*Measuring Biologic Age*
**January 19-20, 2022**

**This meeting will be held virtually via Zoom.**

# How we Age

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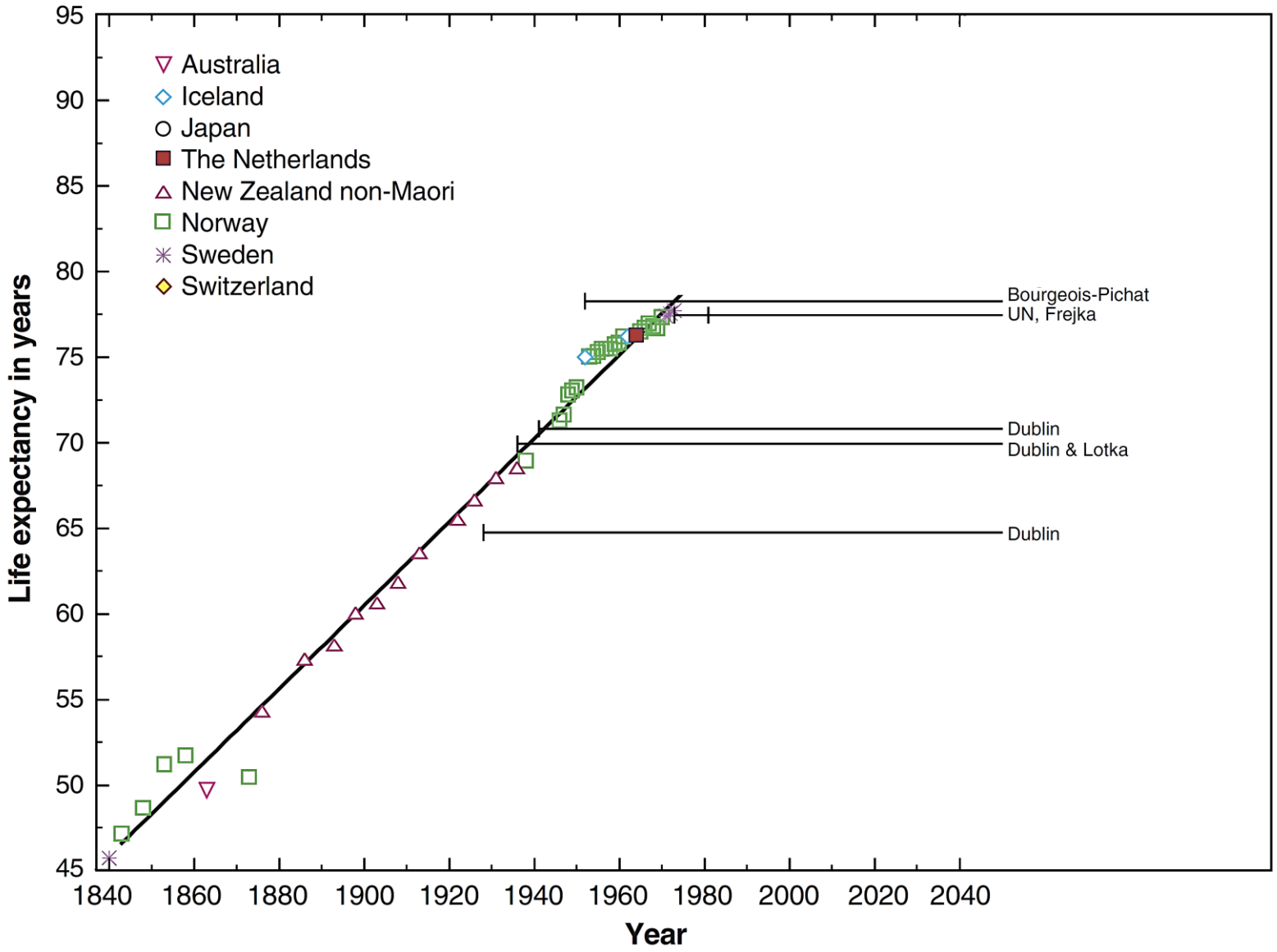
Intramural Research Program
National Institute on Aging, NIH
Baltimore - MD

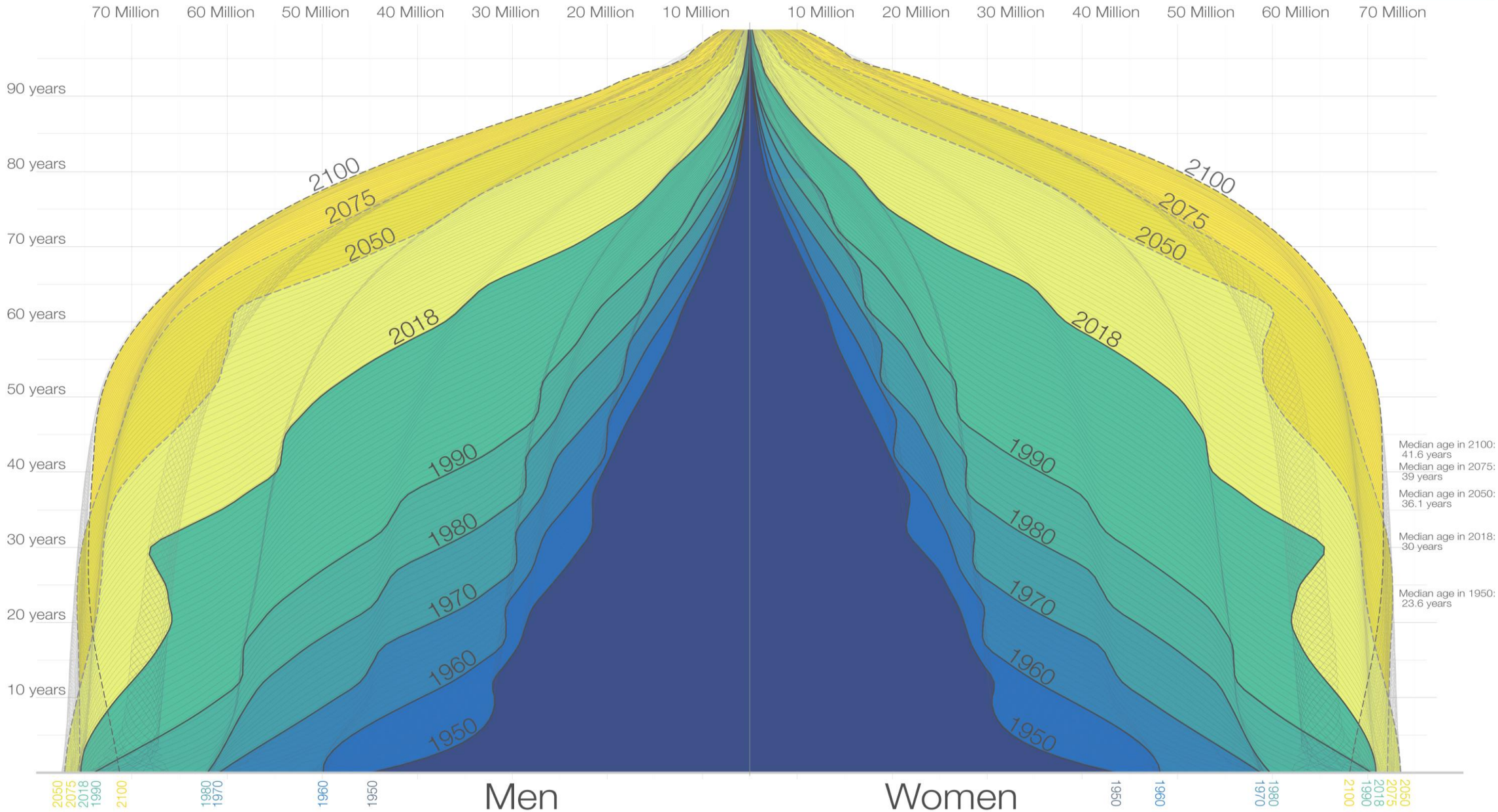
Record female life expectancy 1840 to the present. Horizontal black lines show asserted ceilings on life expectancy, with a short vertical line indicating the year of publication (Vaupel et al 2002).



# The Demography of the World Population from 1950 to 2100

Shown is the age distribution of the world population – by sex – from 1950 to 2018 and the *UN Population Division*'s projection until 2100.

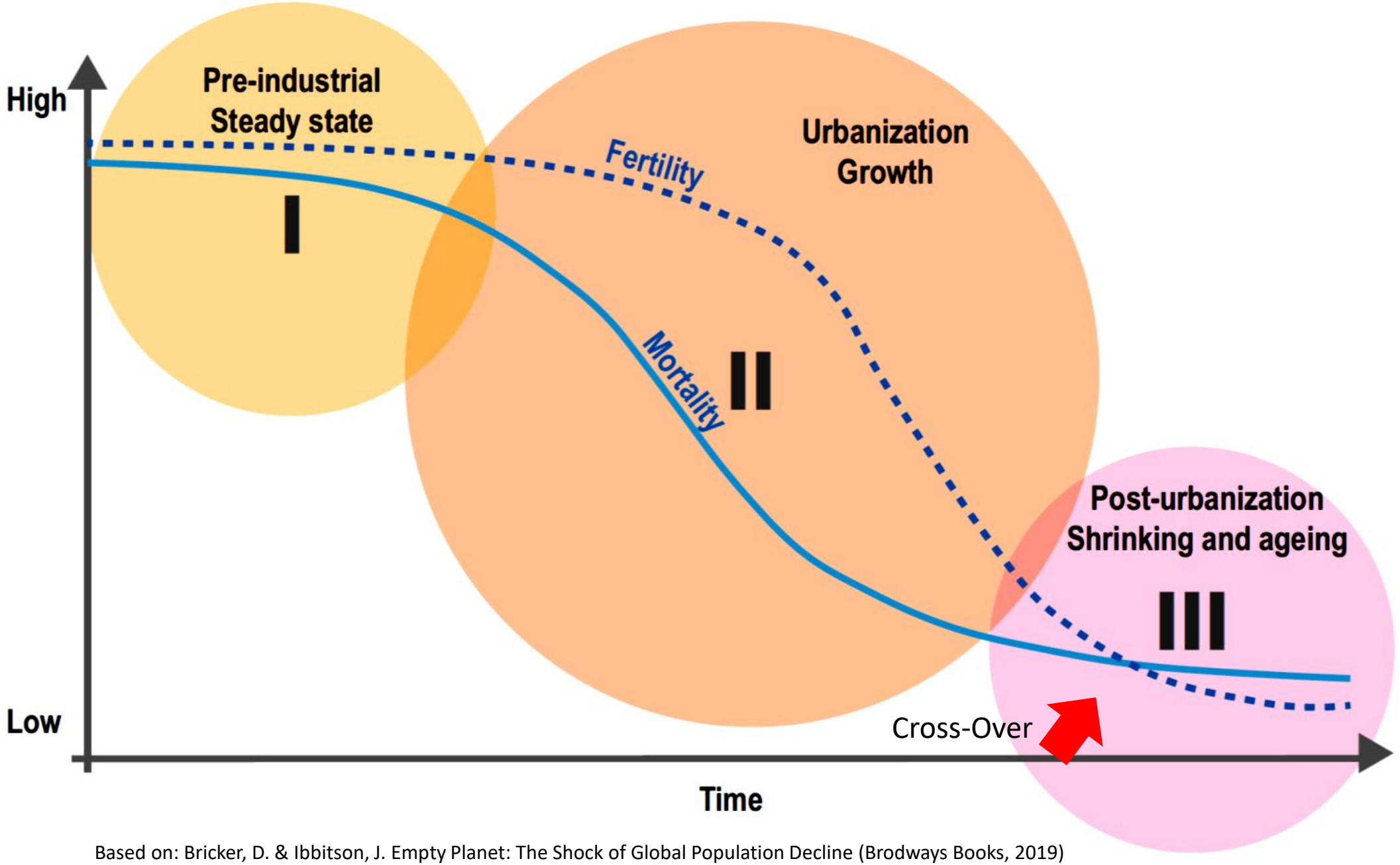
Our World in Data




Data source: United Nations Population Division – World Population Prospects 2017; Medium Variant.
The data visualization is available at OurWorldinData.org, where you find more research on how the world is changing and why.

Licensed under CC-BY by the author Max Roser.

