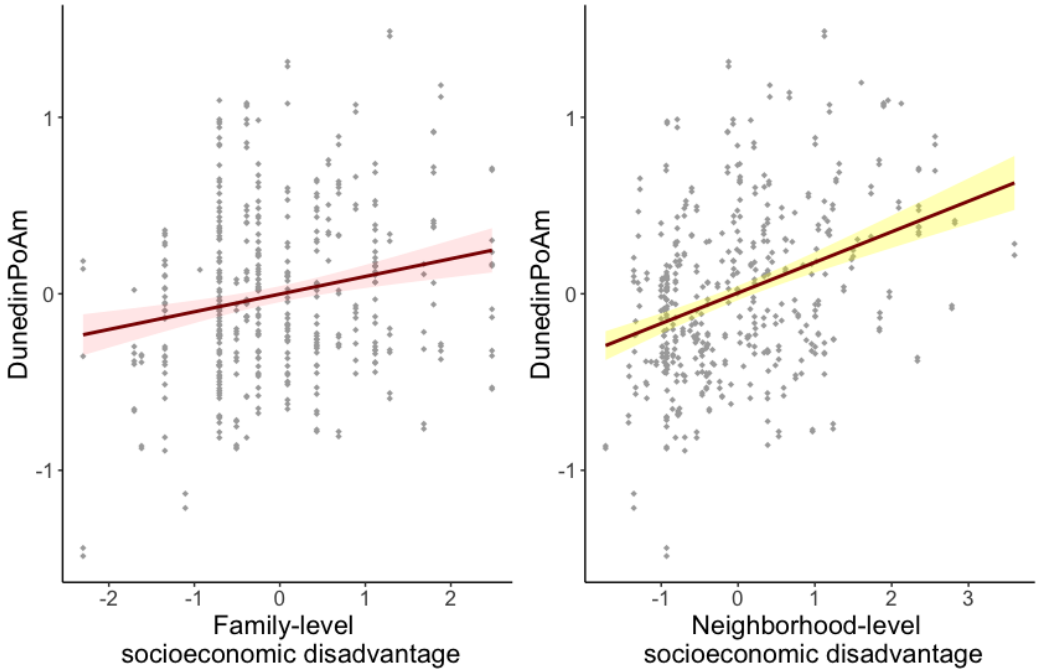
DunedinPoAm is accelerated in young adults exposed to early-life adversity



E-RiSK Study

Belsky et al. 2020 eLife

DunedinPoAm is accelerated in children and adolescents exposed to early-life adversity



Texas Twin Project
Saliva-DNAm analysis

Raffington et al. 2020 BioRxiv

Implications & Opportunities

- Processes of aging that compromise function and drive disability are ongoing from early in life
  - Prevention and intervention should begin early
- Molecular measures of the pace of aging make it possible to observe aging processes in real time
  - Etiology
  - Evaluation of intervention effectiveness
  - Surveillance to monitor population trend

Code to implement DunedinPoAm in Illumina 450k or EPIC array data at https://github.com/danbelsky/DunedinPoAm38

Thank you!

NIH
NIA