

Quantification of Biological Aging

Implications for Clinical Trials of Therapies to Extend Healthy Lifespan

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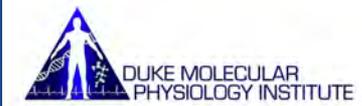


Department of Population Health Sciences

Duke University School of Medicine



Center for the Study of Aging
and Human Development



U24AG047121 (Kraus, Peiper)
P30 AG028716 (Schmader, Morey)
P30AG034424 (O'Rand)
R01 AG032282 (Moffitt)
R21AG054846 (Belsky)



Outline

Introduction

Biological aging is a treatment target for healthspan extension

Part 1. Human trials of geroprotectors

Challenges & opportunities

Part 2. Quantification of biological aging in young adults

Part 3. Testing biological aging in a geroprotector trial

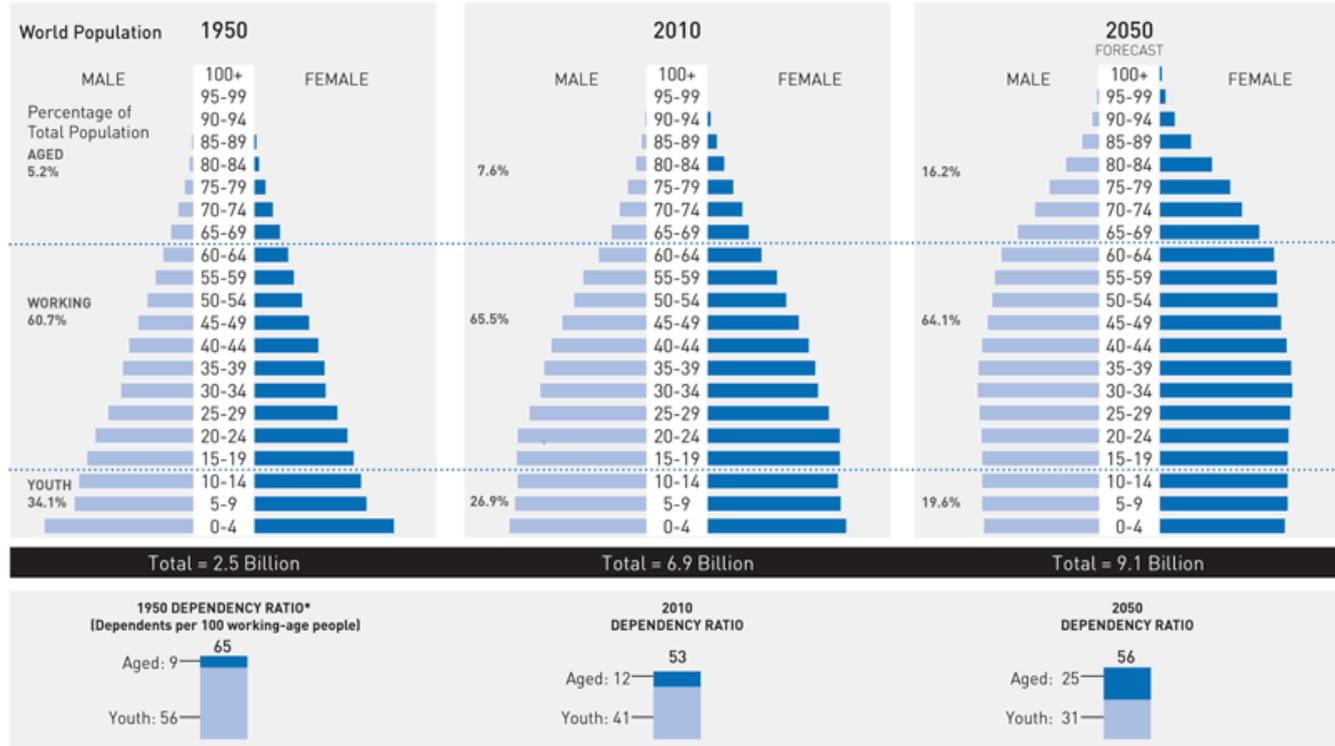
Conclusion

The global population is aging

Strategies are needed to extend healthy lifespan

Exhibit 1: The Aging Global Population, 1950–2050

The percentage of older people (age 65 plus) in the total world population has been steadily increasing since 1950, and it will continue to do so while the percentage of young people declines.

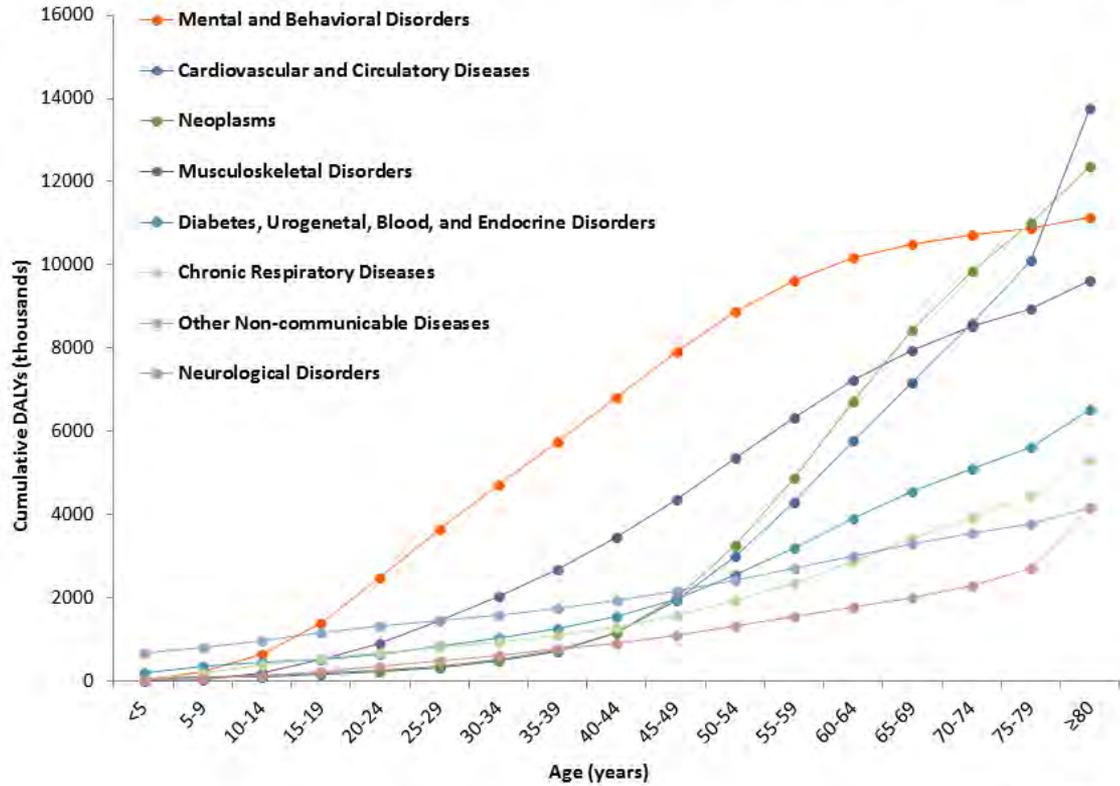


*Overall dependency is the sum of the youth and aged dependencies. Youth dependency is the ratio of youth [0–14] to working-age population [15–64], and aged dependency is the ratio of aged [65+] to working-age population.

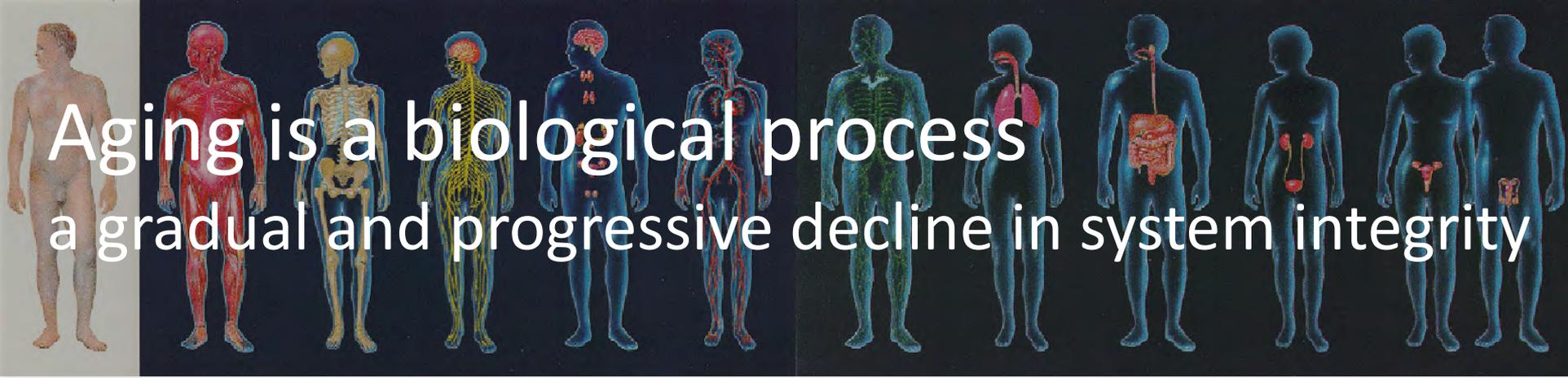
Source: U.N. Population Division, "World Population Prospects: The 2008 Revision" and "World Population Prospects: The 2010 Revision"

Aging itself is a leading risk factor for many diseases

Cumulative U.S. DALYs for the Leading Disease/Disorder Categories by Age (2010)



Data courtesy of WHO

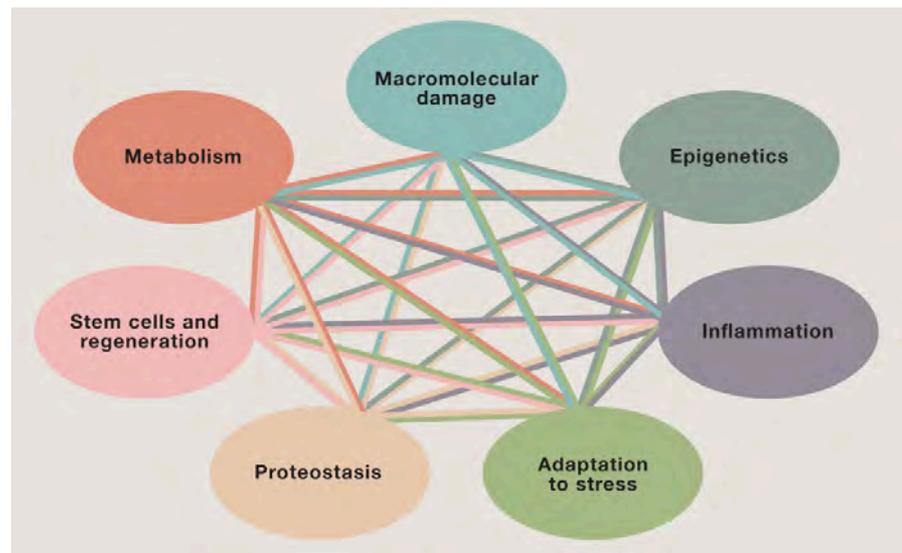


Aging is a biological process
a gradual and progressive decline in system integrity



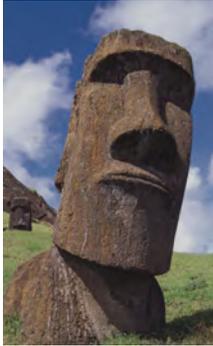
Kennedy et al.
2014 Cell

Lopez-Otin et al.
2013 Cell





Geroprotective Intervention?