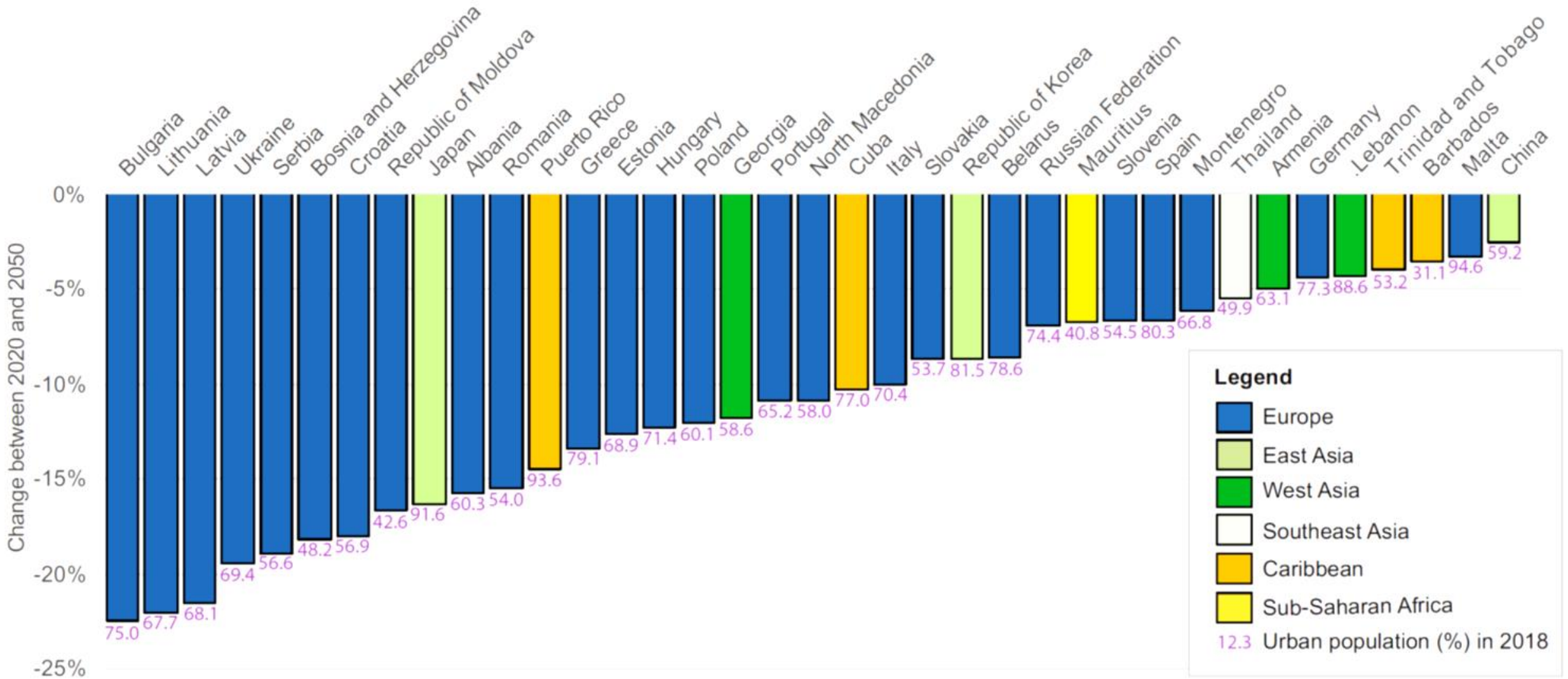
# Evolution of the Relative Levels of Mortality and Fertility Rates Over Time




Based on: Bricker, D. & Ibbitson, J. Empty Planet: The Shock of Global Population Decline (Brodways Books, 2019)

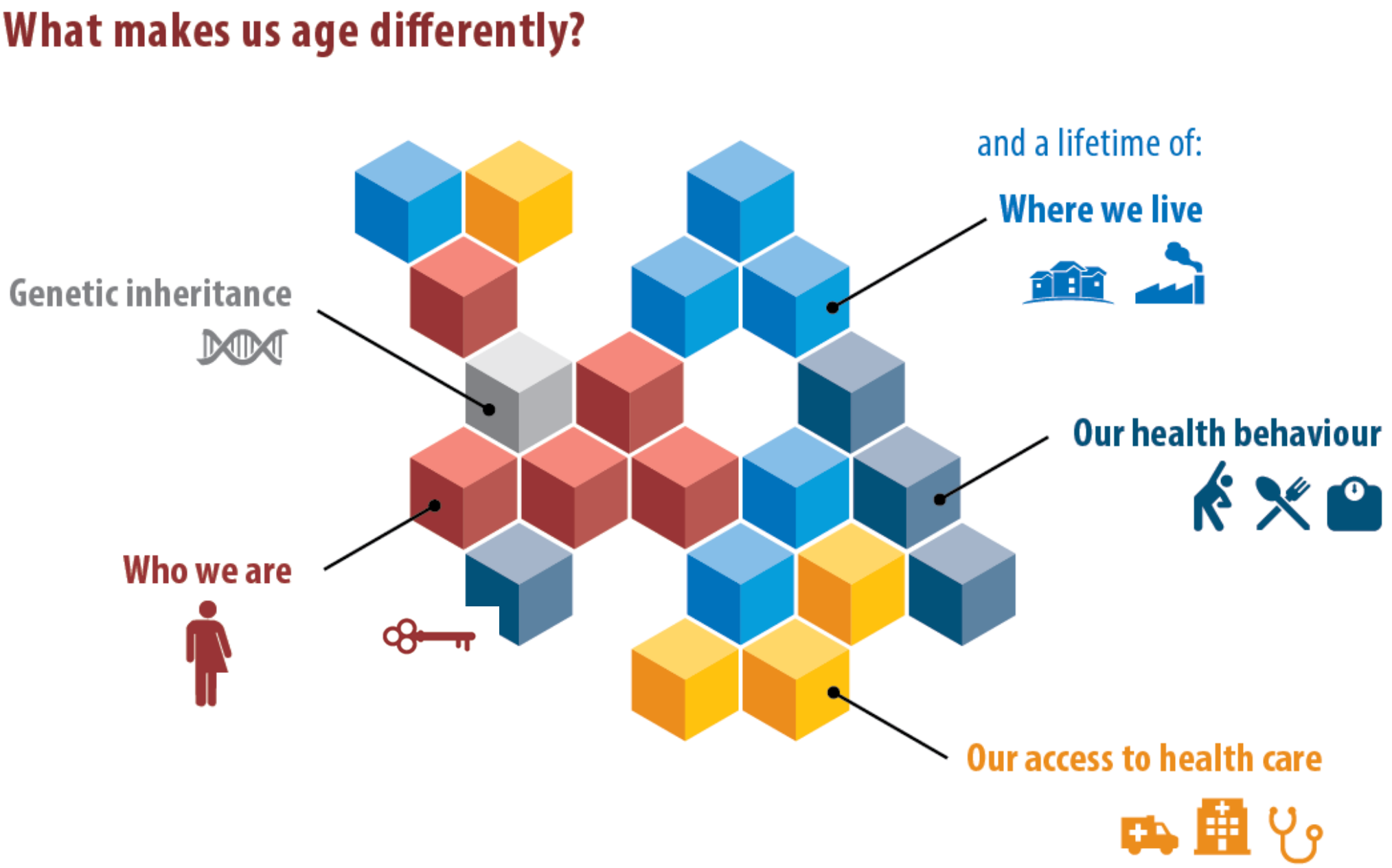
# Countries with the highest projected population shrinking by 2050.

**Note: The bars denote the projected fraction of population shrinking between 2020 and 2050 (in %)**

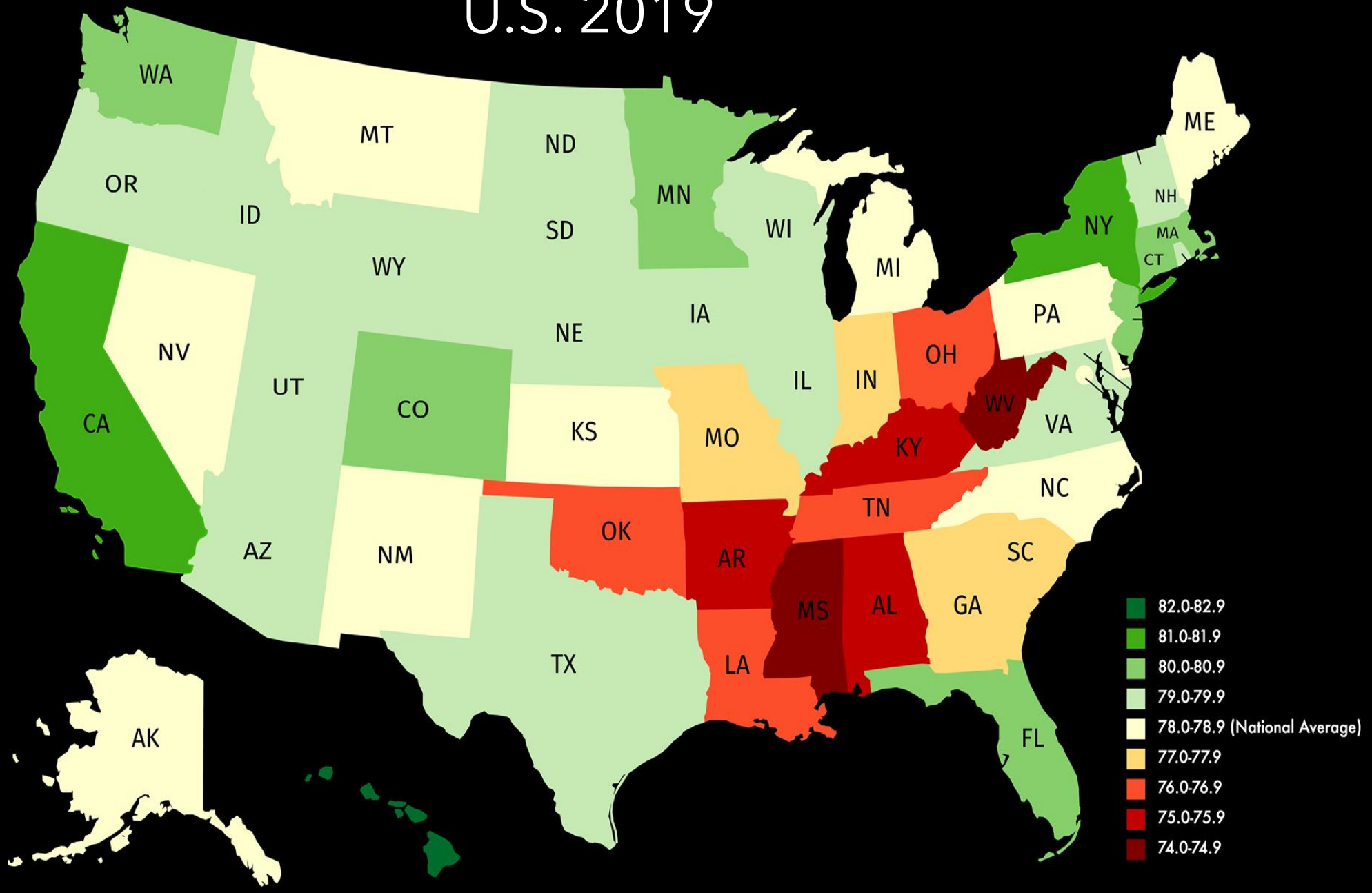



UN. Population Dynamics. World Population Dynamics. World Population Prospects 2019 Revision (United Nations, 2019).

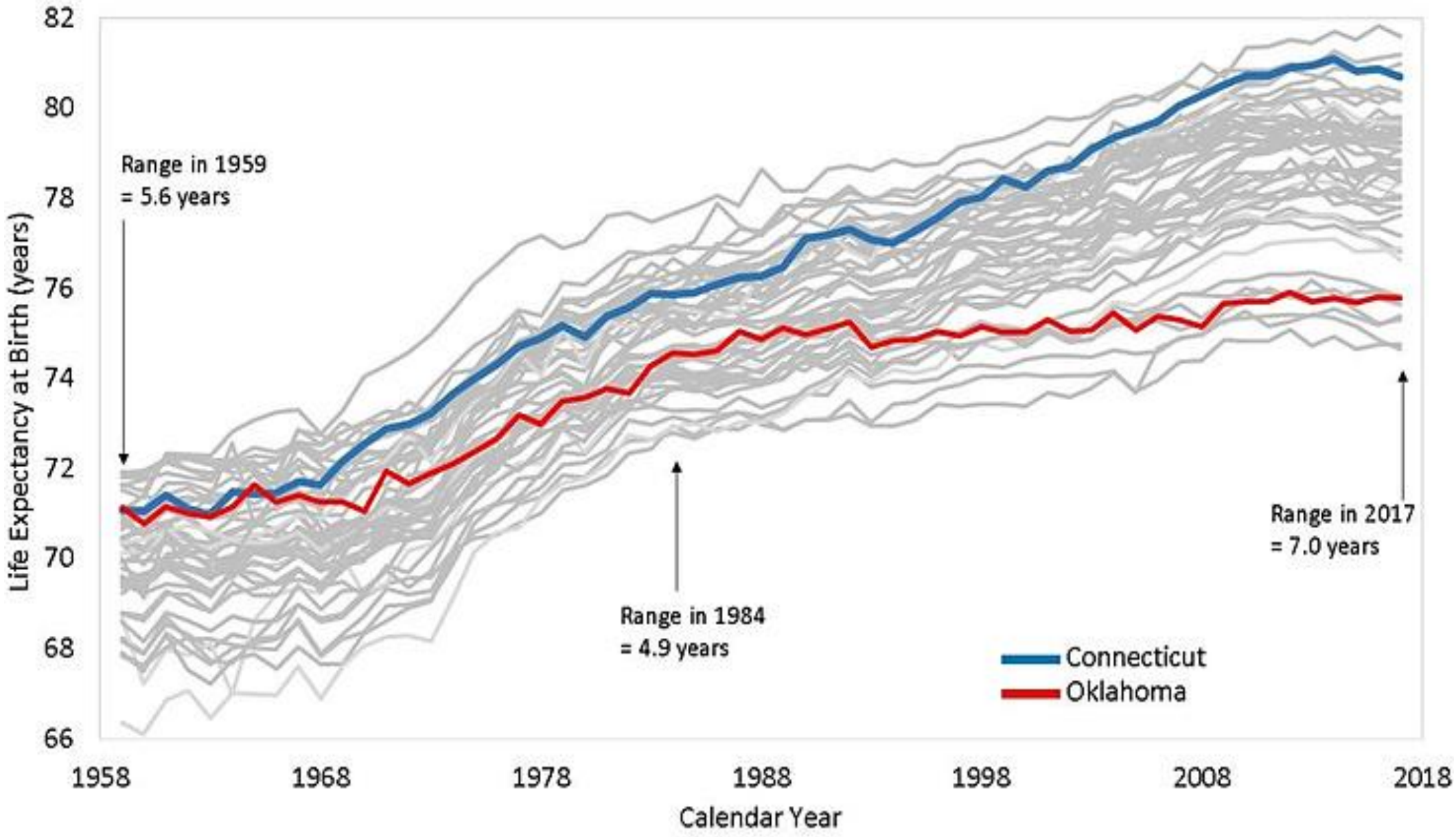
# Increases in Health and Longevity are not Random



