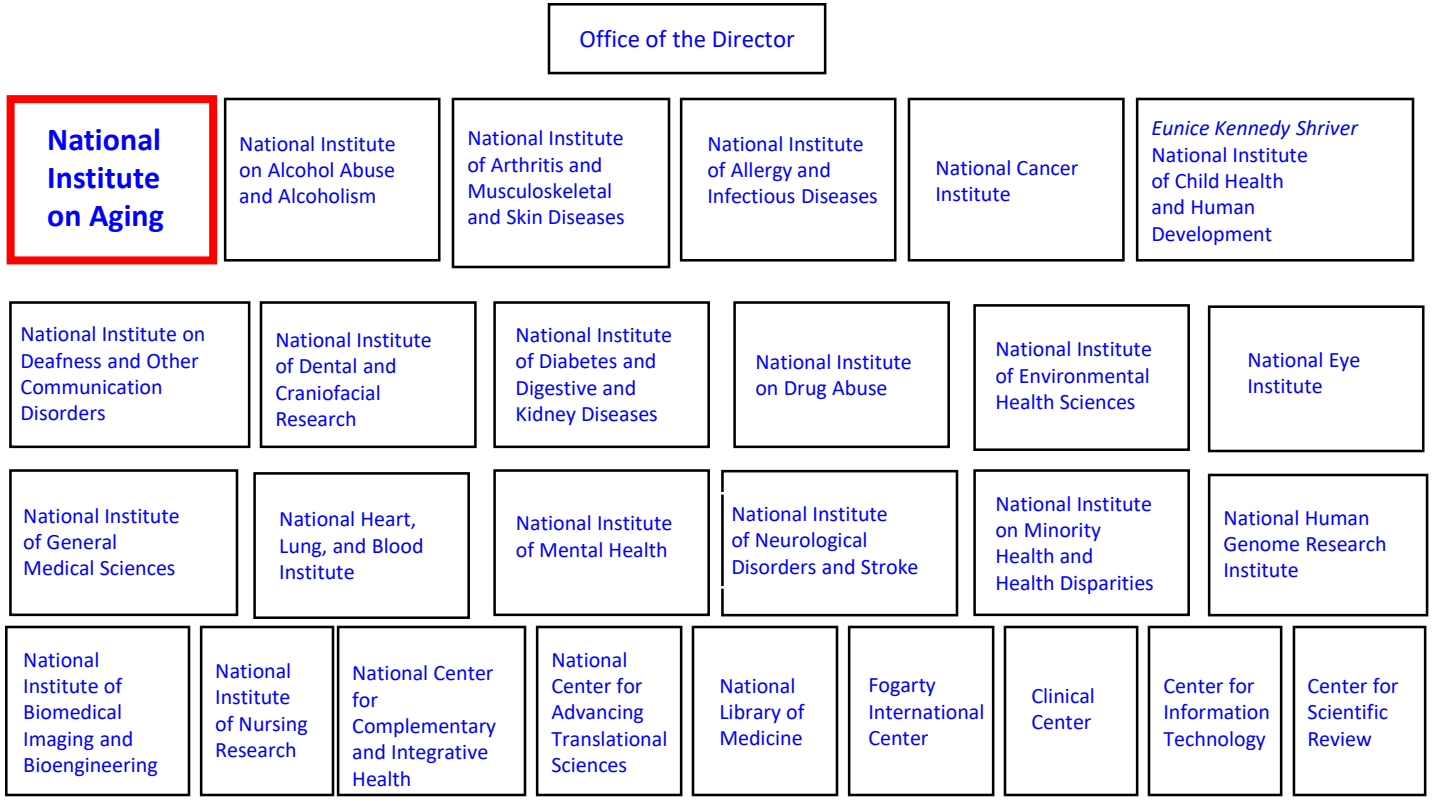
National Institutes of Health



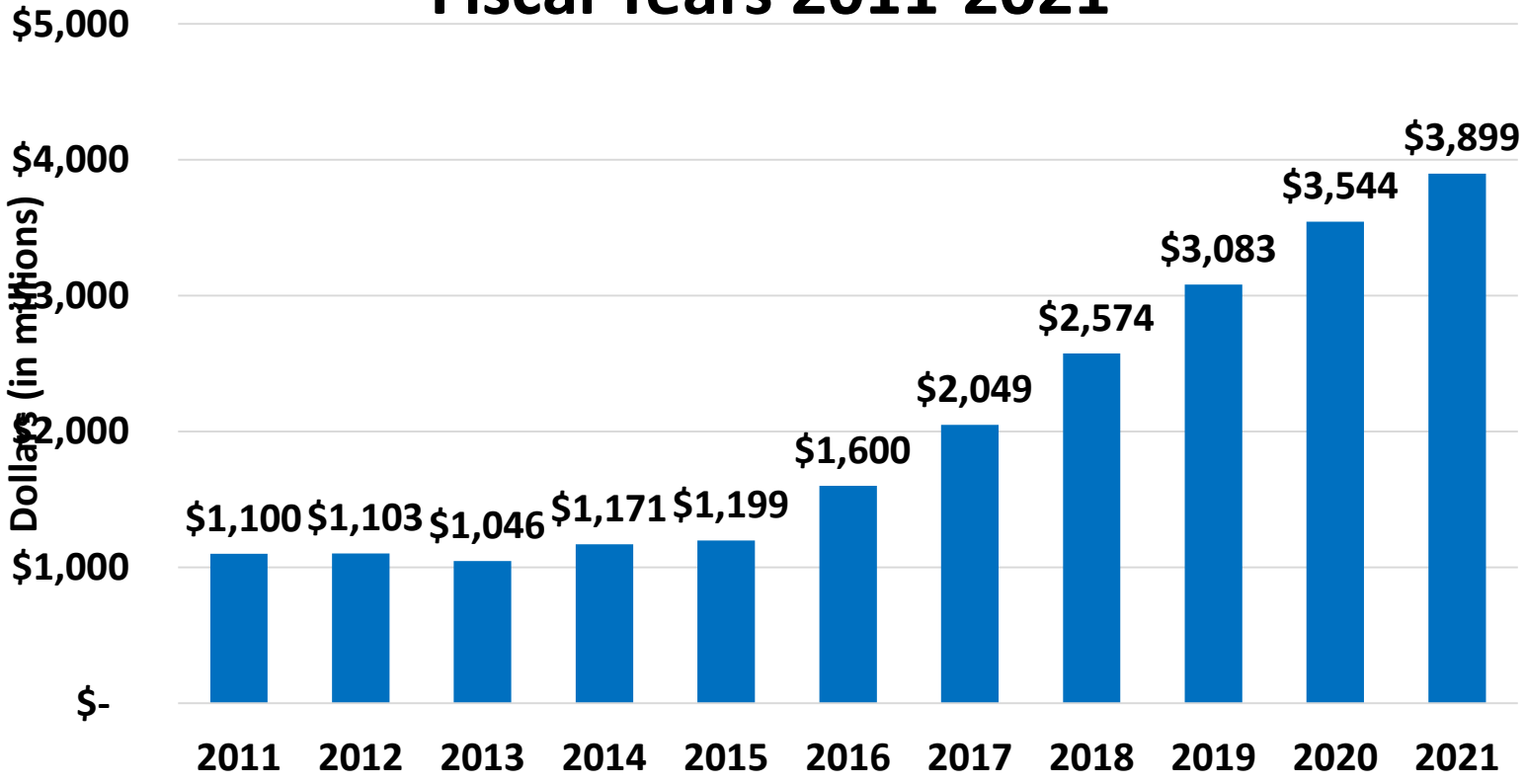
2008

NIA Establishment & Congressional Mandate

The Research on Aging Act of 1974 (Public Law 93-296) enacted on May 31, 1974 established the National Institute on Aging.

The general purpose of the National Institute on Aging is ***the conduct and support of biomedical, social, and behavioral research, training, health information dissemination, and other programs with respect to the aging process and the diseases and other special problems and needs of the aged.***