Evolving theoretical models of aging

Disease → Disability/Frailty → Death



Belsky et al. 2015 PNAS
Moffitt et al. 2016 J Geron A Med Sci

Evolving theoretical models of aging

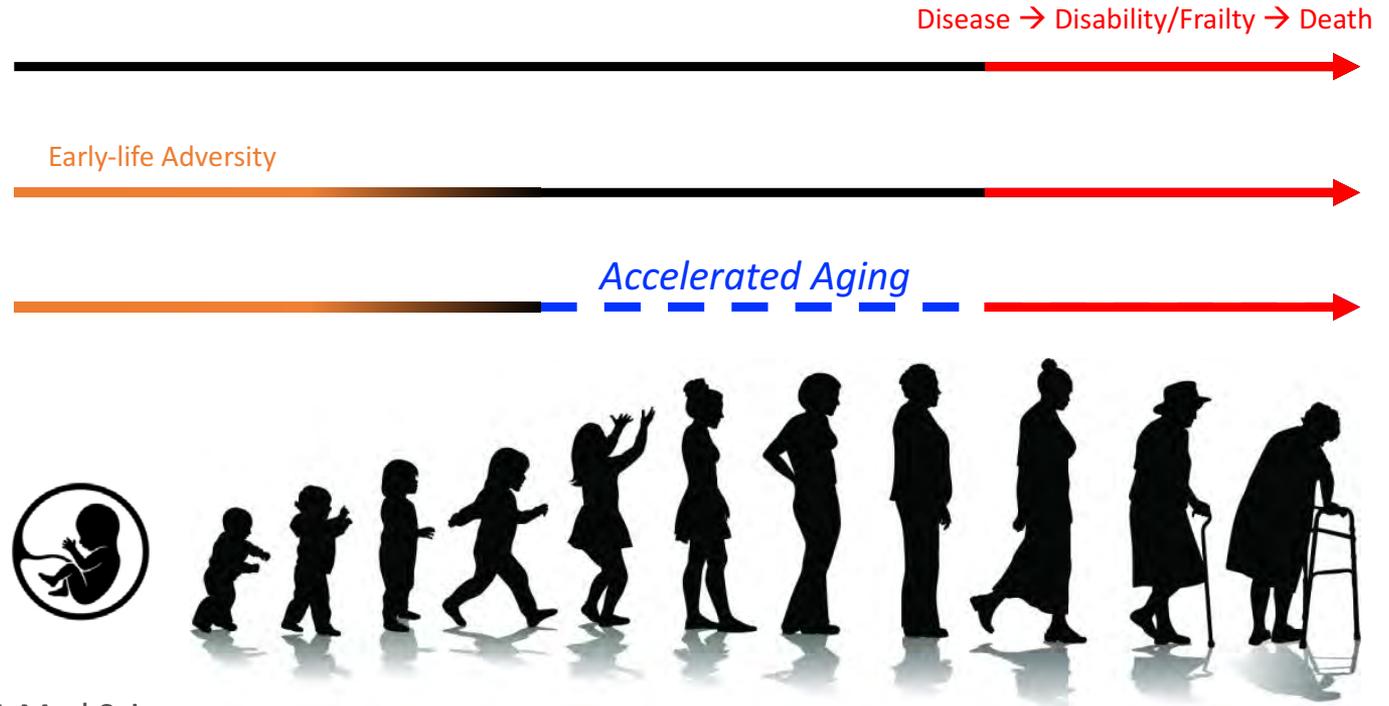
Disease → Disability/Frailty → Death

Early-life Adversity



Belsky et al. 2015 PNAS
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Evolving theoretical models of aging



Belsky et al. 2015 PNAS
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Decades of the Human Life Course

1st

2nd

3rd

4th

5th

6th

7th

8th

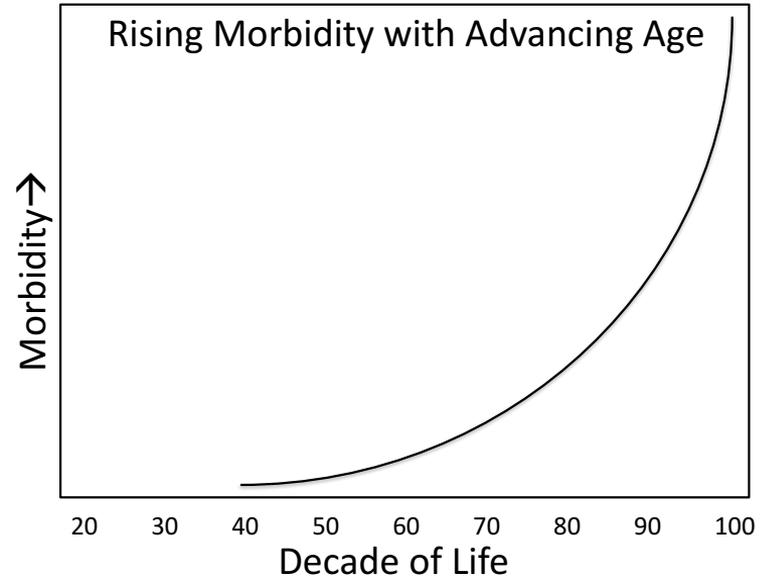
9th

Early-life Adversity

Accelerated Aging

Disease → Disability/Frailty → Death

- Exposures accumulate from early life
- Changes to physiology precede disease onset
- Preventive intervention must begin early



Decades of the Human Life Course

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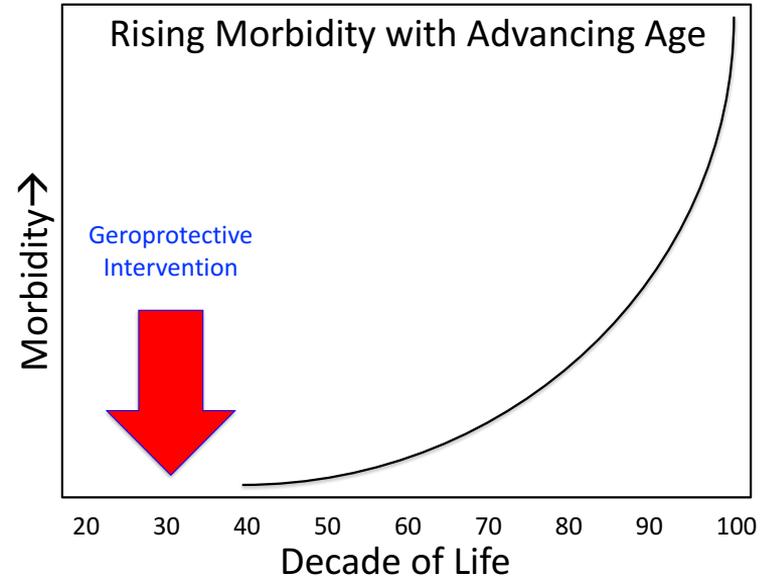
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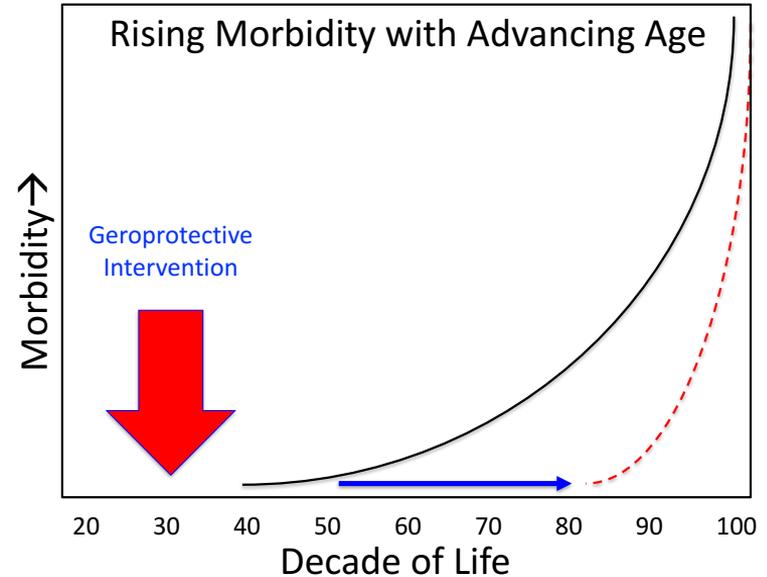
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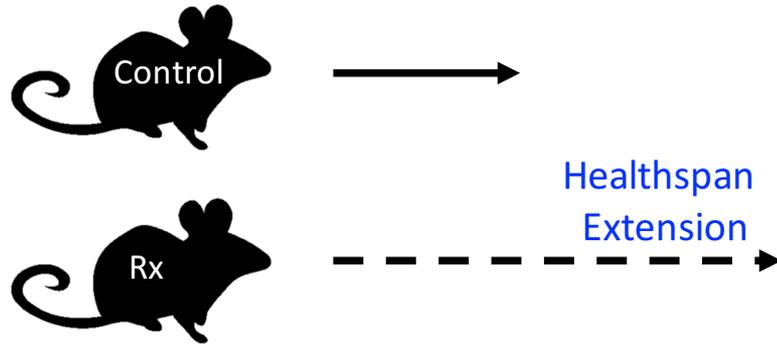
Challenges & opportunities

Part 2. Quantification of biological aging in young adults

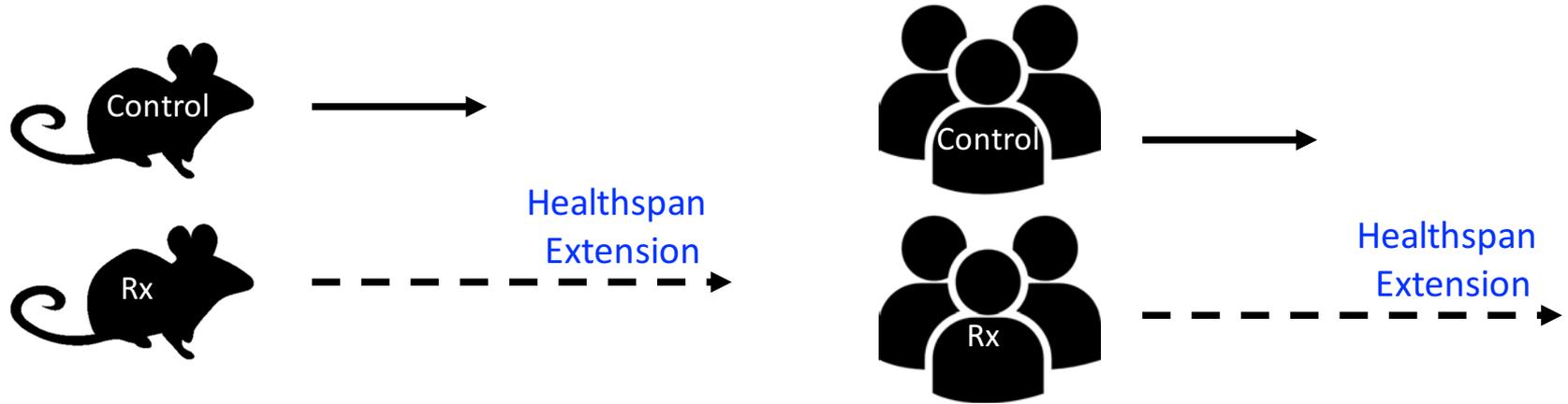
Part 3. Testing biological aging in a geroprotector trial