# The Map of Longevity
# U.S. 2019

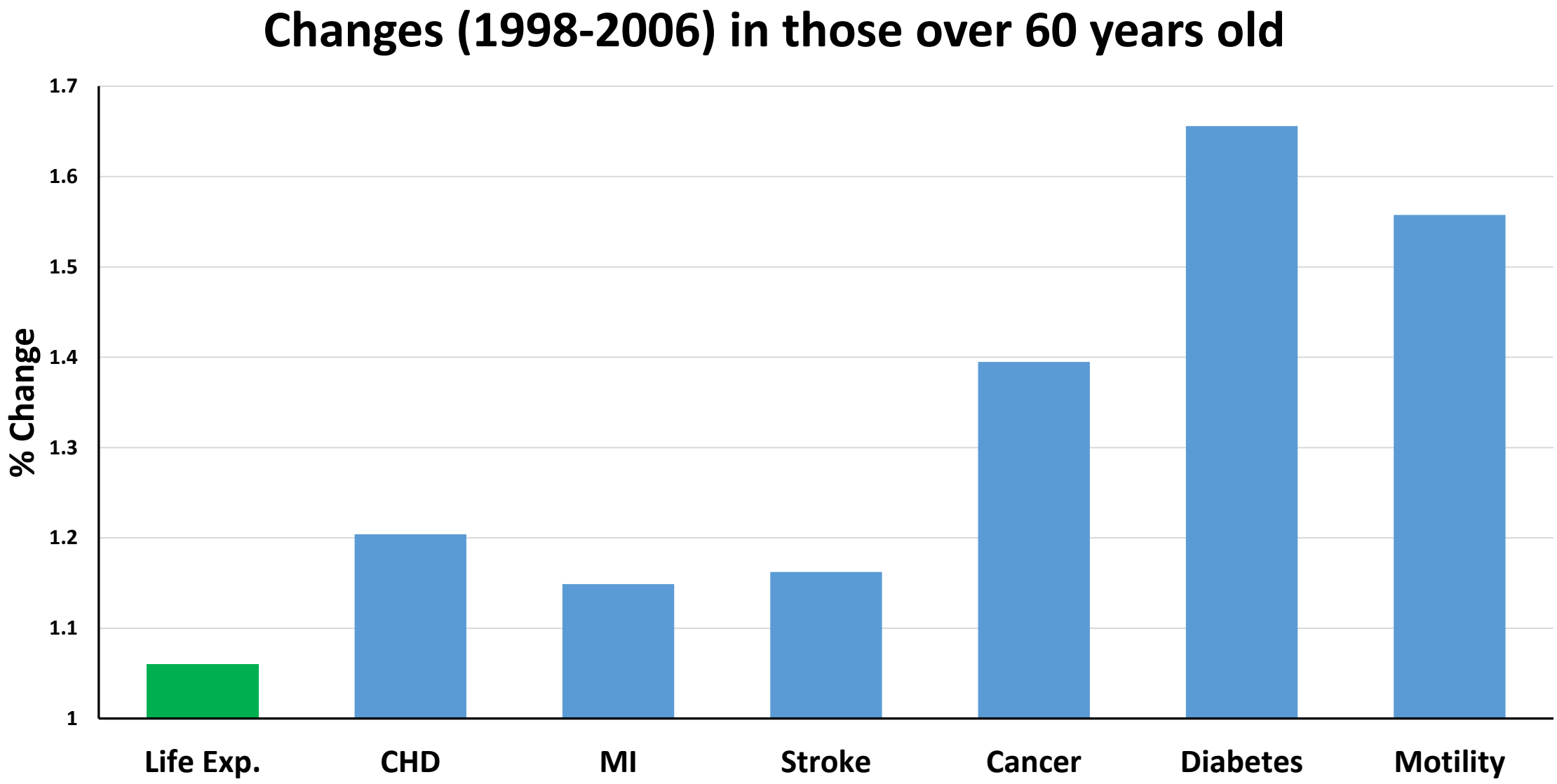


# Changes in Life Expectancy at Birth Between 1958 and 2018 in Different States



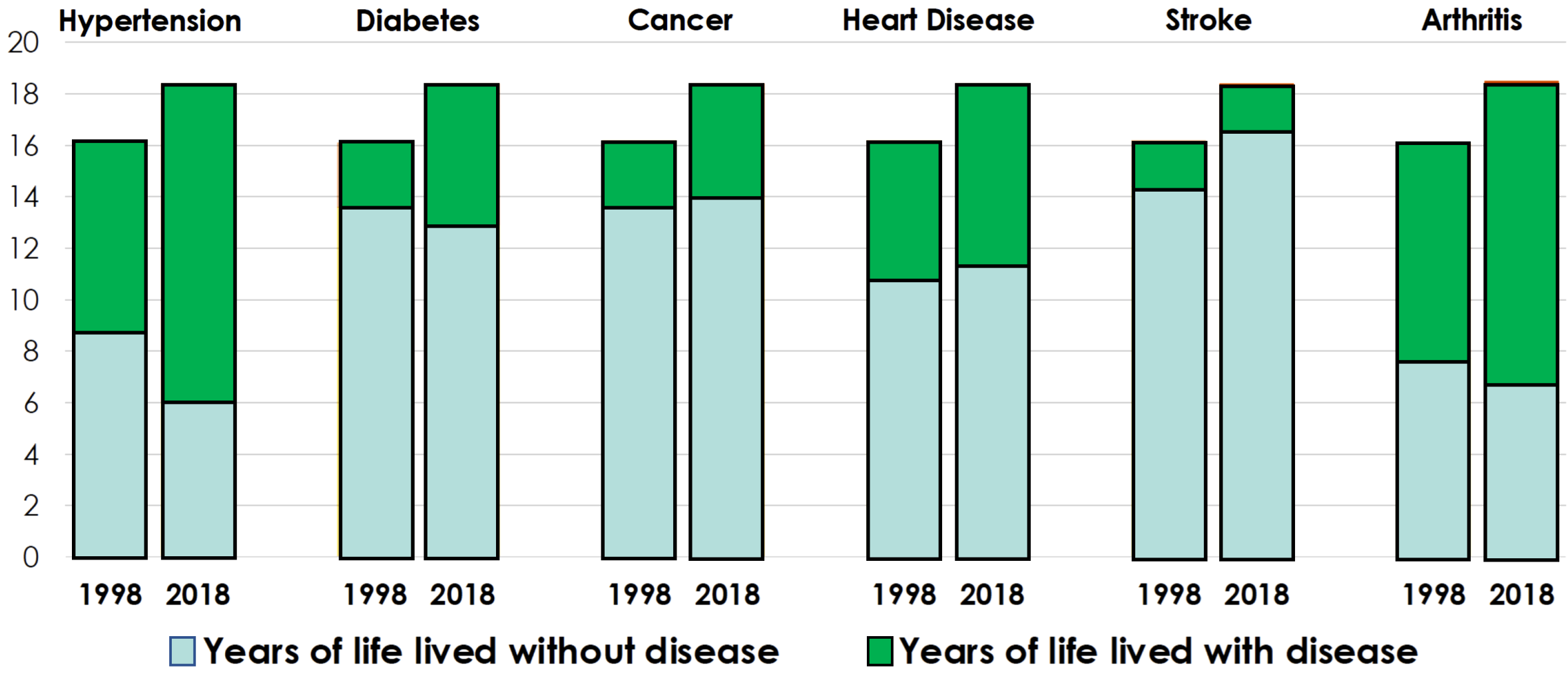

JENNIFER KARAS MONTEZ et al. he Milbank Quarterly, Volume: 98, Issue: 3, Pages: 668-699, First published: 04 August 2020, DOI: (10.1111/1468-0009.12469)

# The Increase in Lifespan is not Matched by Increases in Healthspan

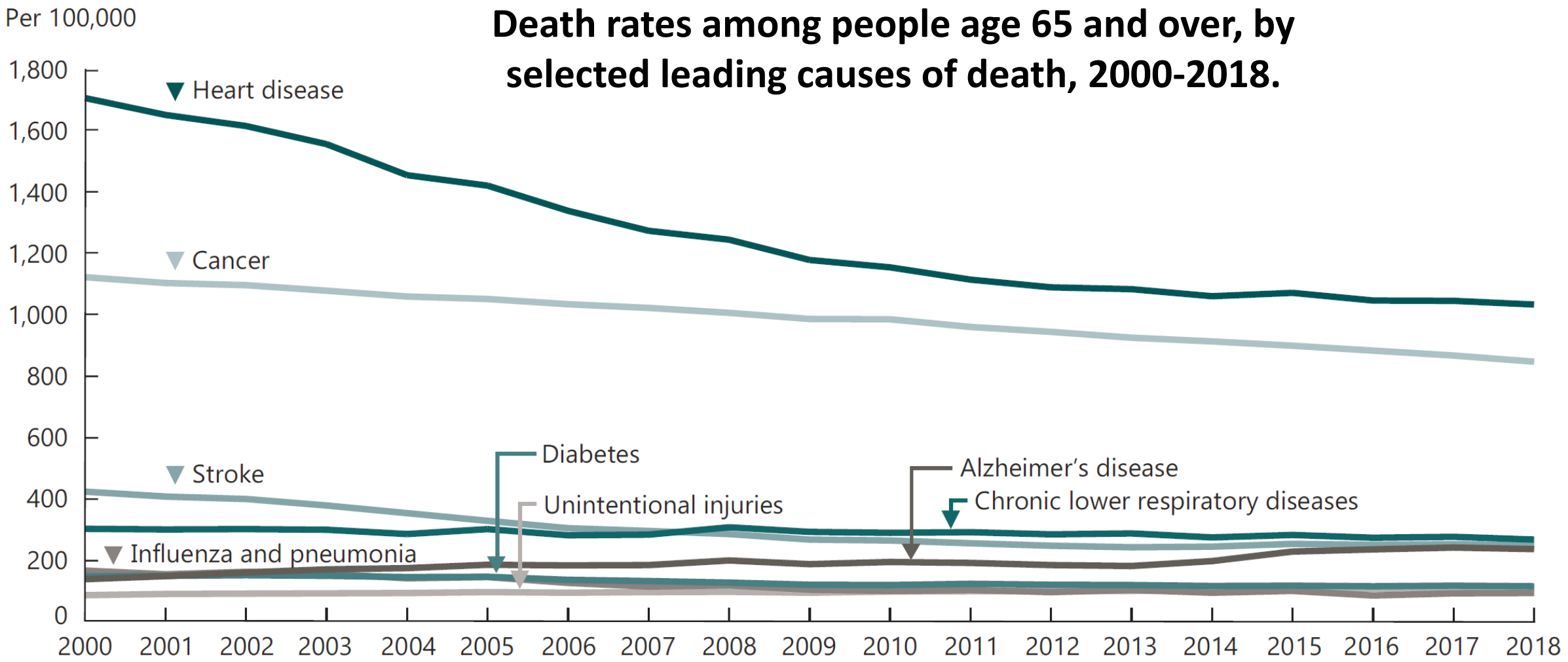



Modified from Crimmins and Beltrán-Sánchez – J. Gerontol B-66:75

# Increase over 20 years in the overall period of time that men over 65 in the U.S. lived with disease, HRS (E. Crimmins, PAA Presidential Address 2021)

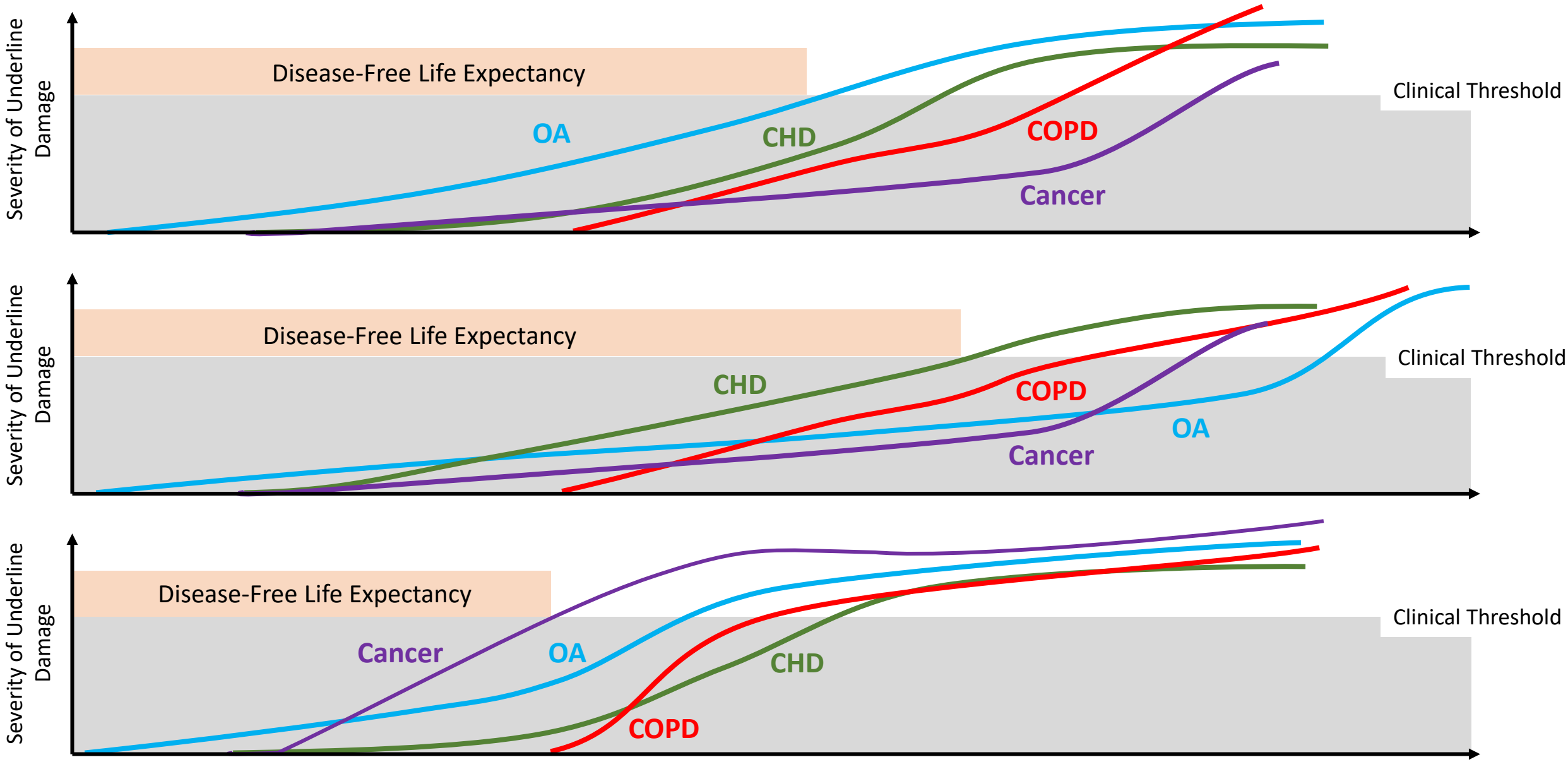


# The Decline of Mortality is Mostly Attributable to Cardiovascular Diseases and (to a lesser extent) Cancer. Chronic Complex Multimorbidity is on the Rise