Conclusion

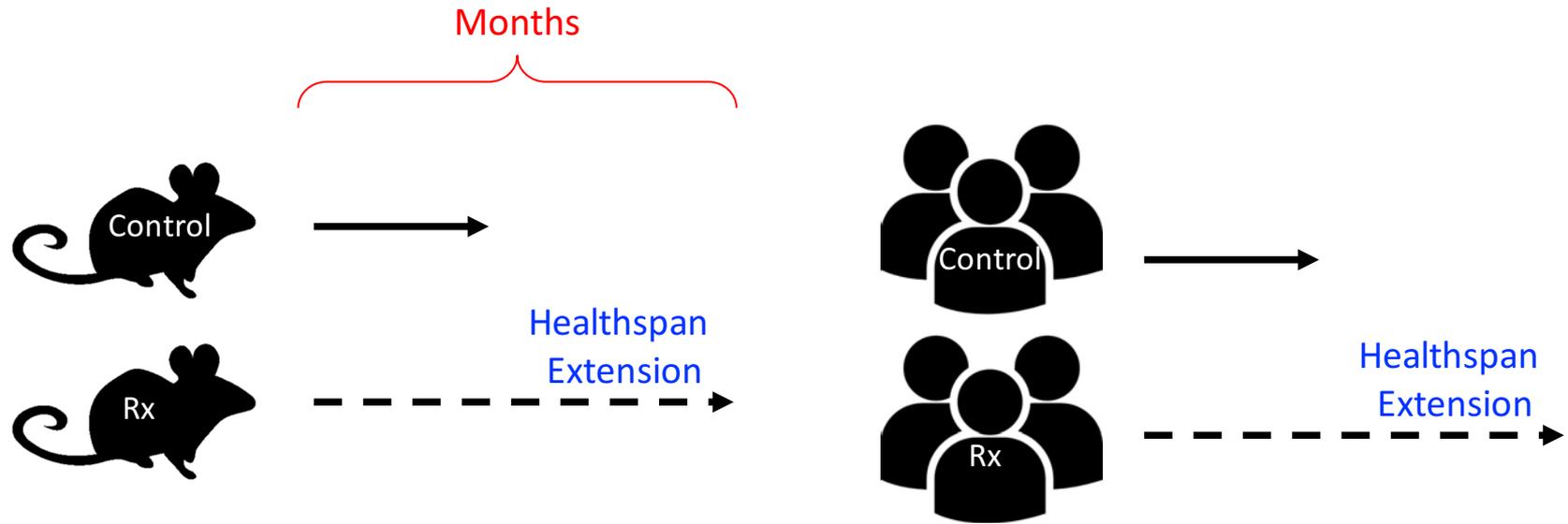
Ideal Geroprotector Trial Design



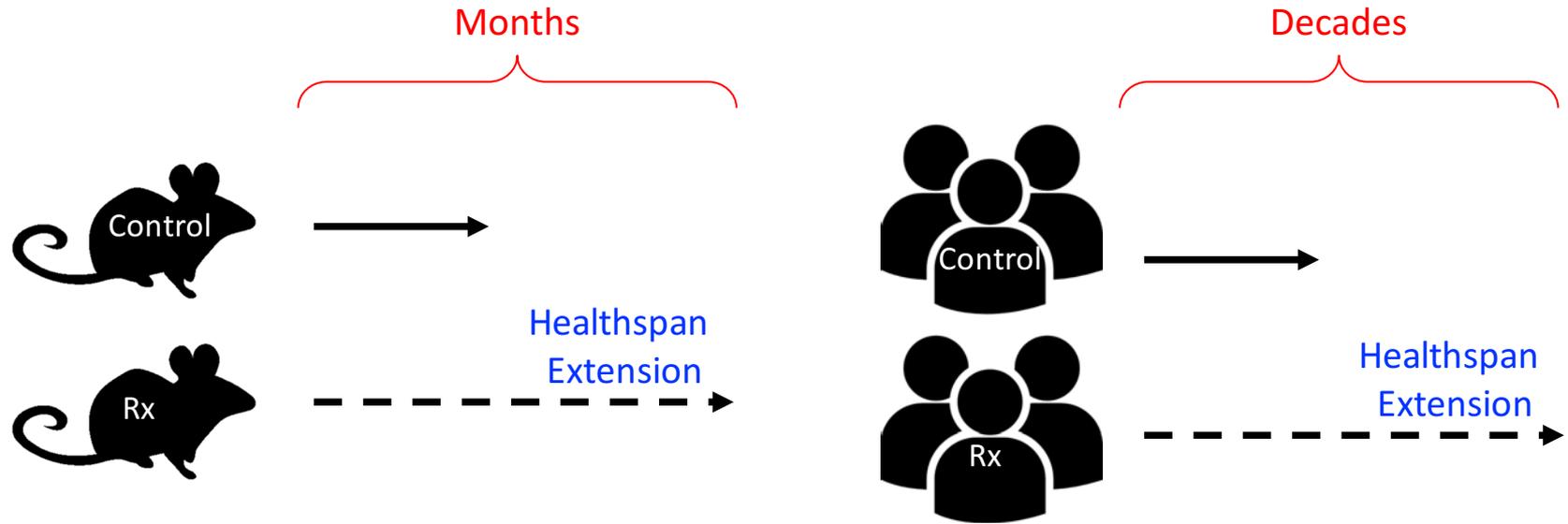
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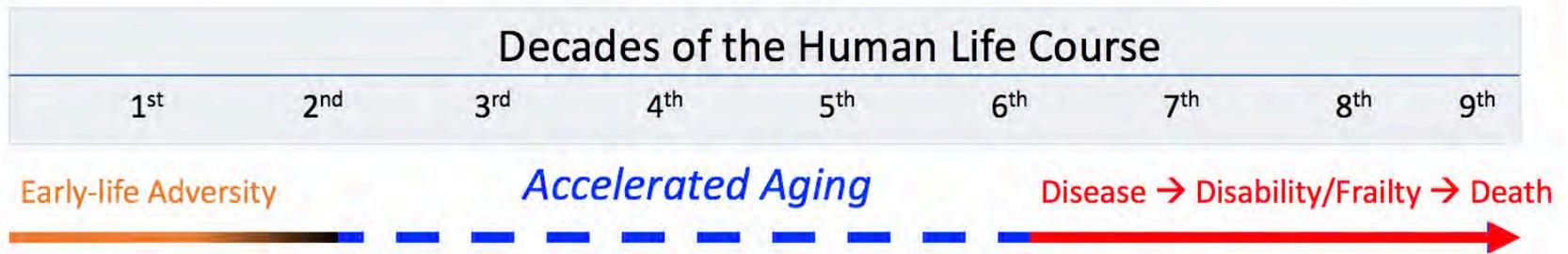
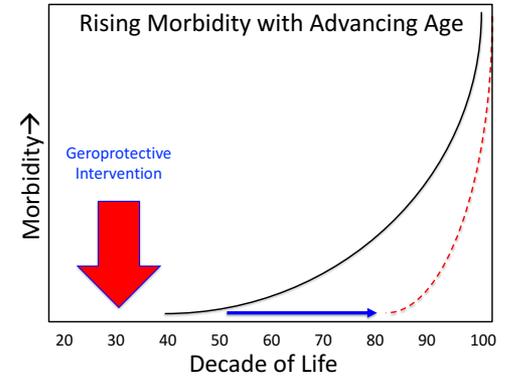
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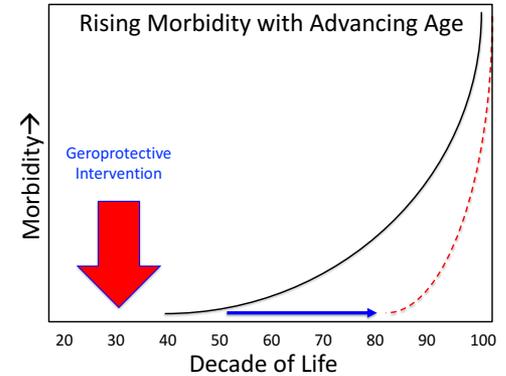
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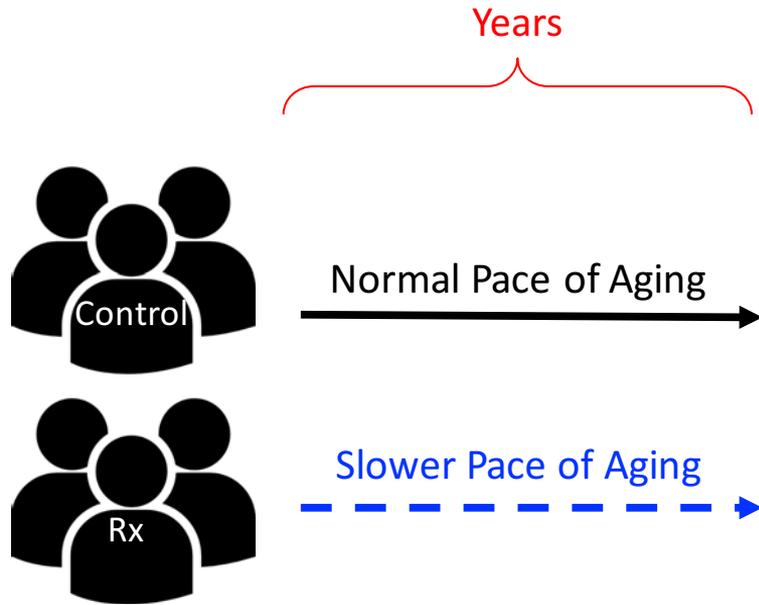
Problem: Healthspan follow-up from midlife prevention takes too long



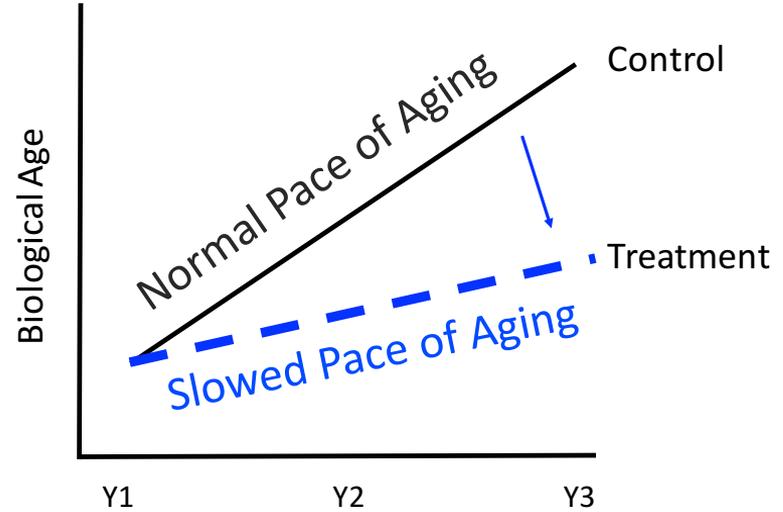
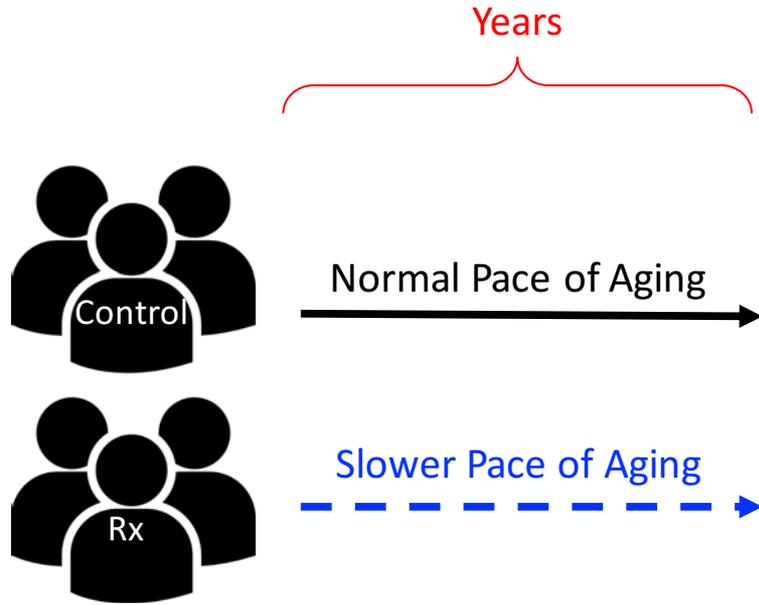
Solution: Measure aging processes as healthspan surrogate endpoint for trial



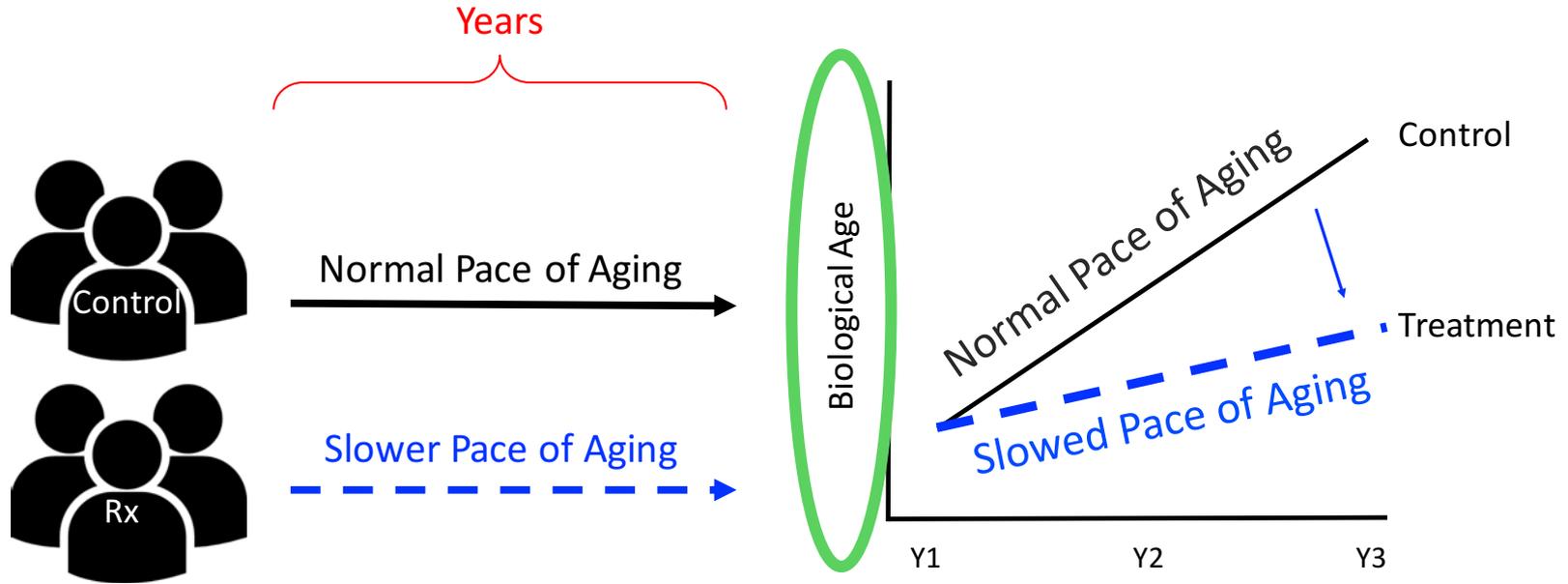
Alternative Geroprotector Trial Design



Alternative Geroprotector Trial Design



Alternative Geroprotector Trial Design



Part 1 Summary

- Biological aging may be a modifiable risk factor for age-related disease and disability
- New (and old) therapies to slow biological aging now have proof-of-concept in animal models, and more are on the way
- Translation of midlife geroprotective interventions to humans faces a barrier – follow-up takes too long
- Translation to humans can be accelerated using study designs that measure biological aging as a surrogate endpoint for healthspan extension

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Dunedin, New Zealand



www.moffittcaspi.com

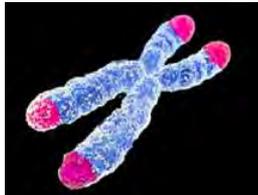


The Dunedin Longitudinal Study

Age	Year	Number	Percent*
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5	1977-78	991	96
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13	1985-86	850	82
15	1987-88	976	95
18	1990-91	993	97
21	1993-94	992	97
26	1998-99	980	96
32	2004-05	972	96
38	2010-12	961	95%
45	2017-18	??	??

* Percent assessed, of those who were alive at each age.

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Can we measure the rate of aging in young, healthy humans?



The Pace of Aging

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

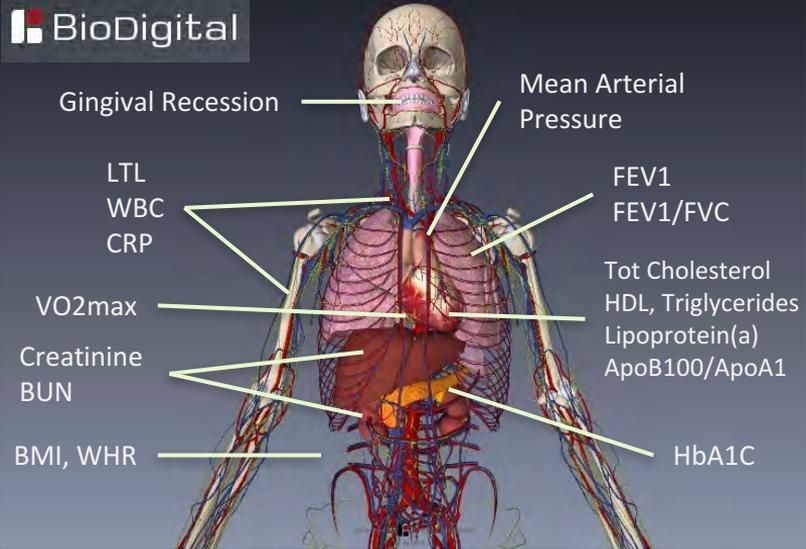
The rate of aging can be inferred from the rate of decline in integrity across multiple organ systems



Belsky et al. 2015 PNAS

The Pace of Aging

BioDigital

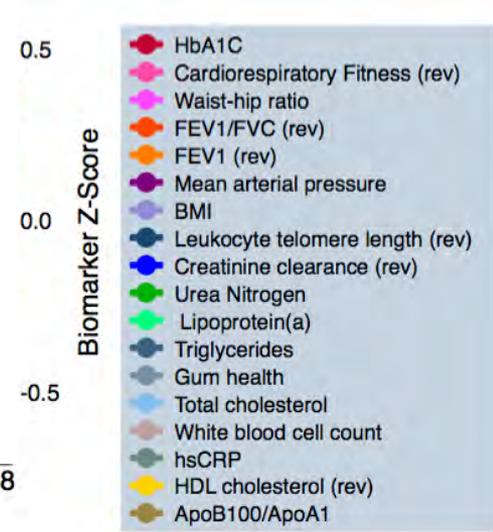
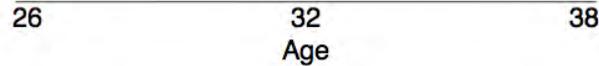
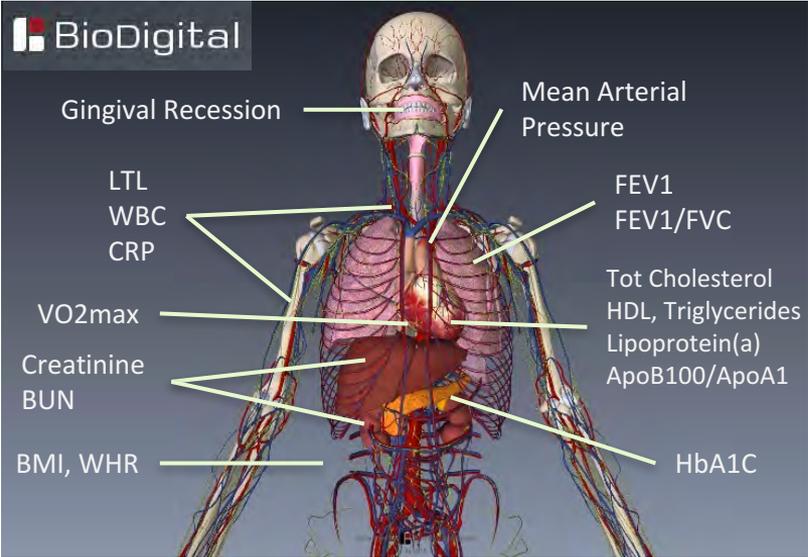


Quantification of biological aging in young adults
Belsky et al. 2015 PNAS

Belsky et al. 2015 PNAS

The Pace of Aging

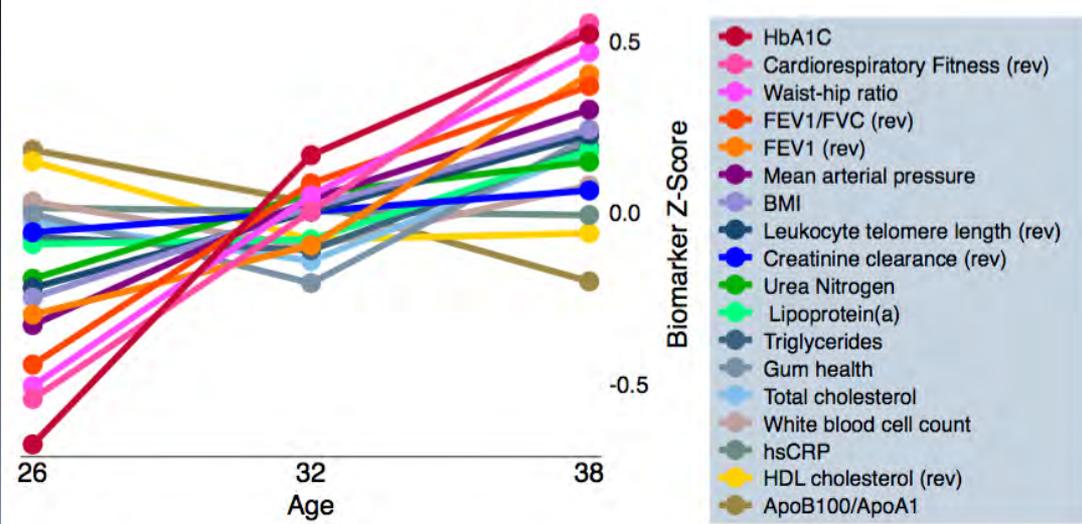
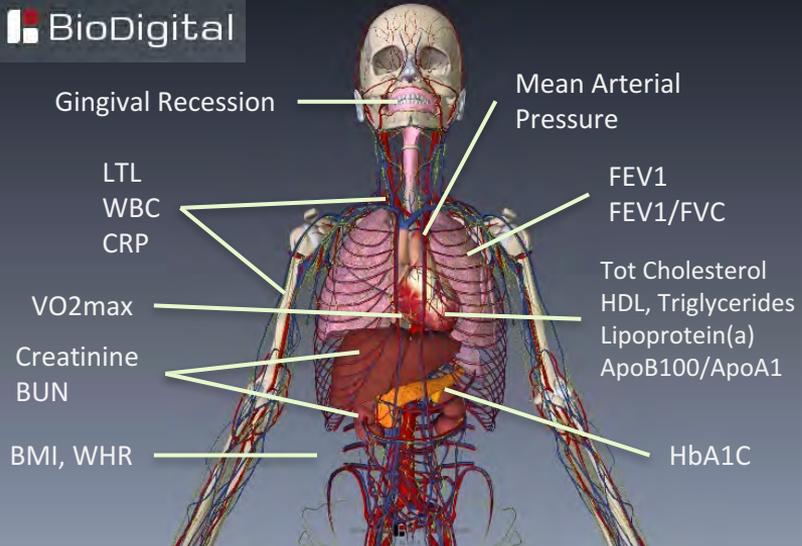
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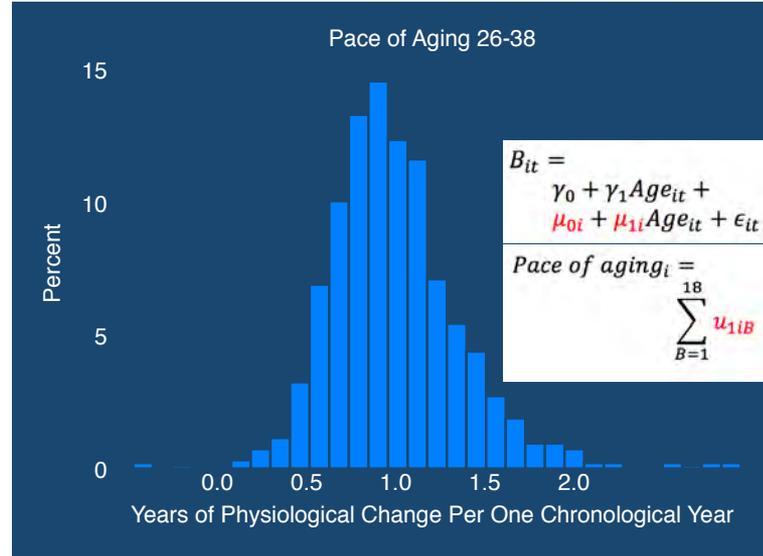
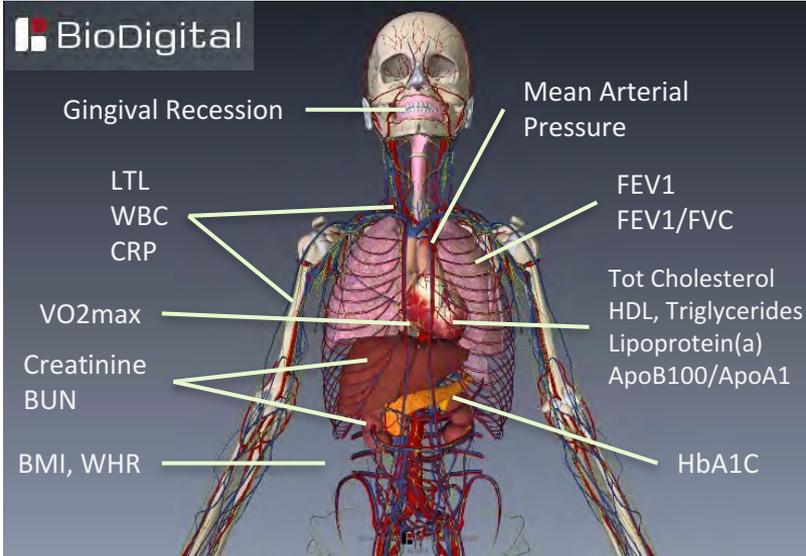
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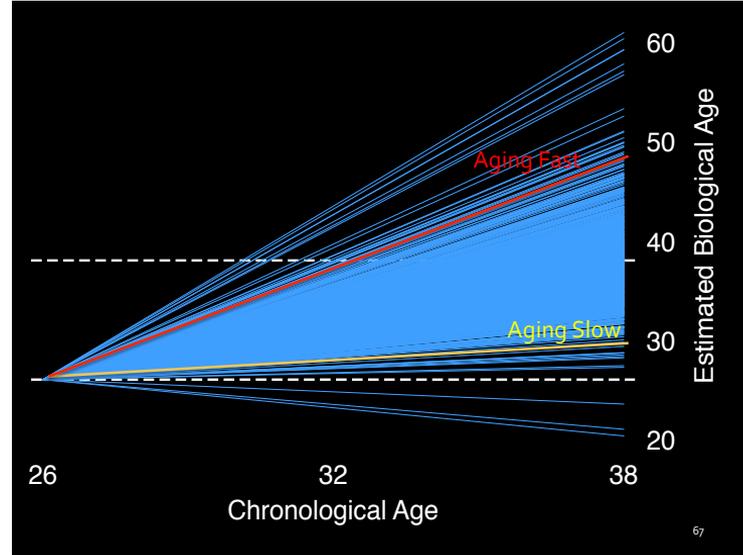
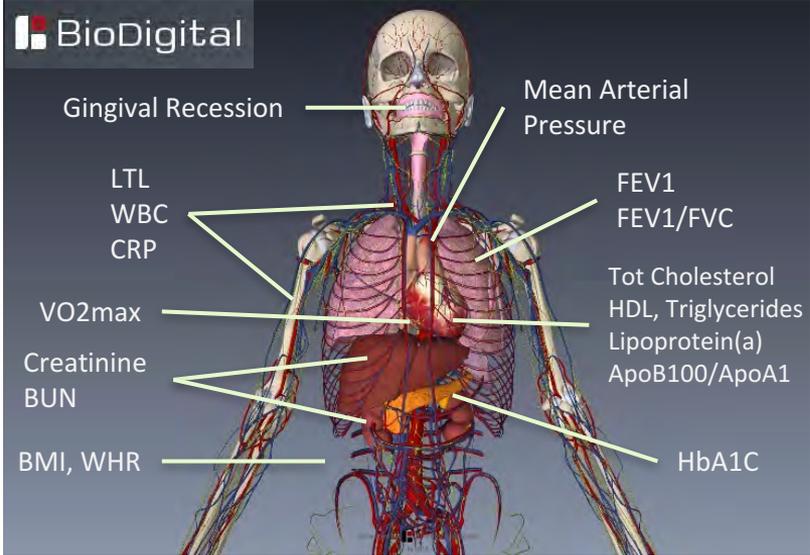
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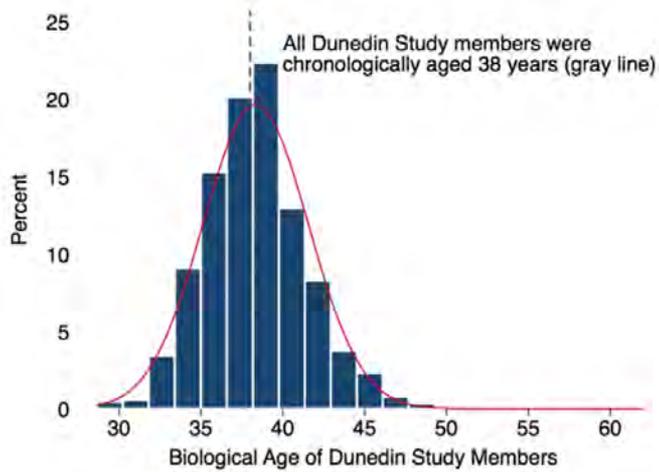
BioDigital