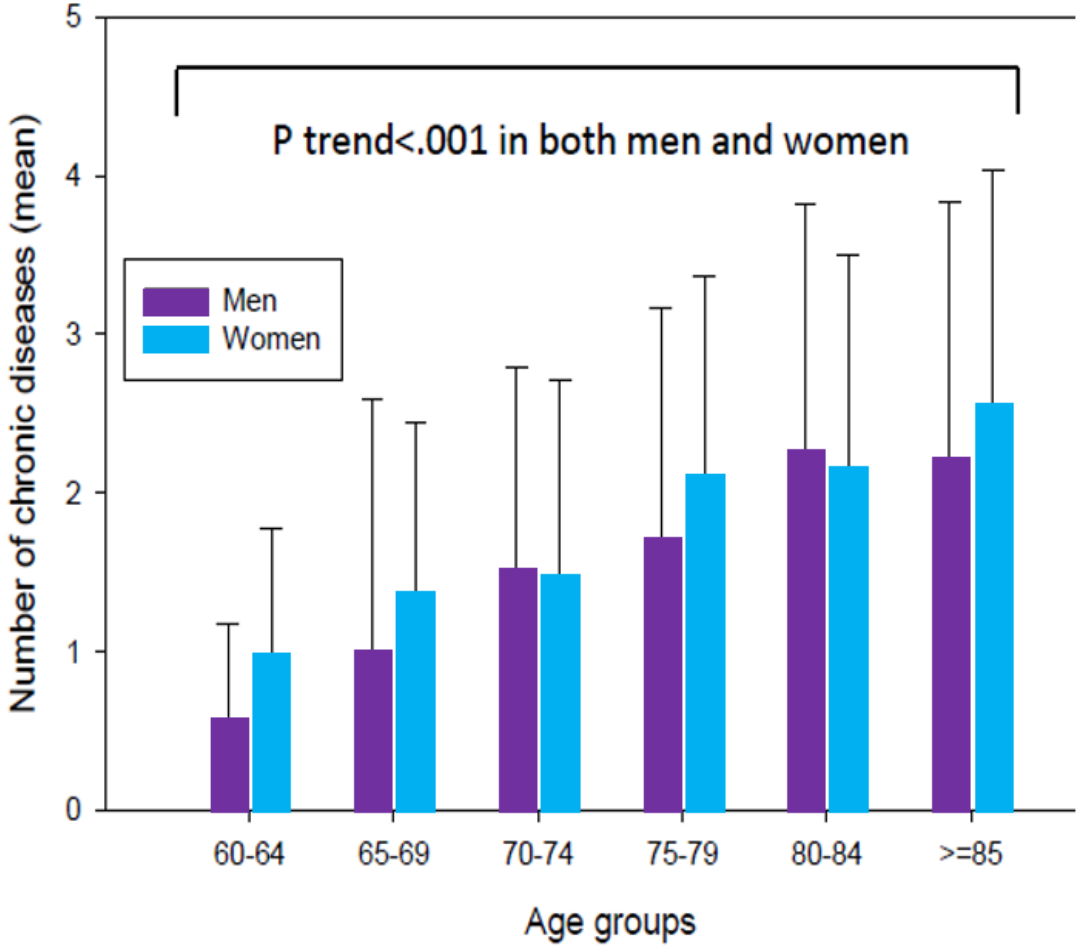


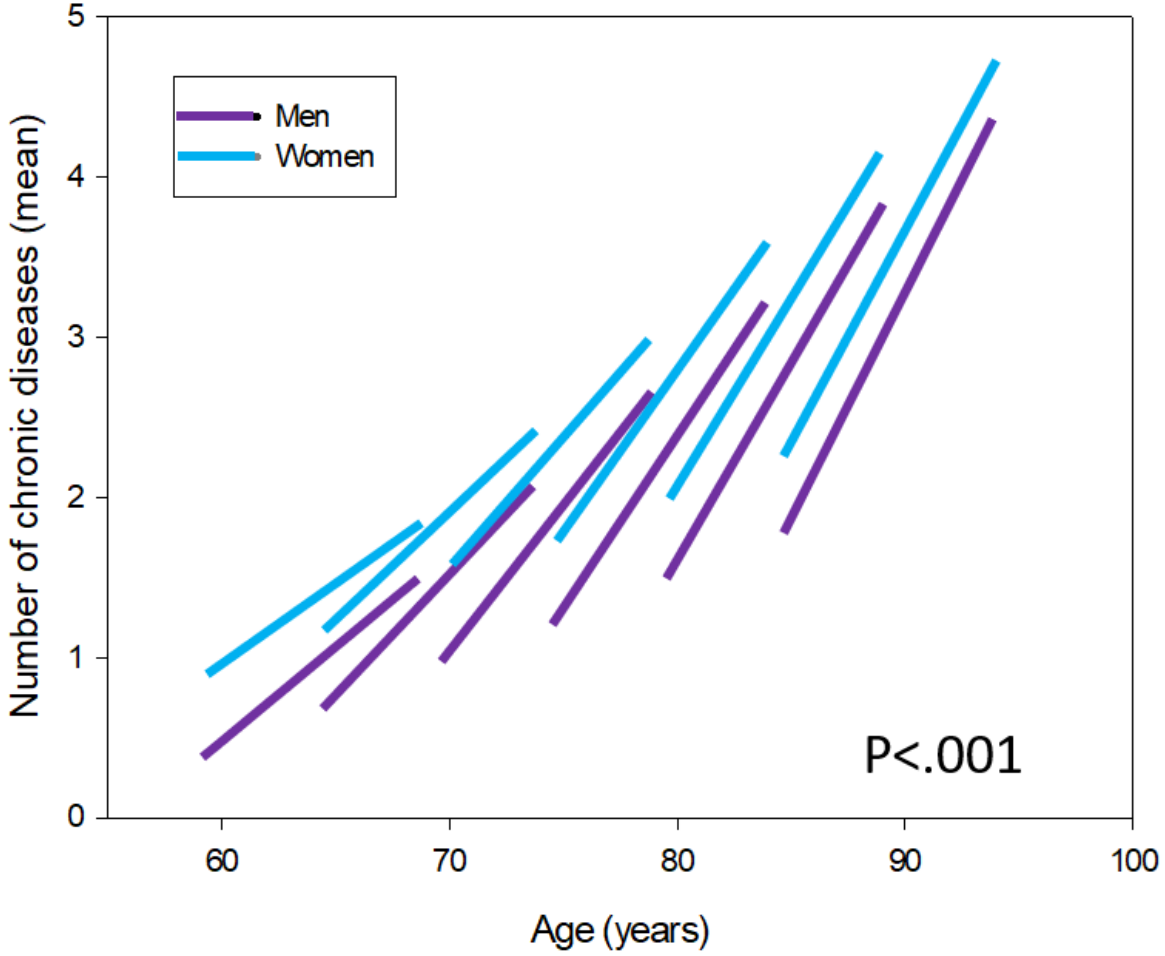

Rates are age adjusted using the 2000 U.S. standard resident population.
SOURCE: National Center for Health Statistics, National Vital Statistics System

# Aging is the Strongest Risk Factors for All major Age-Related Chronic Diseases



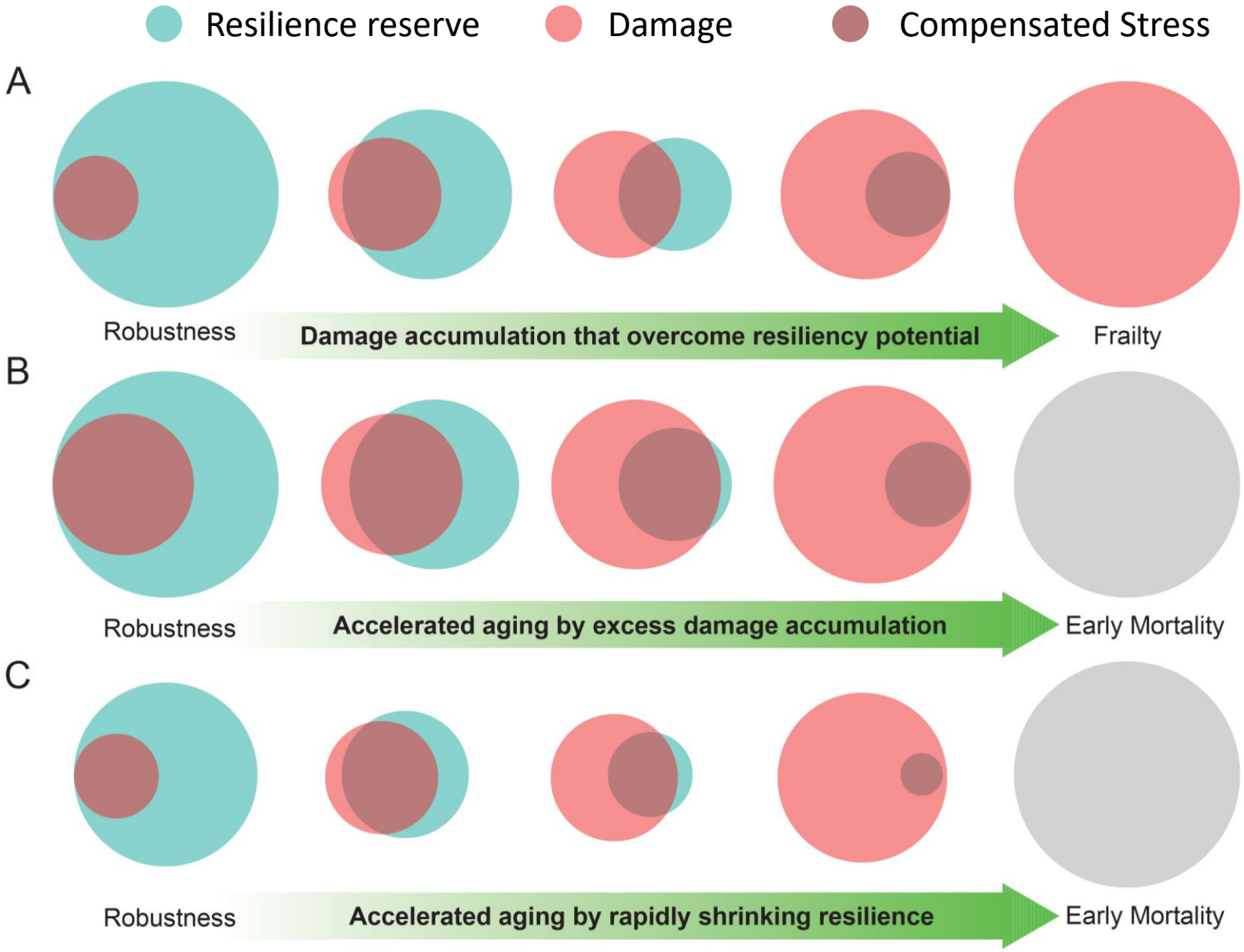
# Aging and Multimorbidity

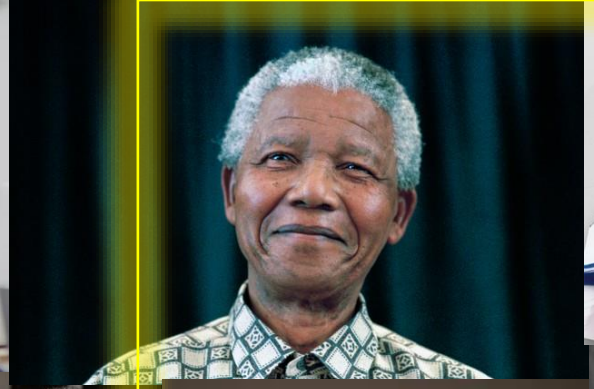


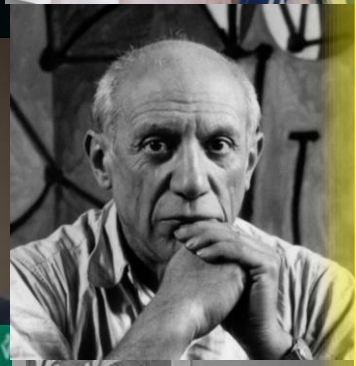



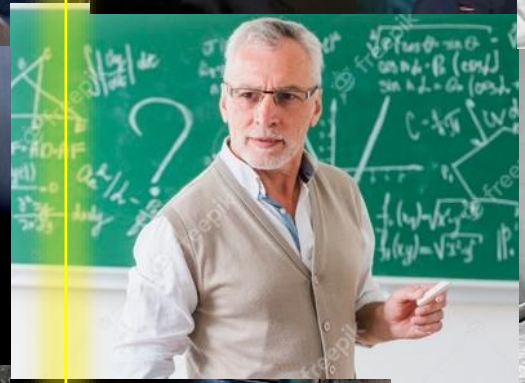
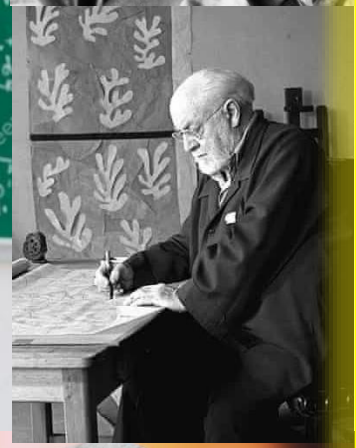

Fabbri E et al. J Gerontol A Biol Sci Med Sci. 2015 Jan;70(1):63-70

# A Model of Intrinsic Aging



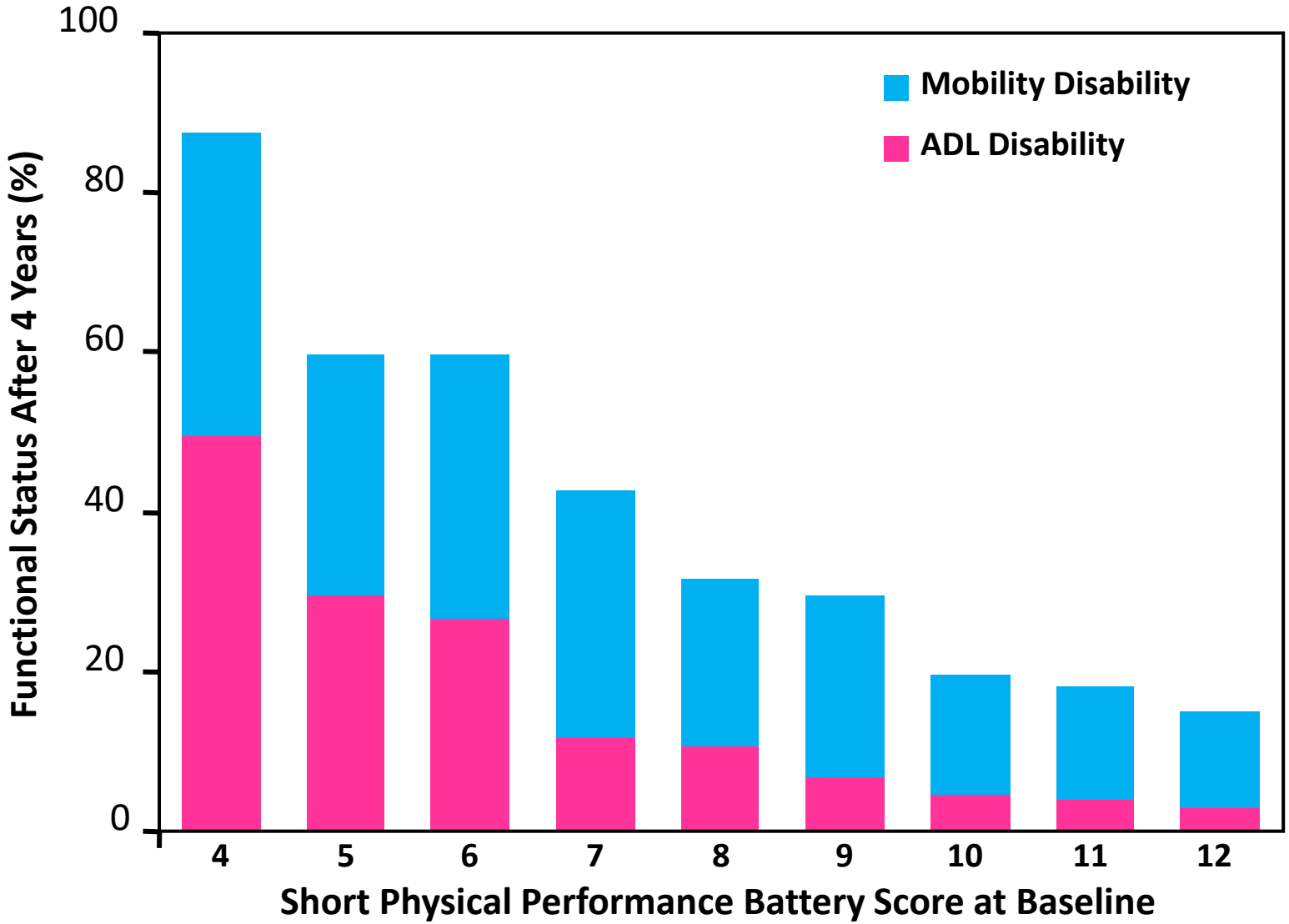




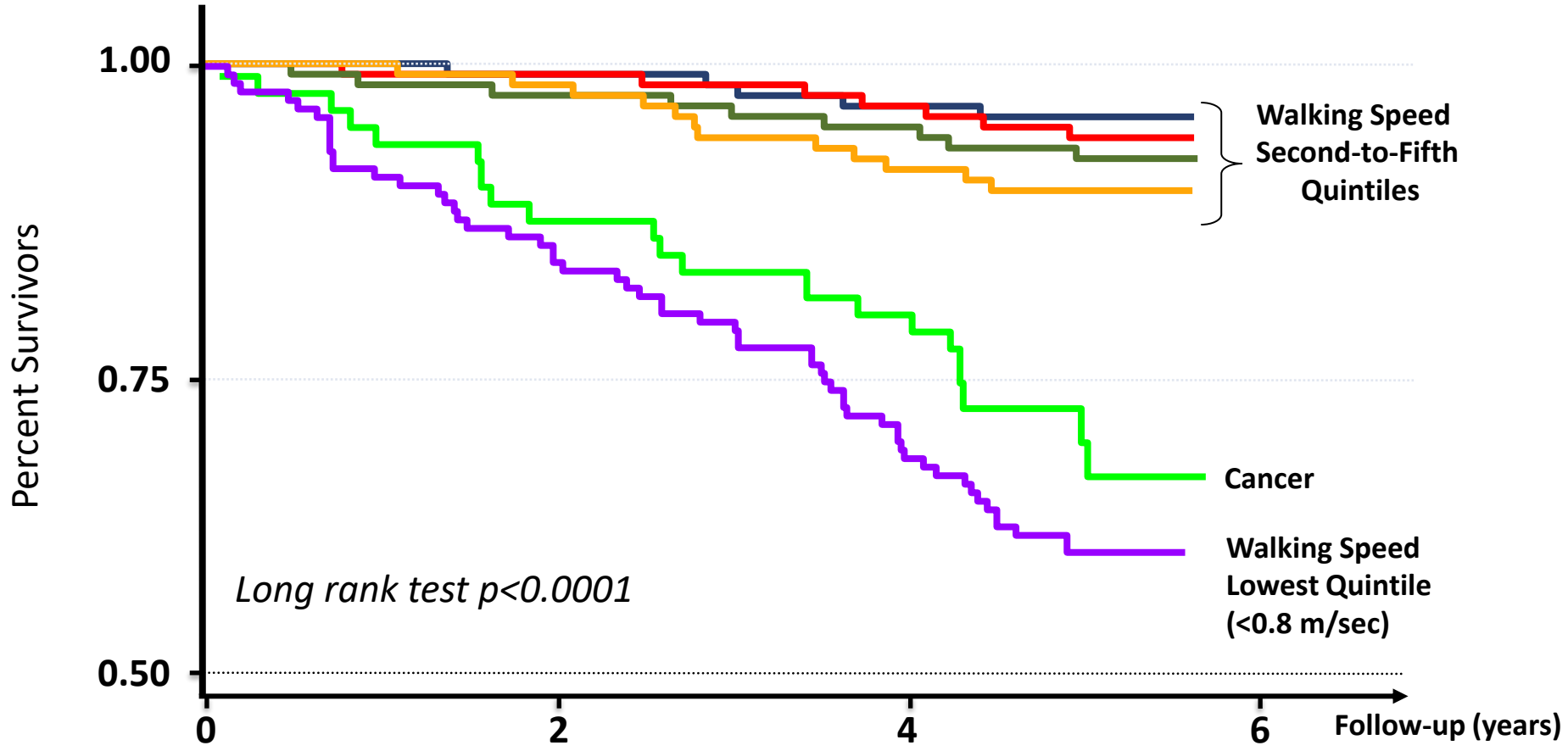
# LOWER-EXTREMITY FUNCTION IN PERSONS OVER THE AGE OF 70 YEARS AS A PREDICTOR OF SUBSEQUENT DISABILITY

JACK M. GURALNIK, M.D., PH.D., LUIGI FERRUCCI, M.D., PH.D., ELEANOR M. SIMONSICK, PH.D., MARCEL E. SALIVE, M.D., M.P.H., AND ROBERT B. WALLACE, M.D.



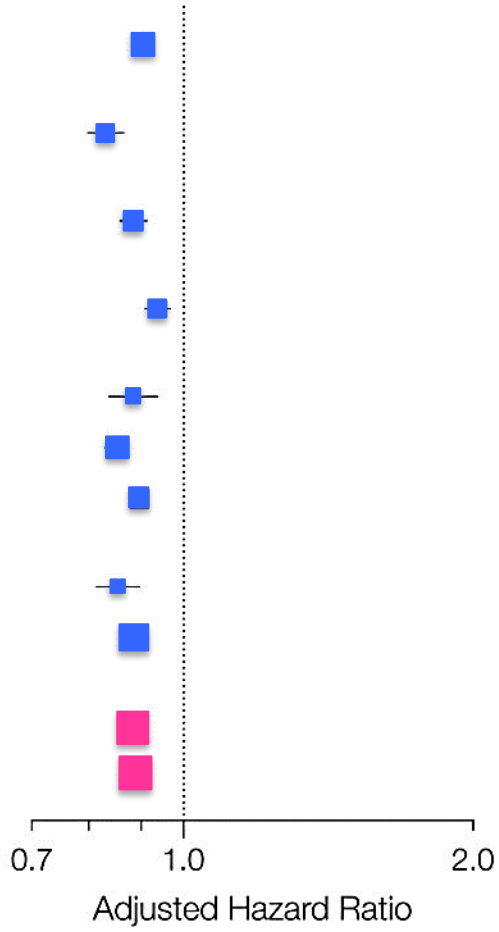

N Engl J Med 1995;332:556-61

# Walking Speed is a Powerful Predictor of Mortality



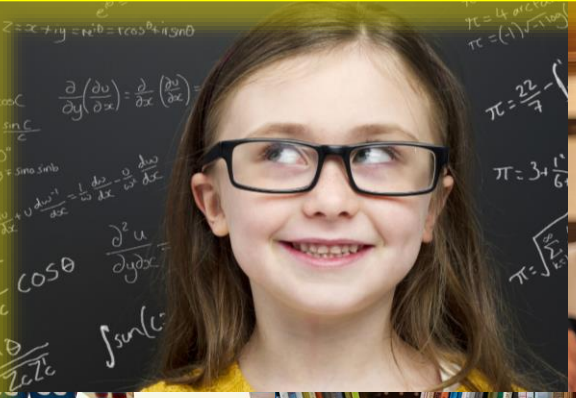
# Age-Adjusted Hazard Ratio for Death per 0.1-m/s Higher Gait Speed

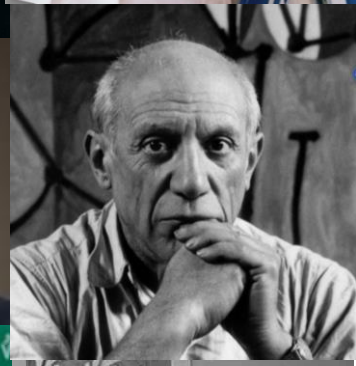
| | No. of Deaths | Total Sample Size |
|---|---|---|
| Cardiovascular Health Study,[22] 1991 | 3851 | 5801 |
| Established Populations for the Epidemiologies Study of the Elderly,[23] 1985 | 1955 | 2128 |
| Health, Aging, and Body Composition Study,[11,12] 2009, 2005 | 848 | 3048 |
| Hispanic Established Populations for Epidemiological Study of the Elderly,[13] 1999 | 972 | 1905 |
| Invecciare in Chianti,[17] 2000 | 187 | 972 |
| Osteoporotic Fractures in Men,[20] 2005 | 1073 | 5833 |
| Third National Health and Nutrition Examination Study,[21] 2004 | 2837 | 3958 |
| Predicting Elderly Performance,[28] 2003 | 293 | 491 |
| Study of Osteoporotic Fractures,[26] 1990 | 5512 | 10349 |
| Pooled (random effects) | | |
| Pooled (shared frailty model) | | |

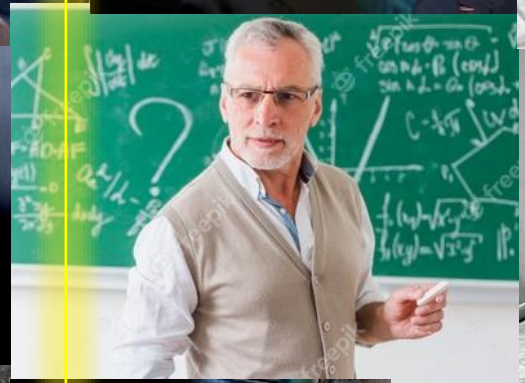
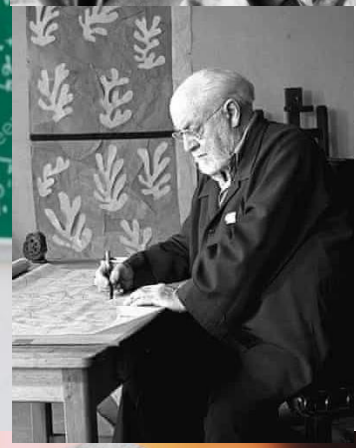



**Studenski, S. et al. JAMA 2011;305:50-58**

Copyright restrictions may apply.