Belsky et al. 2015 PNAS

Cross-sectional measurement of biological age

Klemera-Doubal Method Biological Age



$$B_{EC} = \frac{\sum_{j=1}^m (x_j - q_j) \frac{k_j}{s_j^2} + \frac{C}{s_B^2}}{\sum_{j=1}^m \left(\frac{k_j}{s_j} \right)^2 + \frac{1}{s_B^2}}$$



Klemera & Doubal 2006 *Mech Ag Dev*

- Albumin
- Alkaline Phosphatase
- BUN
- Creatinine
- CRP
- HbA1c
- SBP
- Total cholesterol
- CMV
- FEV1

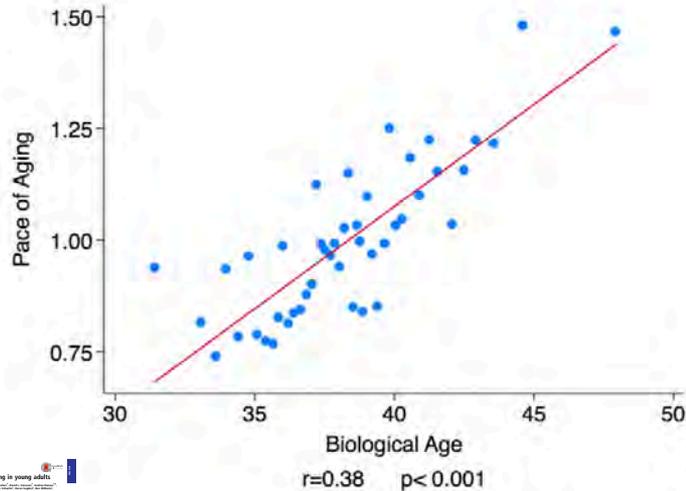


Levine 2013 *J Gerontol A*



Belsky et al. 2015 *PNAS*

Cross-sectional measurement reflects recent rate of change



Klemera-Doubal Method Biological Age

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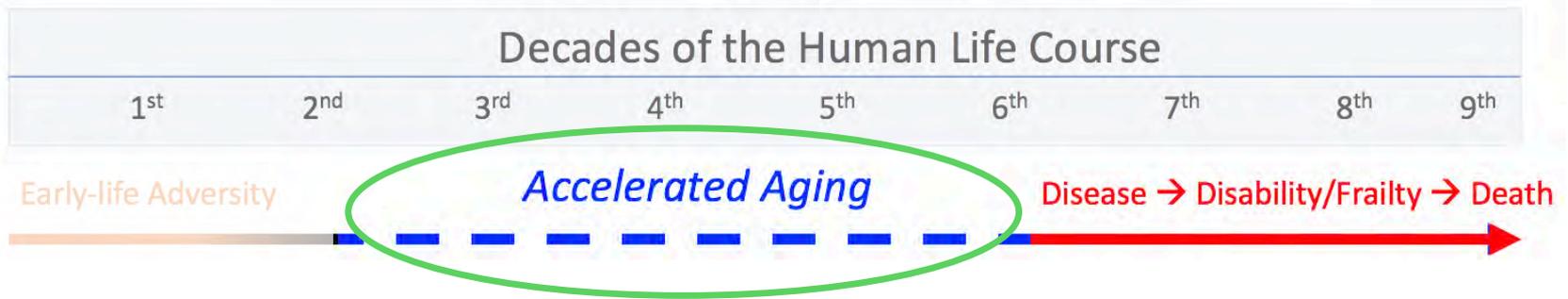


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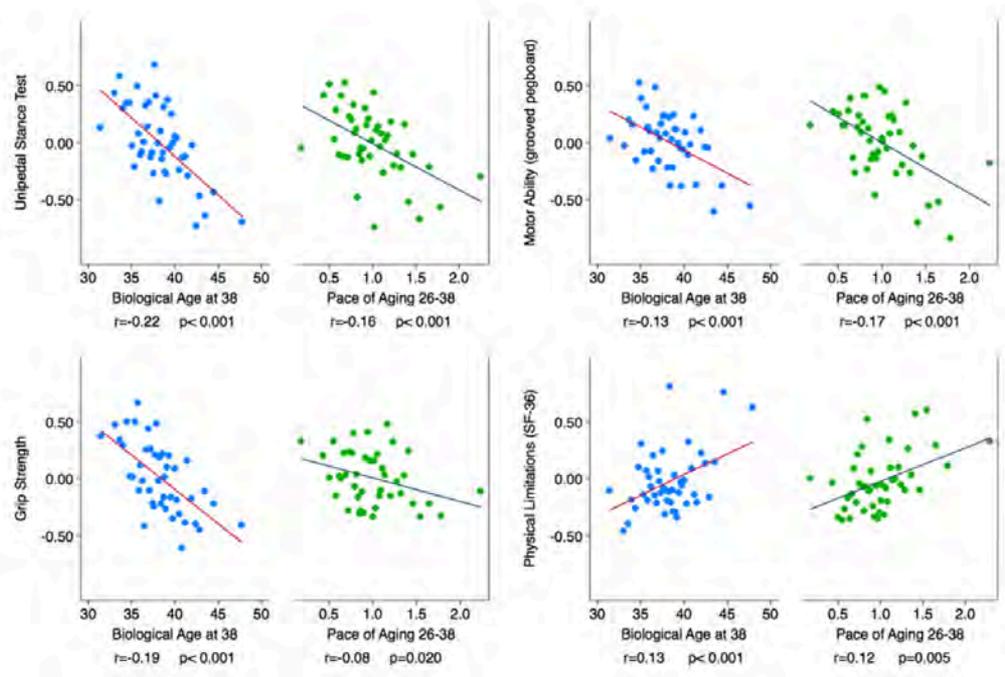
Does variation in rate of aging predict signs of aging?



Faster aging predicts poor physical function



	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	(1)	(2)	(3)
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	(1)	(2)	(3)
5. Lifting or carrying groceries	(1)	(2)	(3)
6. Climbing several flights of stairs	(1)	(2)	(3)
7. Climbing one flight of stairs	(1)	(2)	(3)
8. Bending, kneeling, or stooping	(1)	(2)	(3)
9. Walking more than a mile	(1)	(2)	(3)
10. Walking several blocks	(1)	(2)	(3)
11. Walking one block	(1)	(2)	(3)
12. Bathing or dressing yourself	(1)	(2)	(3)

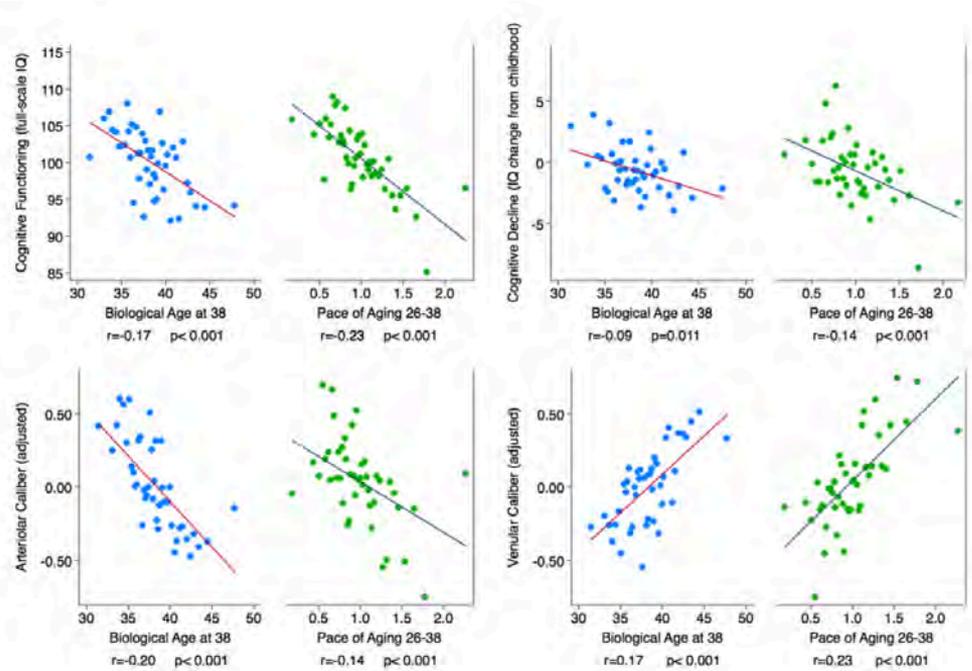
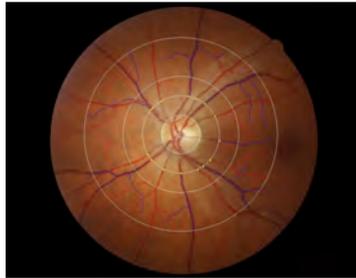


Quantification of biological aging in young adults

Research from the University of Pennsylvania and other institutions, published in PNAS, shows that faster biological aging is associated with poorer physical function. The study used a composite score of physical function tests to measure biological age. The findings suggest that lifestyle factors like exercise and diet can influence biological aging and, consequently, physical health.

Belsky et al. 2015 PNAS

Faster aging predicts declining brain health



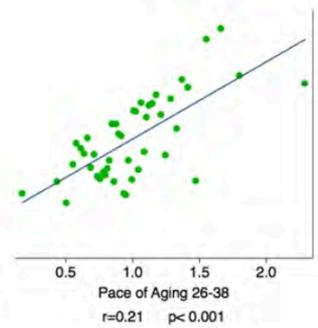
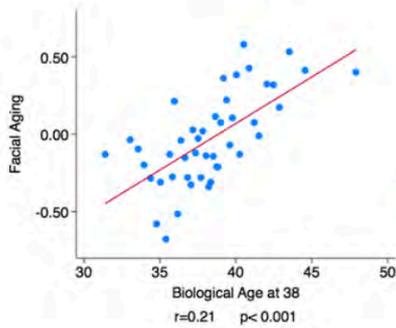
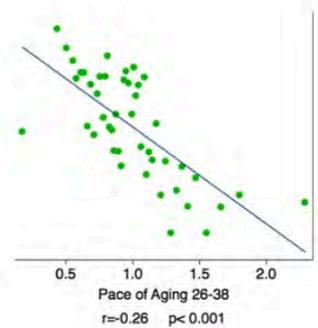
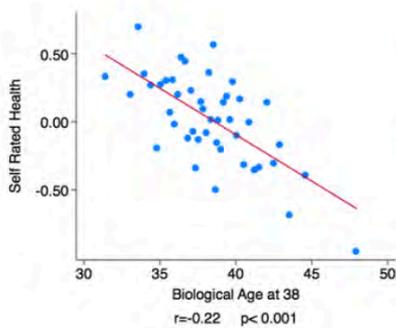
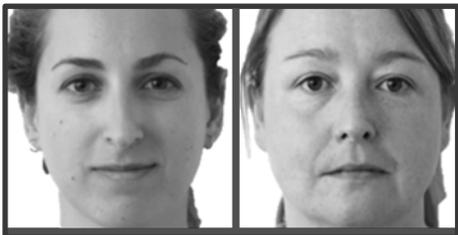
Quantification of biological aging in young adults
Belsky et al. 2015 PNAS

Belsky et al. 2015 PNAS

Faster aging predicts subjective signs

1. In general, would you say your health is:

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5



Belsky et al. 2015 PNAS

Part 2 Interim Summary

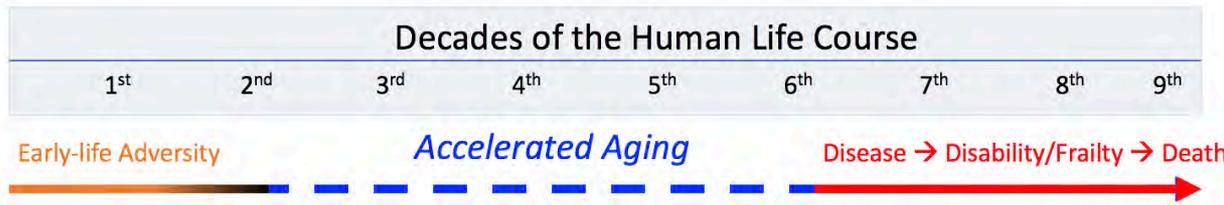
- The rate of aging can be measured in healthy young adults
Repeated-measures clinical-exam and blood-test data can track aging-related changes decades in advance of disease onset
- The aging rate in healthy young adults is already variable
- A faster rate of aging correlates with deficits in physical and cognitive function and subjective signs of aging

Do early-life risks accelerate the pace of aging?