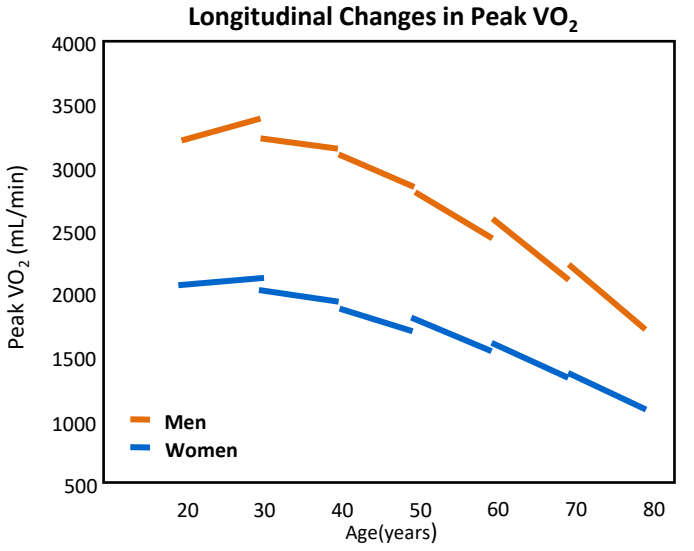
# Changes in Energy Regulation with Aging

- Lower Peak $VO_2$
- Lower Resting Metabolic Rate
- Greater energetic cost of walking

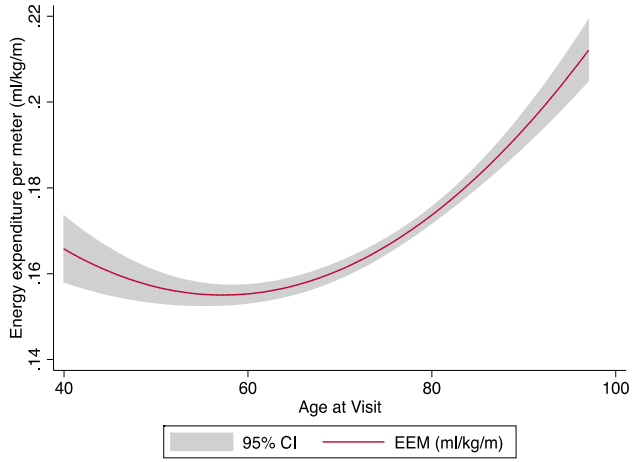
Energy Reserves Expressed as:

Cost of walking (ml/kg/min)

Peak $VO_2$ (ml/kg/min)

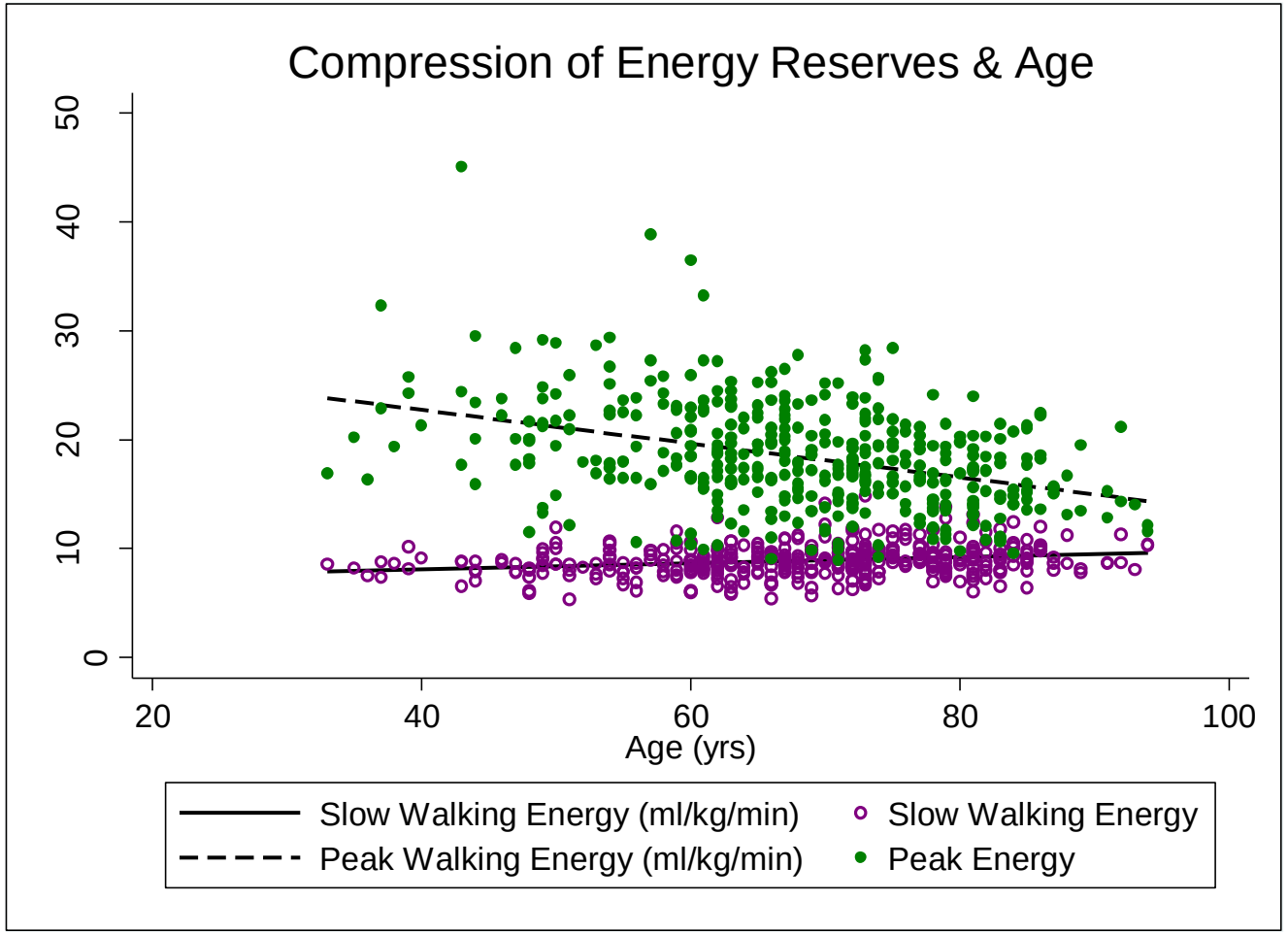



Fleg, et al, Circulation, 2005



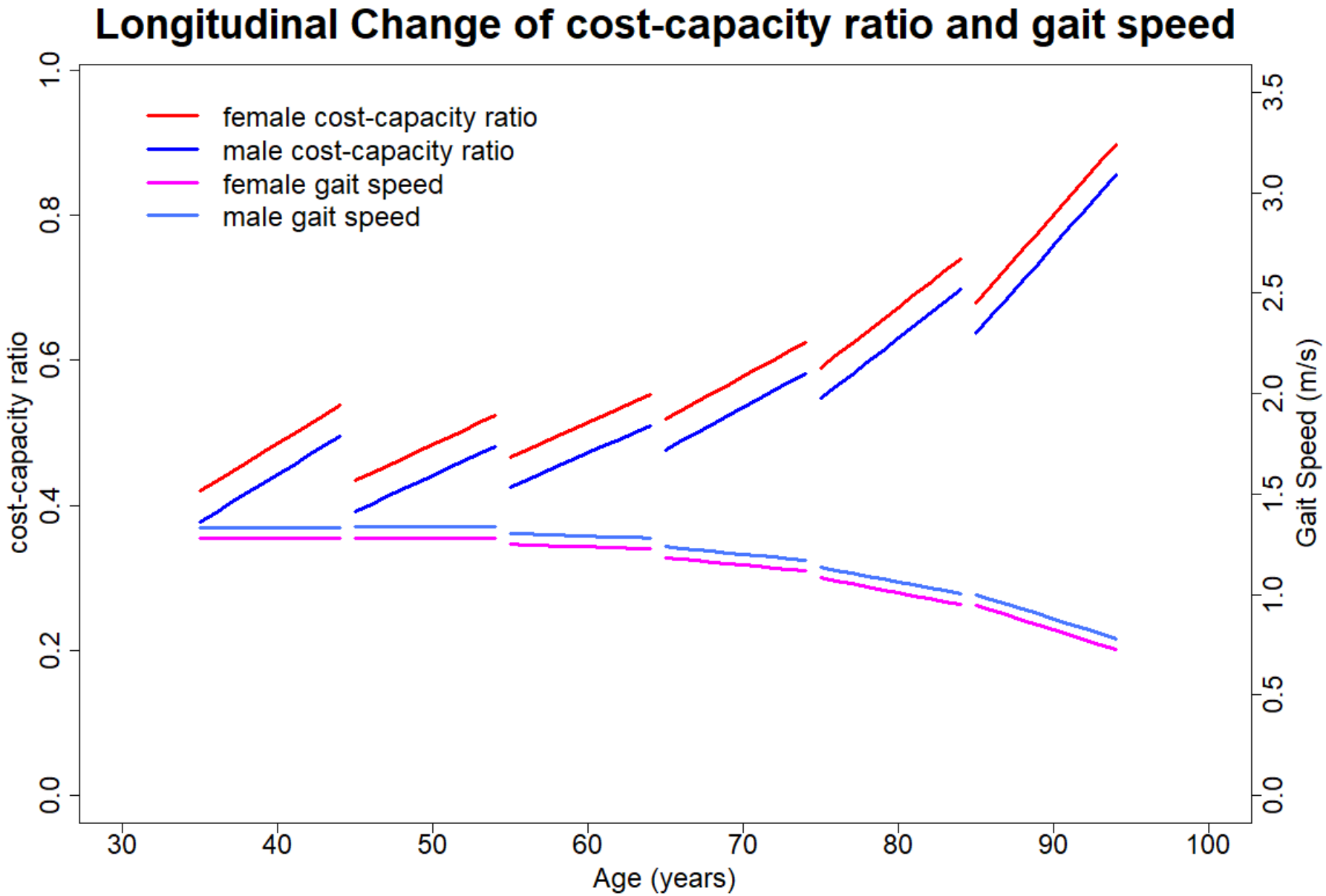

Schrack JA, et al. JGMS, 2016

# Energy Reserves & Aging



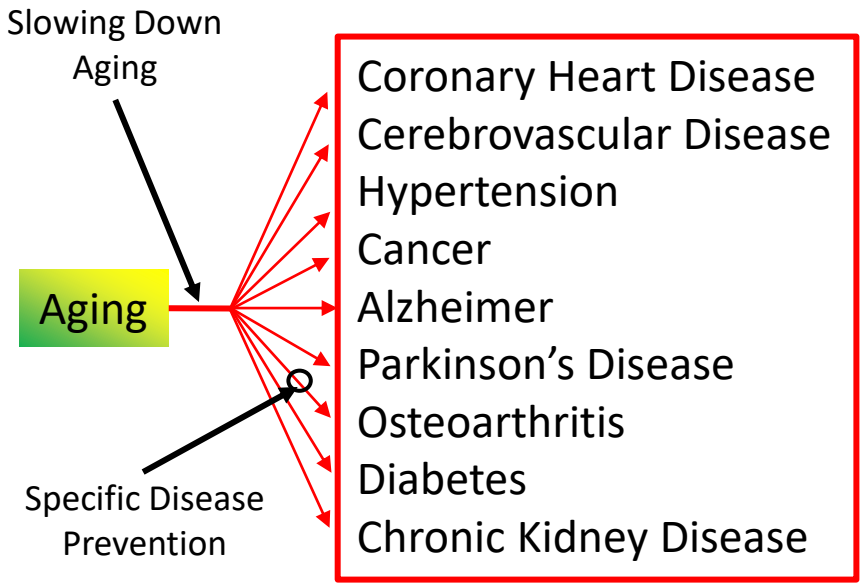

- Younger, healthier persons tend to walk at < 50% of their peak $VO_2$
- Older adults with a higher costs and lower capacity tend walk with an energetic cost that is close to peak $VO_2$

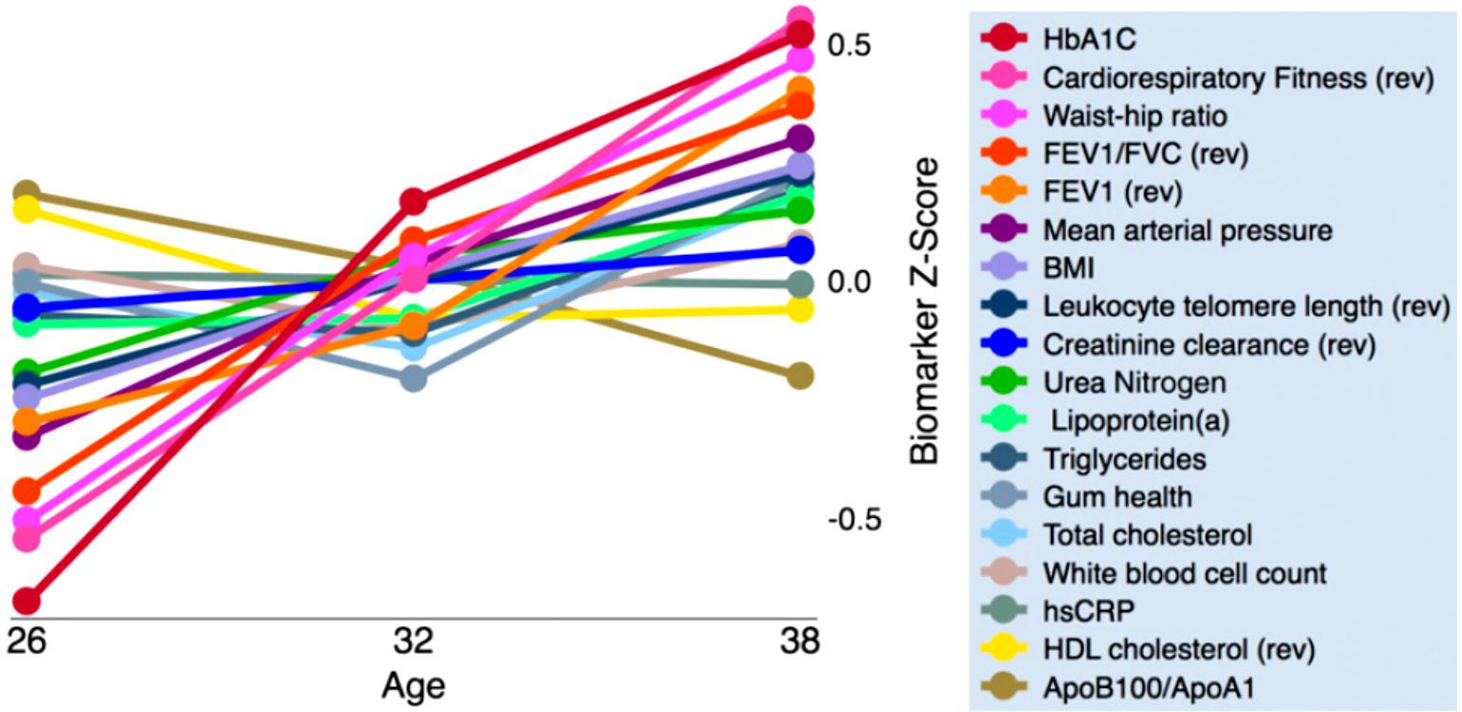
Schrack et al. *Am. J. Phys. Med. Rehabil.* • Vol. 91, No. 9, September 2012