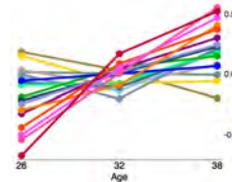


Belsky et al. 2017
Aging Cell

Life-Course Design

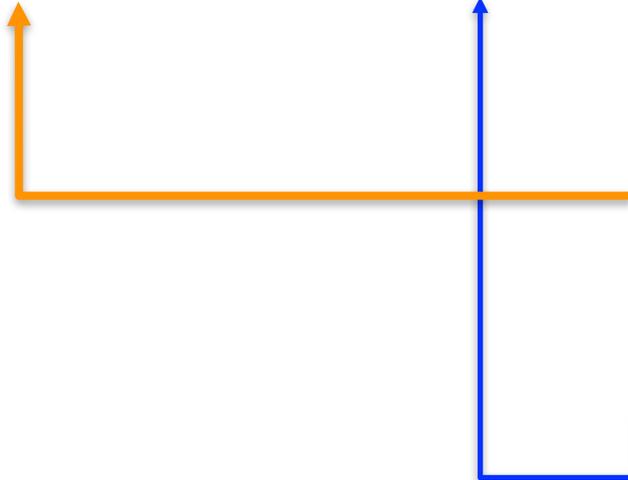
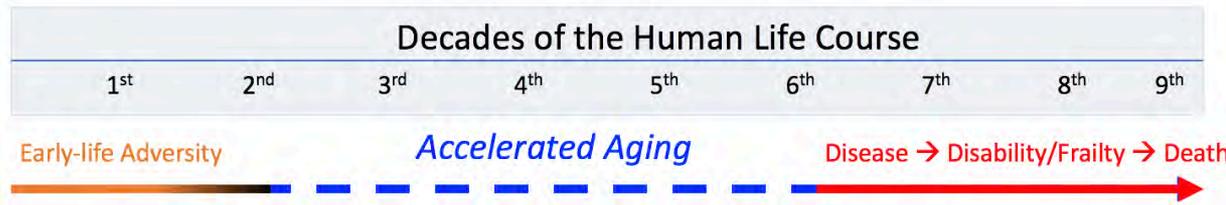


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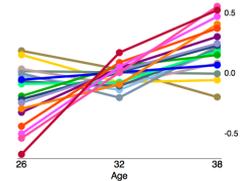


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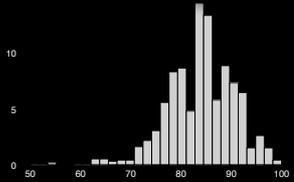


Impact of early parental history characteristics on the risk of child maltreatment: A meta-analysis of longitudinal studies

Belsky et al. 2017
Aging Cell



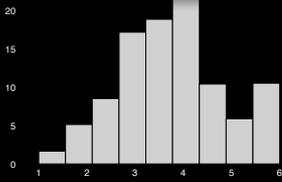
Familial Longevity



Age of longest-lived grand parent



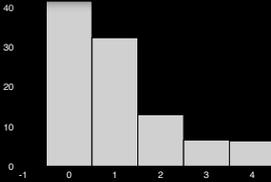
Childhood SES



Based on parental occupation
Birth-age 15



ACEs

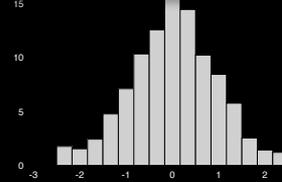


5 types of child harm
Physical abuse
Emotional abuse
Sexual abuse
Physical neglect
Emotional neglect

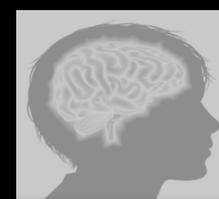
5 types of household dysfunction
Substance abuse
Mental illness
Incarceration
Partner violence
Parental loss
Ages 3-15



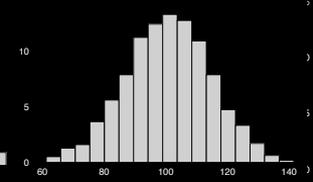
Childhood Health



Lung function
Blood pressure
Anthropometry
Balance & Motor
Clinical interview
Ages 3, 5, 7, 9, 11



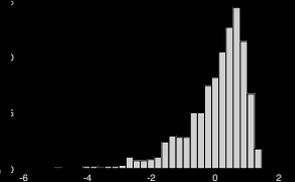
Childhood IQ



Wechsler Intelligence Scales for Children (WISC)
Ages 7, 9, 11, 13



Childhood Self-Control

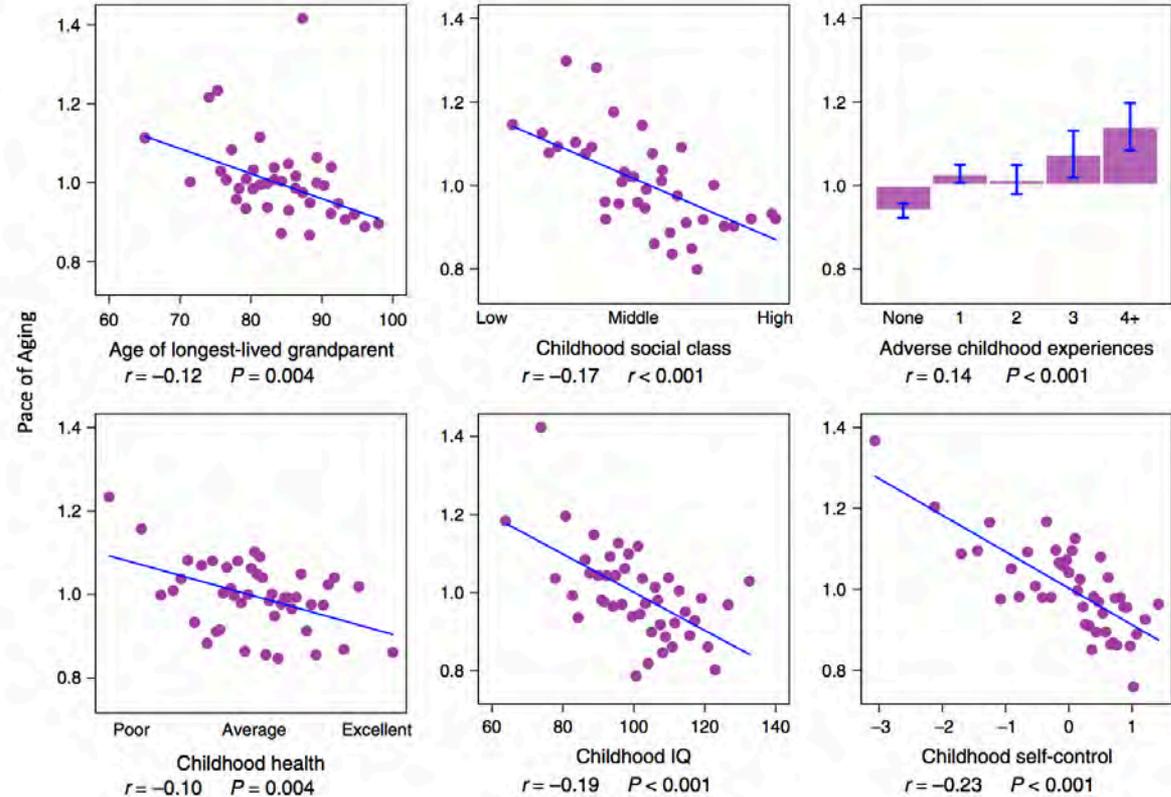


Observational ratings, parent, teacher, & self-reports of hyperactivity, lack of persistence, inattention, impulsive aggression, impulsivity
Ages 3-11 years



Belsky et al. 2017
Aging Cell

Midlife pace of aging has origins in childhood



Belsky et al. 2017
Aging Cell

Retrospective Personal-History Risk Assessment for Screening Geroprotector Trial Participants

<15min battery
5-point scale



Construct	Measurement
Familial Longevity	Grandparent > 80y (life expectancy)
Childhood Social Class	Low (e.g. low-skill occupation)
ACEs	CDC ACE Inventory
Childhood IQ	Low education
Childhood Self-Control	5-item Nurse rating



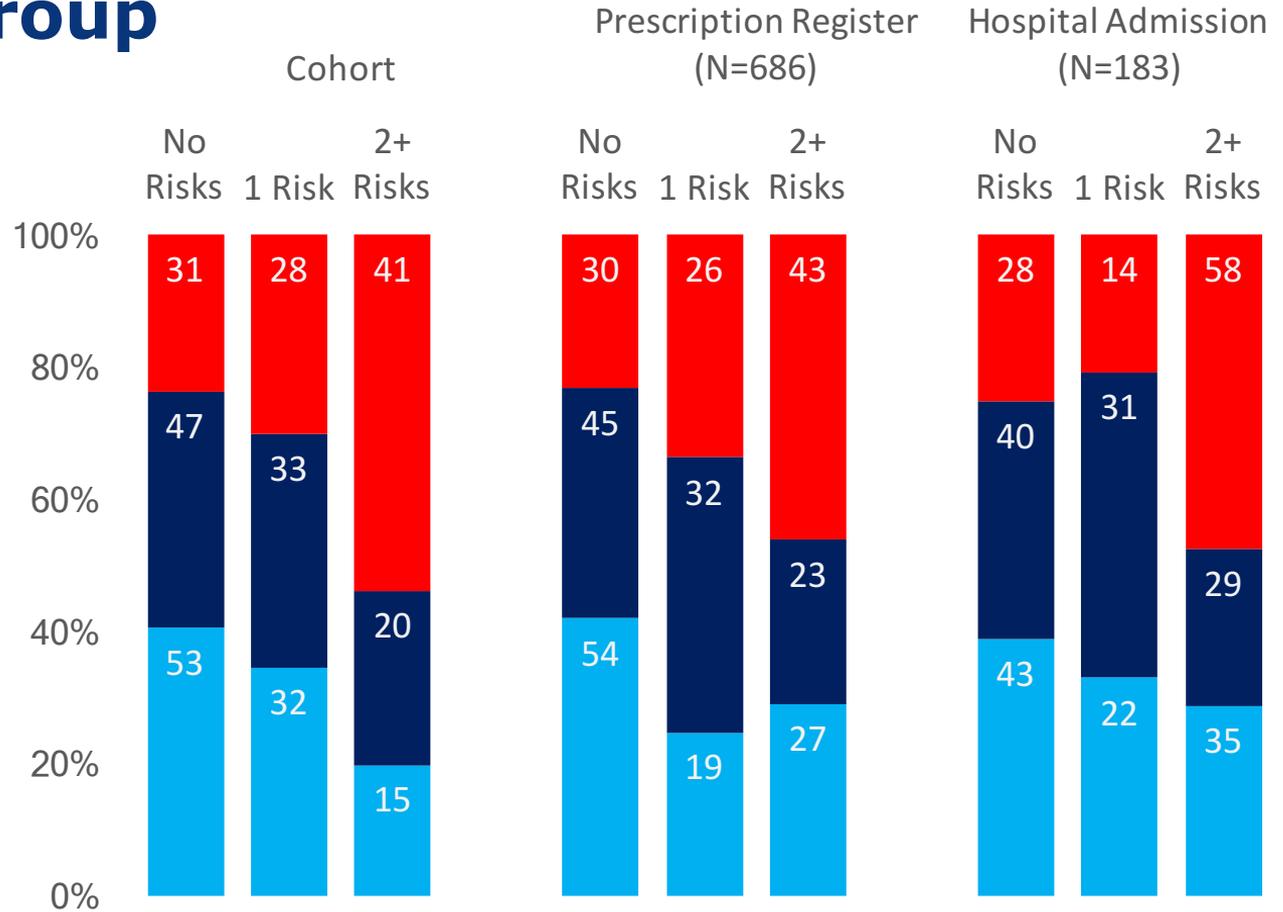
Belsky et al. 2017
Aging Cell

Personal-history risk assessment identifies fast-aging group

Pace of Aging



Belsky et al. 2017
Aging Cell



Part 2 Summary

- The rate of aging can be measured in healthy young adults
Repeated-measures clinical-exam and blood-test data can track aging-related changes decades in advance of disease onset
- The aging rate in healthy young adults is already variable
- A faster rate of aging correlates with deficits in physical and cognitive function and subjective signs of aging
- Midlife aging rate has origins in childhood
Possible to screen participants to balance enrollment in geroprotector trials

Outline

Introduction

Biological aging is a treatment target for healthspan extension

Part 1. Human trials of geroprotectors

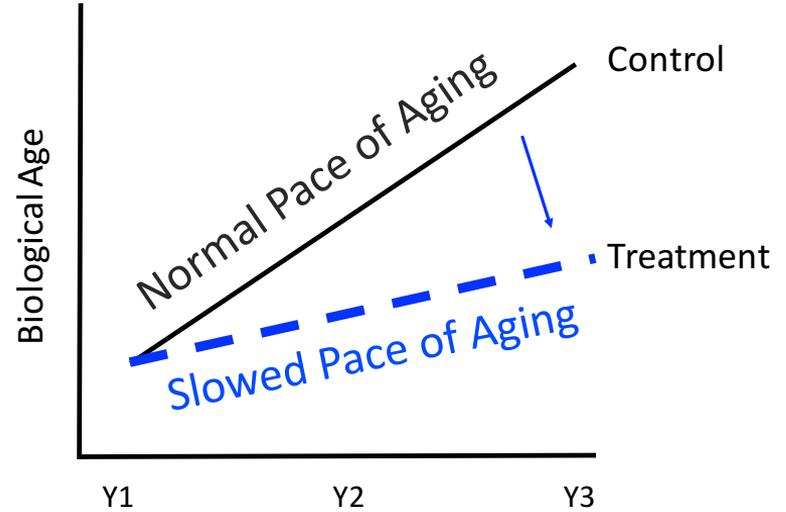
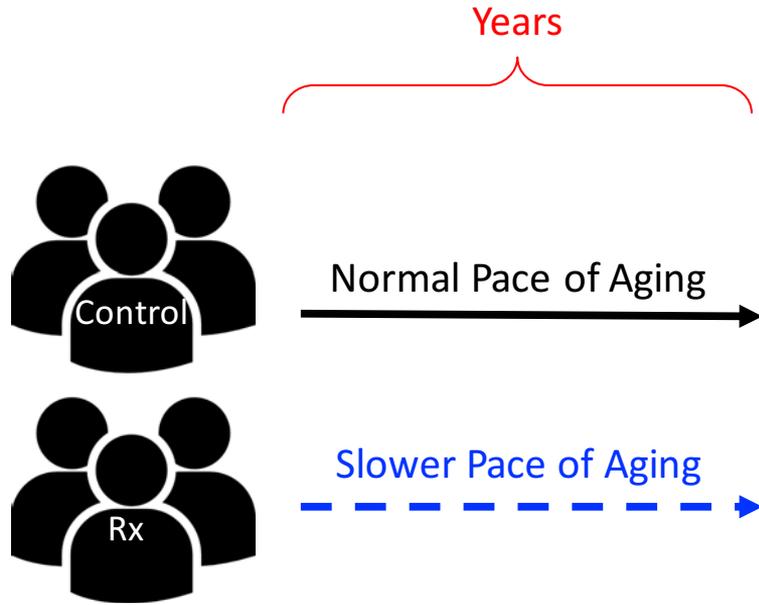
Challenges & opportunities

Part 2. Quantification of biological aging in young adults

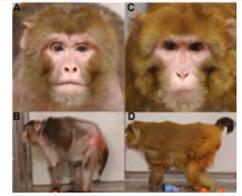
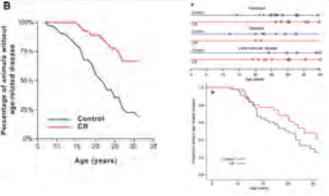
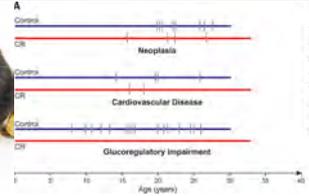
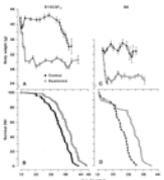
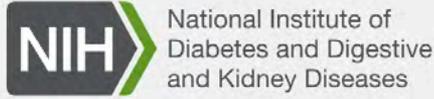
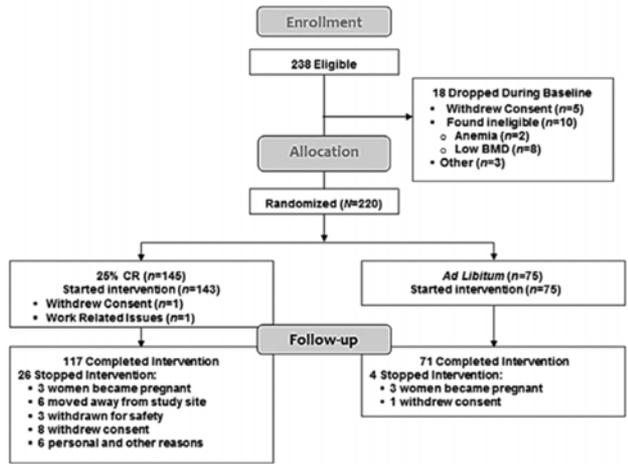
Part 3. Testing biological aging in a geroprotector trial

Conclusion

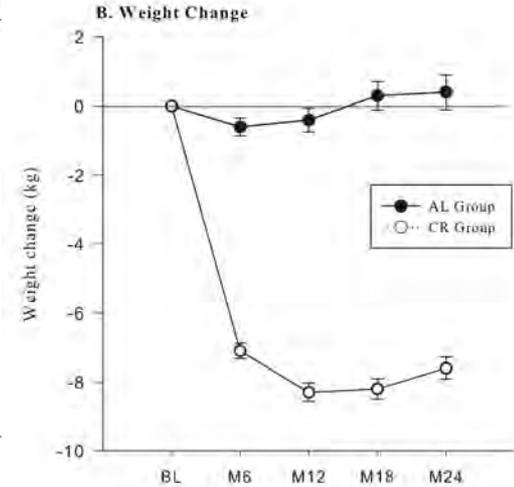
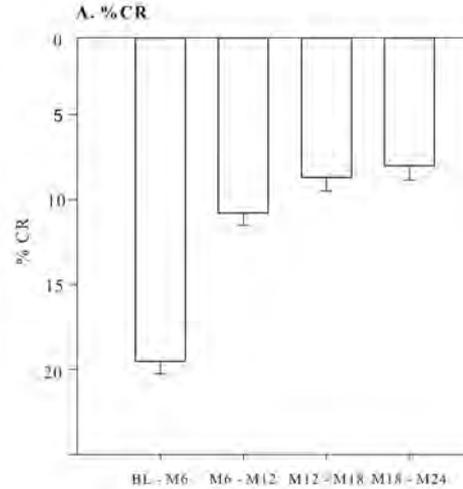
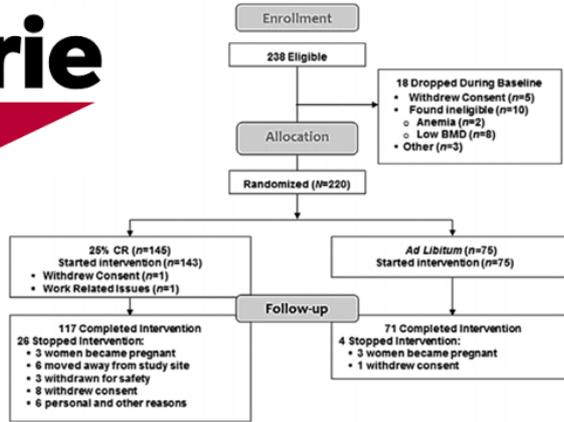
Alternative Geroprotector Trial Design



<https://calerie.duke.edu/>



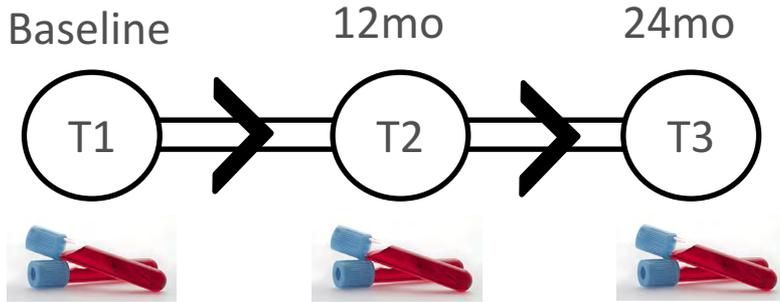
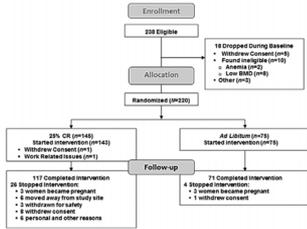
Weindruch & Walford 1982 Science
 Colman et al. 2009 Science
 Mattison et al. 2014 Nature
 Colman et al. 2014 Nat Comm



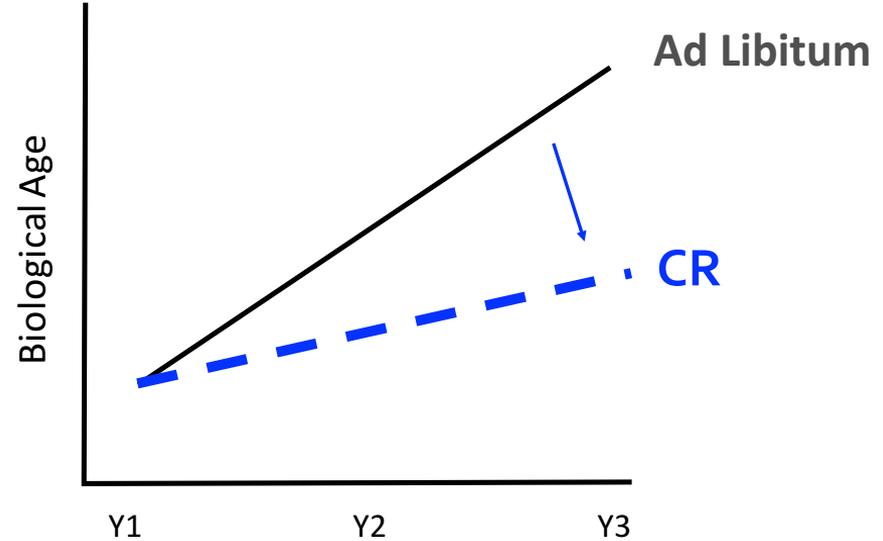
Ravussin et al. 2015 *JGMS*

N=145 Randomized to 25% CR (12% achieved)

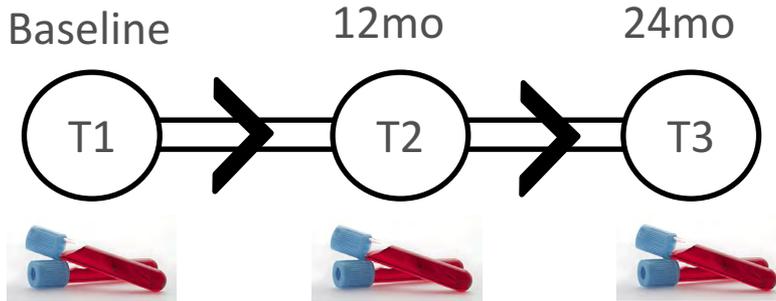
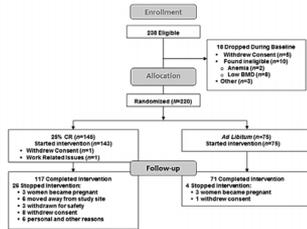
N=75 Randomized to AL (2% CR on average)



Hypothesis



Belsky et al. 2017 *JGBS*



Belsky et al. 2017 *JGBS*

Repeated measures of biological age

- Klemra-Doubal method Biological Age
- Homeostatic Dysregulation

Albumin
Alkaline Phosphatase
BUN
Creatinine
CRP
HbA1c (glucose)
SBP
Total cholesterol
Uric Acid
WBC

Biological Age

$$B_{EC} = \frac{\sum_{j=1}^m (x_j - q_j) \frac{k_j}{s_j} + \frac{C}{s_B}}{\sum_{j=1}^m \left(\frac{k_j}{s_j}\right)^2 + \frac{1}{s_B}}$$

$$D_M(\vec{x}) = \sqrt{(\vec{x} - \vec{\mu})^T S^{-1} (\vec{x} - \vec{\mu})}$$



Y1

Y2

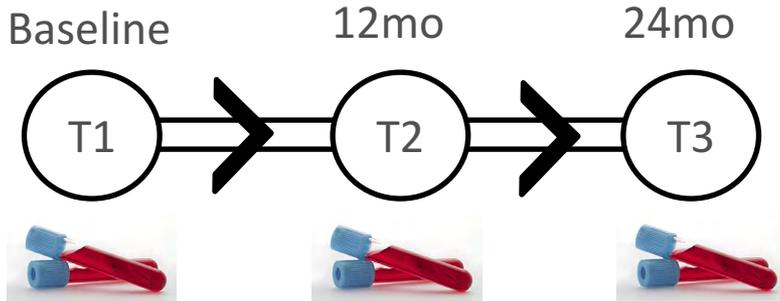
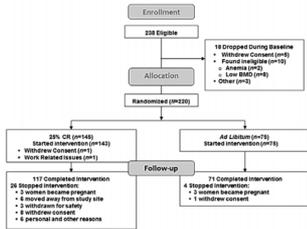
Y3