Longitudinal Change of cost-capacity ratio and gait speed
female cost-capacity ratio
male cost-capacity ratio
female gait speed
male gait speed
cost-capacity ratio
Gait Speed (m/s)
Age (years)
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
30
40
50
60
70
80
90
100

# Assessing the Rate of Aging

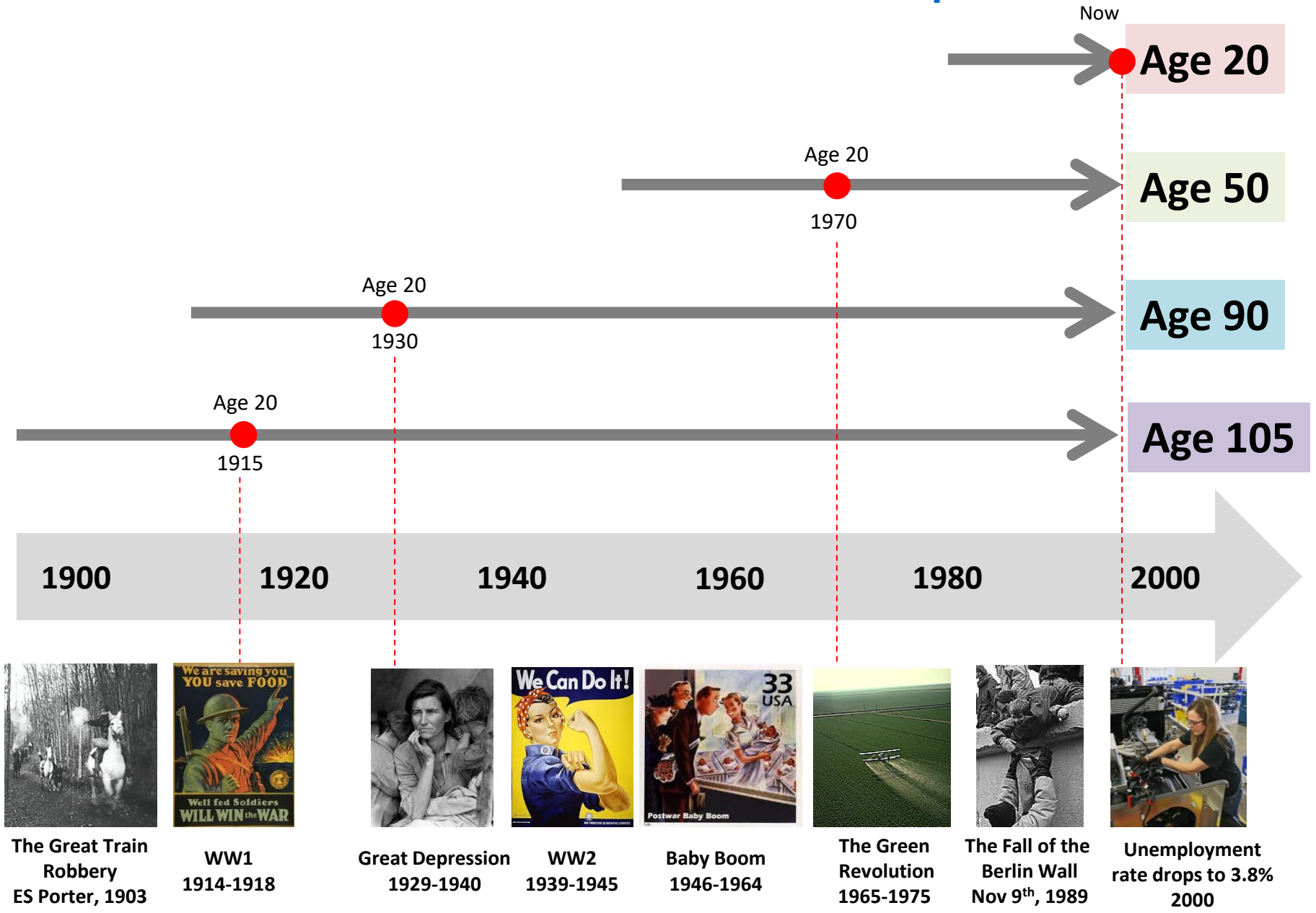
- Interfering with the fundamental basic mechanisms of aging may reduce the age-related global susceptibility to age-related chronic diseases (Seals & Melov, 2014, left figure).
- But. . . can we slow down aging? . . And, before that, **<u>can we measure aging?</u>**



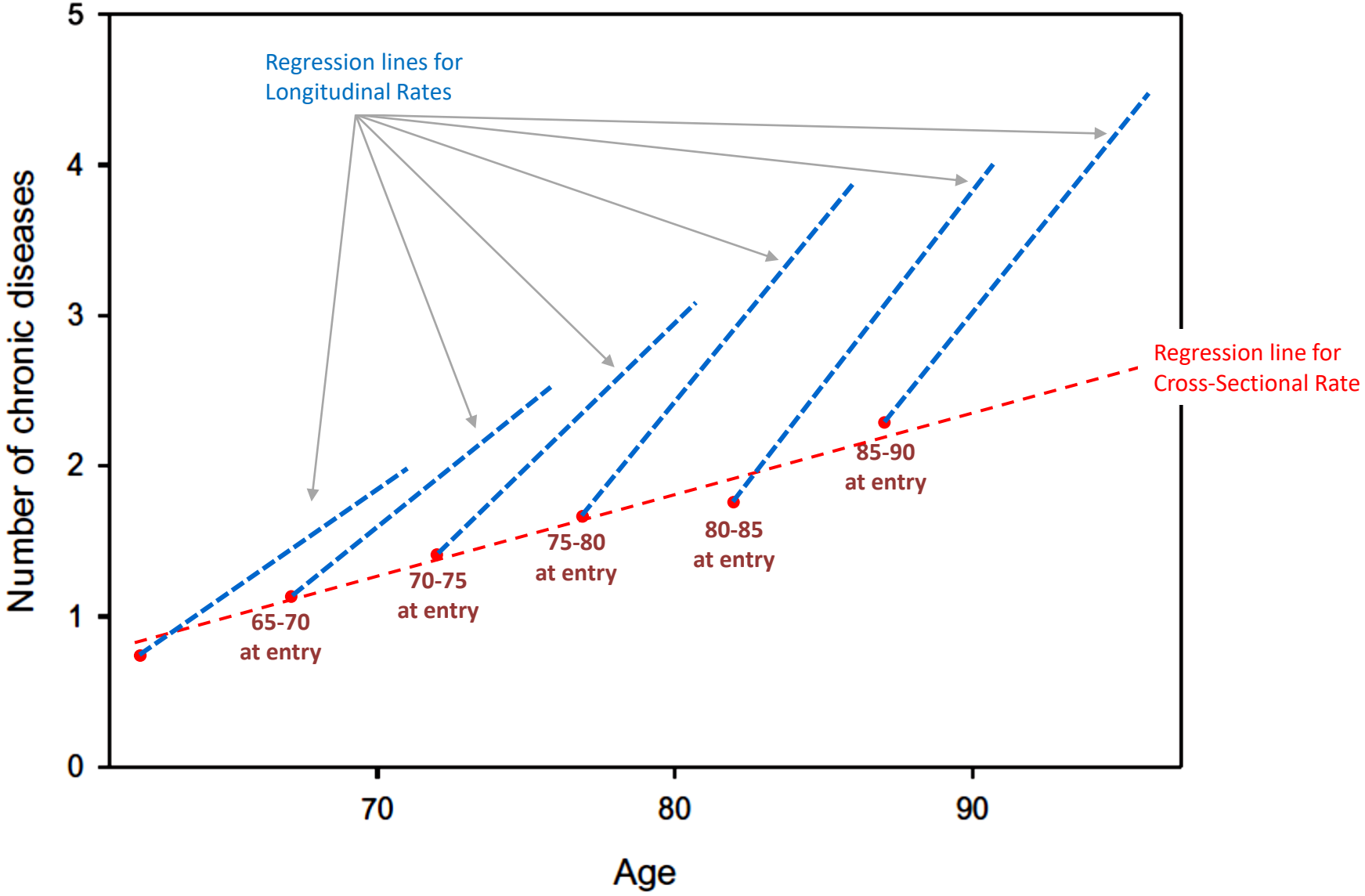




Belsky DW et al. Proc Natl Acad Sci U S A. 2015 Jul 28;112(30):E4104-10.

# Why Longitudinal Studies?
## 1. To deal with different lifetime exposures

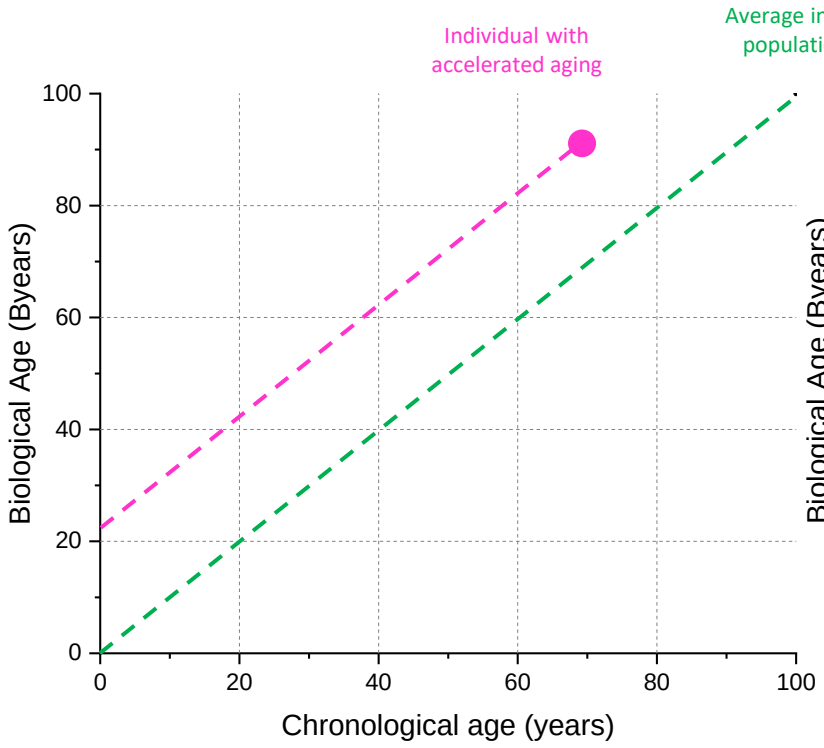


# Why Longitudinal Studies?
# 2. To deal with selective mortality or loss to follow-up (real data from BLSA)

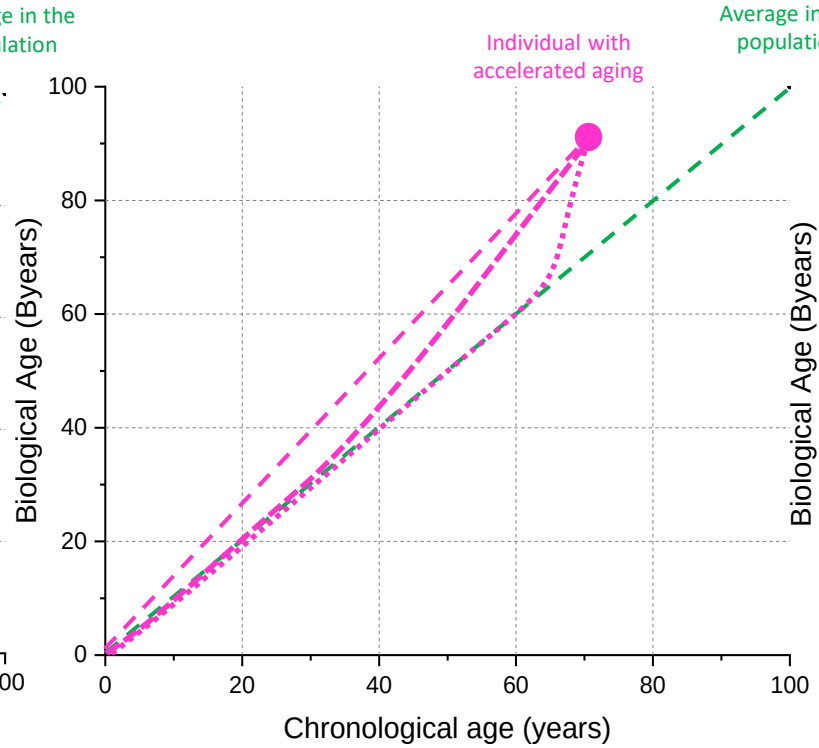


# Accelerated Aging Comes in Many Flavors

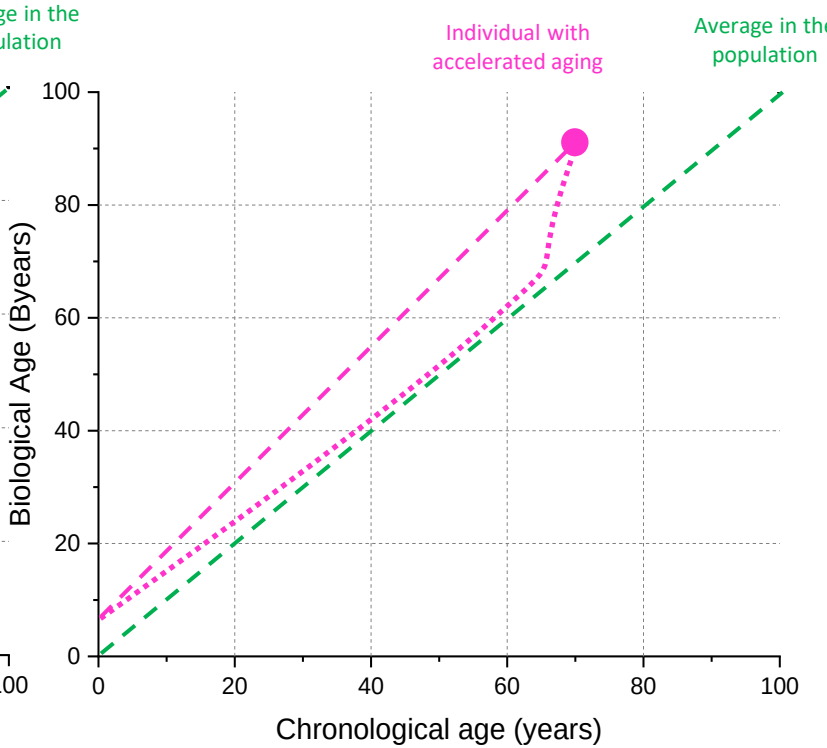
Studying longitudinal relationships between chronological and biological age is fundamental to understand mechanisms of accelerated aging and develop strategies aimed at slowing down the pace of aging, thereby preventing chronic diseases and functional decline.