Klemra & Doubal 2006 *Mech Ag Dev*

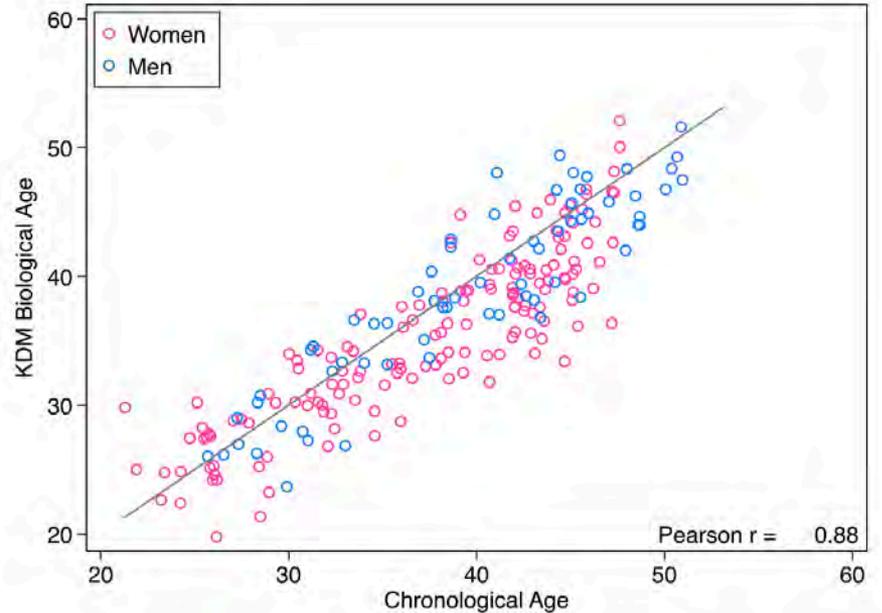
Levine 2013 *JGBS*

Cohen et al. 2013 *Mech Ag Dev*

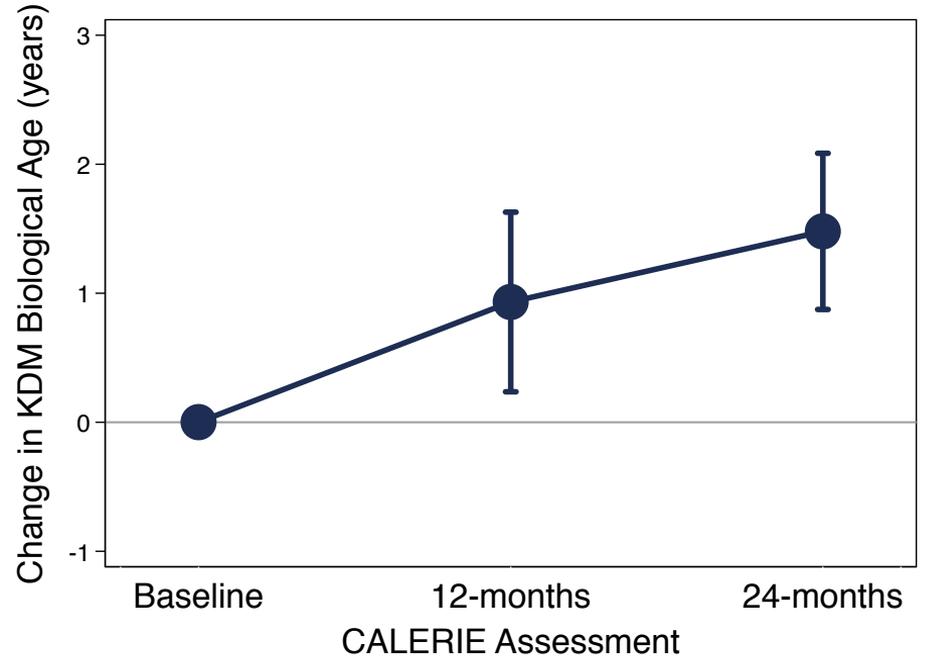
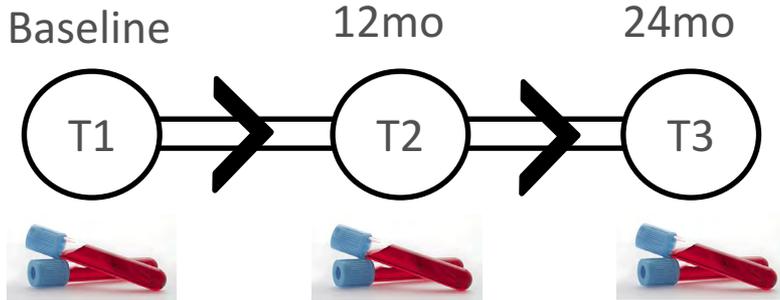
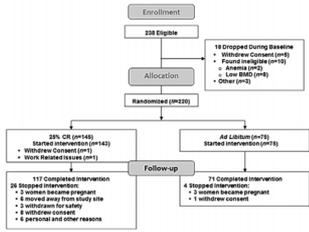
Li et al. 2015 *Aging Cell*



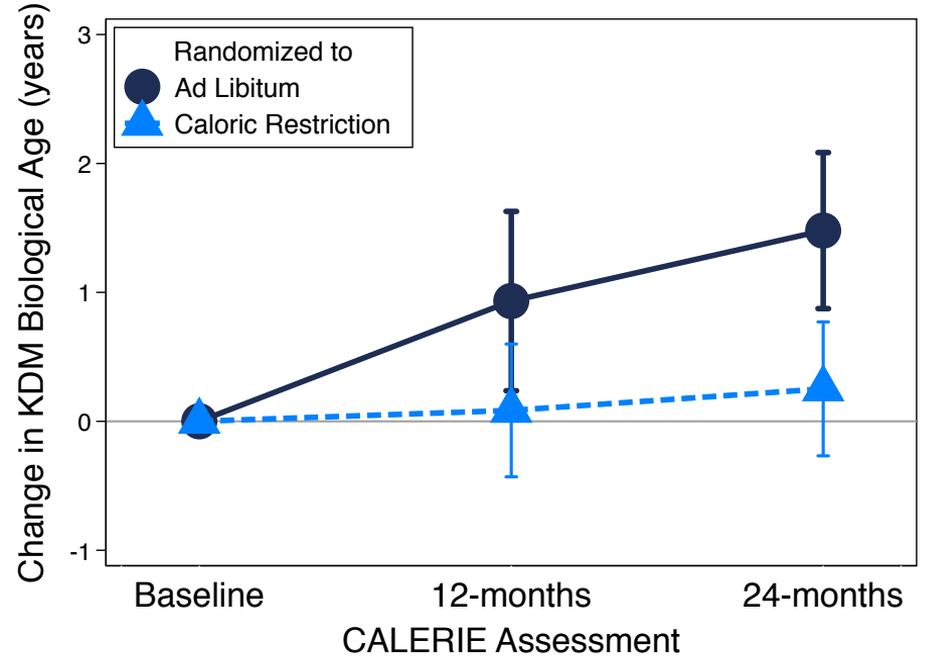
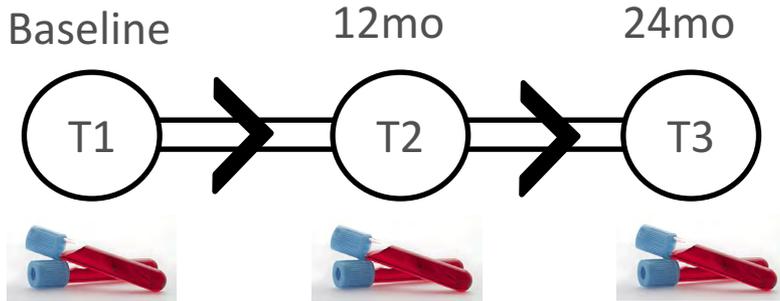
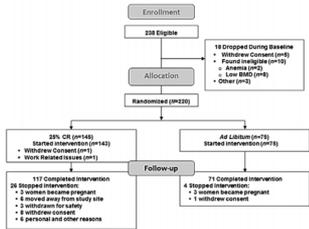
Klemera-Doubal method Biological Age at baseline



Belsky et al. 2017 *JGBS*



Belsky et al. 2017 *JGBS*



Belsky et al. 2017 *JGBS*

Part 3 Summary

- Moderate ($\sim 10\%$) CR slows the rate of biological aging as measured from physiology
- Implementation of biological aging measures within already-collected data from RCTs can advance validation efforts
- Long-term follow-up will be needed (and should be planned for)

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Conclusion

Conclusions

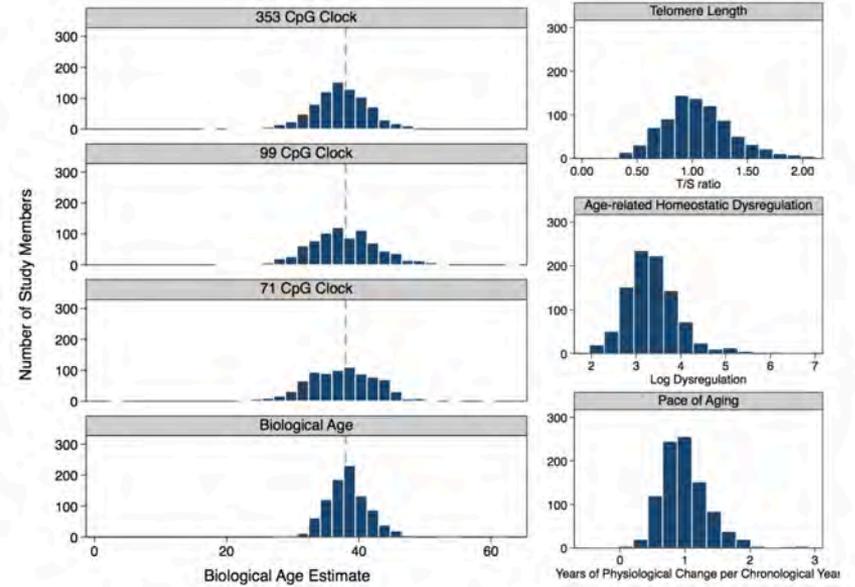
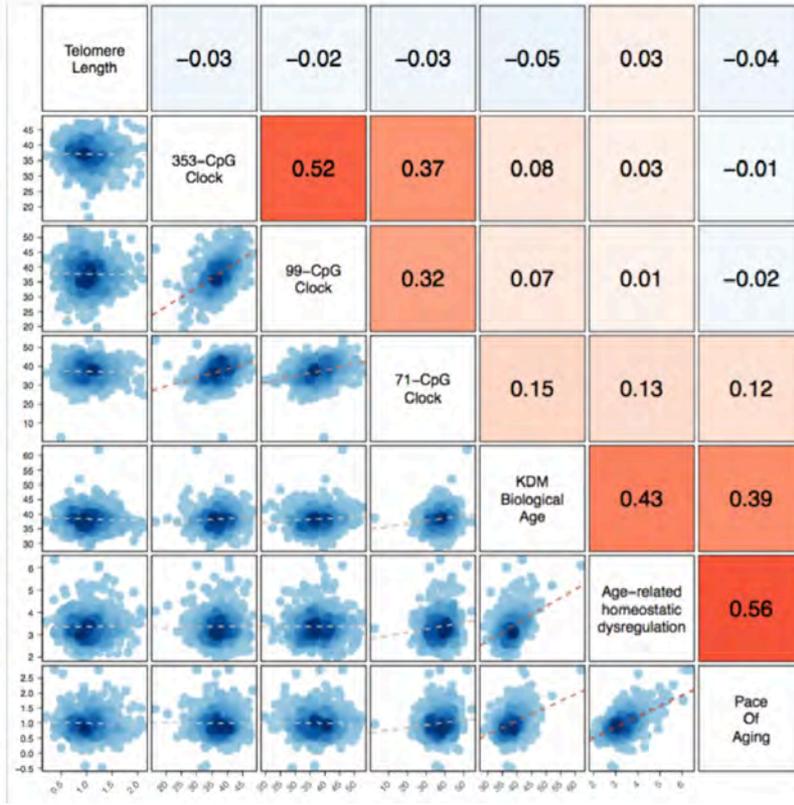
- Aging is a lifelong process with effects already manifest by midlife
- The midlife rate of aging is variable in apparently healthy adults

Interventions to slow aging should begin early

- The midlife rate of aging can be measured
- The midlife rate of aging can be modified (e.g. by CR)

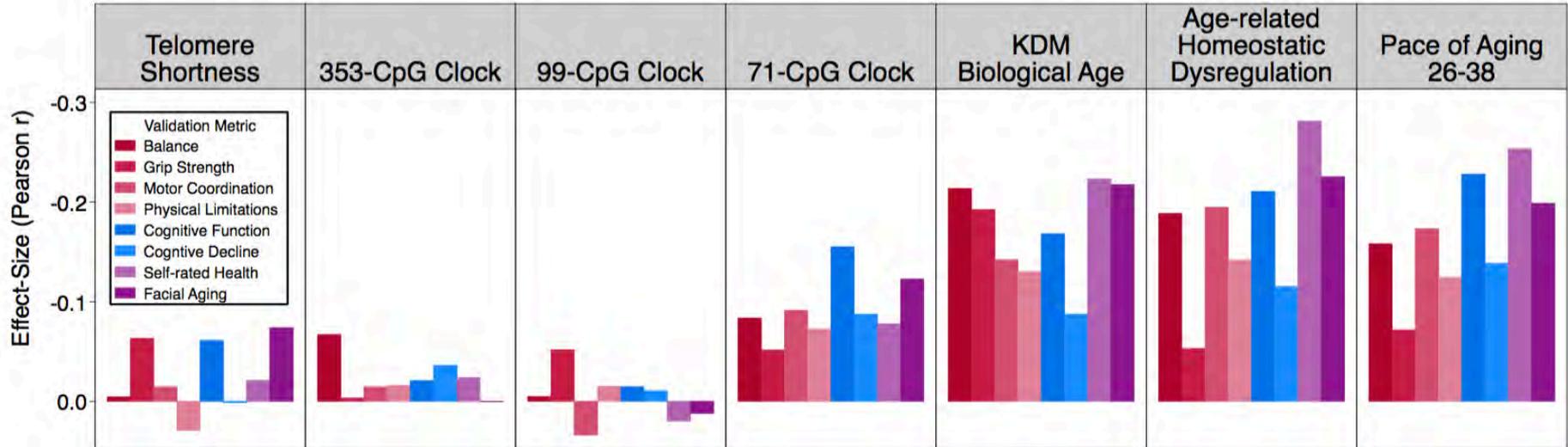
Geroprotector trials should consider the rate of change in biological age as a surrogate endpoint for healthspan extension

Not all measures of aging measure the same thing



Belsky et al. AJE 2017

Not all measures of aging measure the same thing



Next Steps

- Refine measures to quantify biological aging

Critical validation is that rate of change predicts healthspan

- Expand scope of intervention testing

Exercise trials and other lifestyle interventions are low hanging fruit

But Rx is the frontier



National Institute
on Aging



Thank You!



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and HUMAN DEVELOPMENT