Older biological age at birth and "normal" pace afterward.

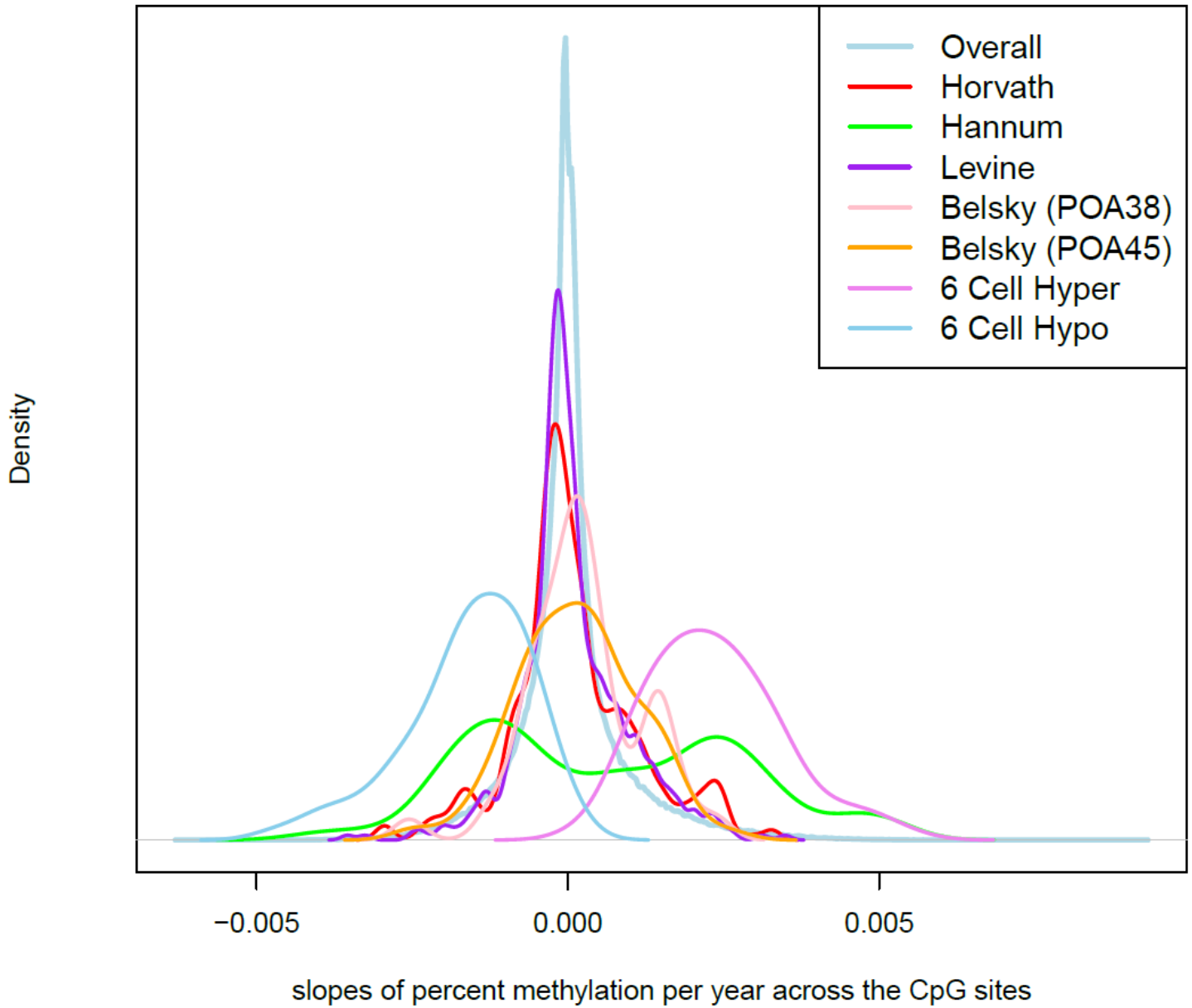



Normal biological age at birth and "accelerated" pace afterwards.



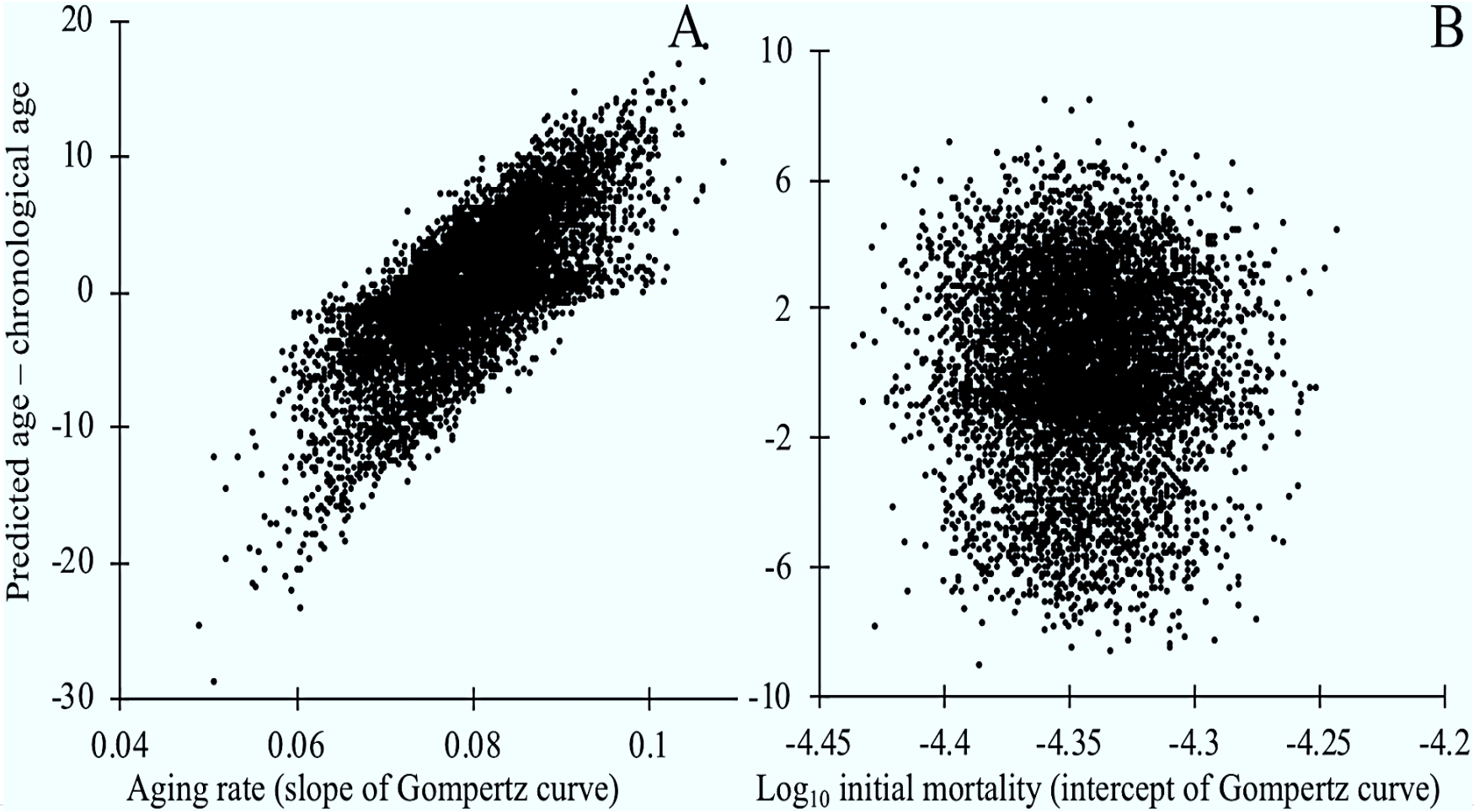

Both older biological age at birth and "accelerated" pace afterwards.

## Distribution of slopes of percent methylation per year across clocks



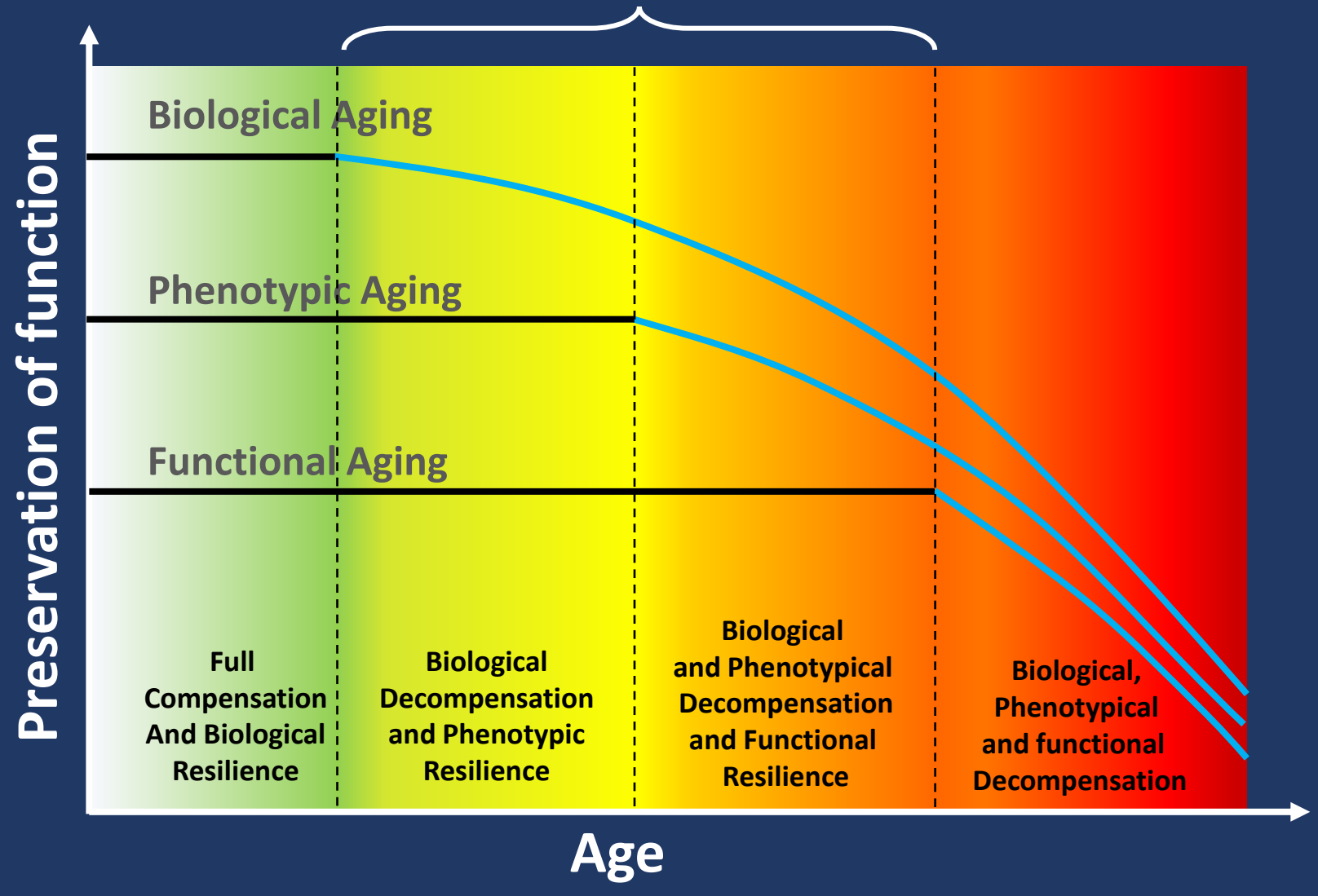
# Biomarkers for Aging Identified in Cross-sectional Studies Tend to Be Non-causative

Individuals with lower intrinsic mortality rates are likely to survive to older ages than their peers with high mortality rates and are more likely to be observed at older ages. This bias, known as “cohort selection”, complicates the search for biomarkers of aging




The deviation between an individual’s chronological age and predicted age informs the rate of aging, as measured by the slope of the Gompertz mortality curve (A), but not the intercept of the Gompertz mortality curve (B)

# A Word of *Caution*: Reslience affects the Temporal Relationships Between Metrics of Aging



# "It would be so nice if something made sense for a change."

(Alice's Adventures in Wonderland; July 4, 1865 - Charles L. Dodgson)