NIA Appropriations
Fiscal Years 2011-2021

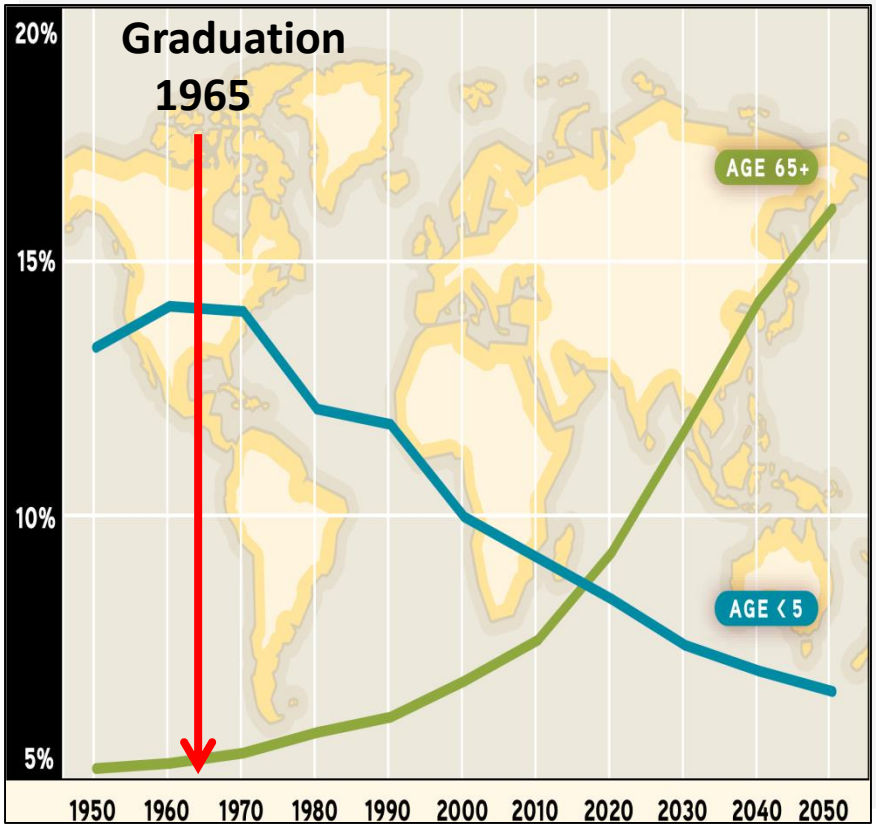


Challenges at age 80

1) Demographics of aging
2) What can be done to improve healthspan?
   Correlations and clinical trials
3) Alzheimer's disease
4) Biology of aging

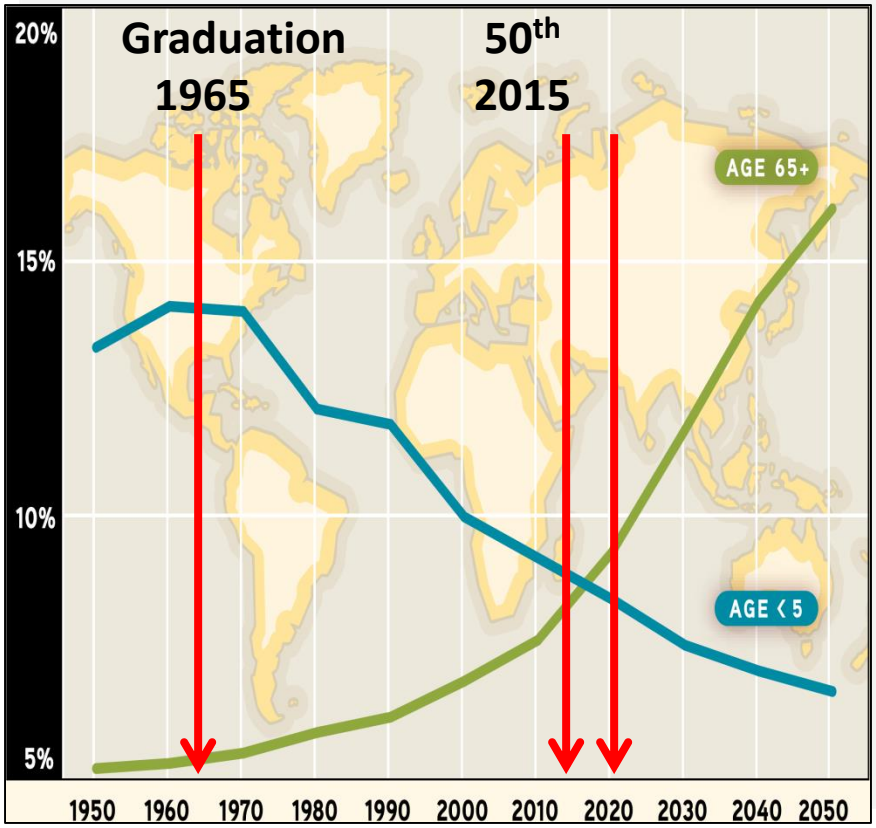
Demographics of Aging

YOUNG CHILDREN AND OLDER PEOPLE AS A PERCENTAGE OF GLOBAL POPULATION



United Nation Department of Economic and Social Affairs, Population Division.*World Population Prospects. The 2004 Revision*. New York: United Nations, 2005 in *Why Population Aging Matters: A Global Perspective* at www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/GlobalAging.htm

YOUNG CHILDREN AND OLDER PEOPLE AS A PERCENTAGE OF GLOBAL POPULATION



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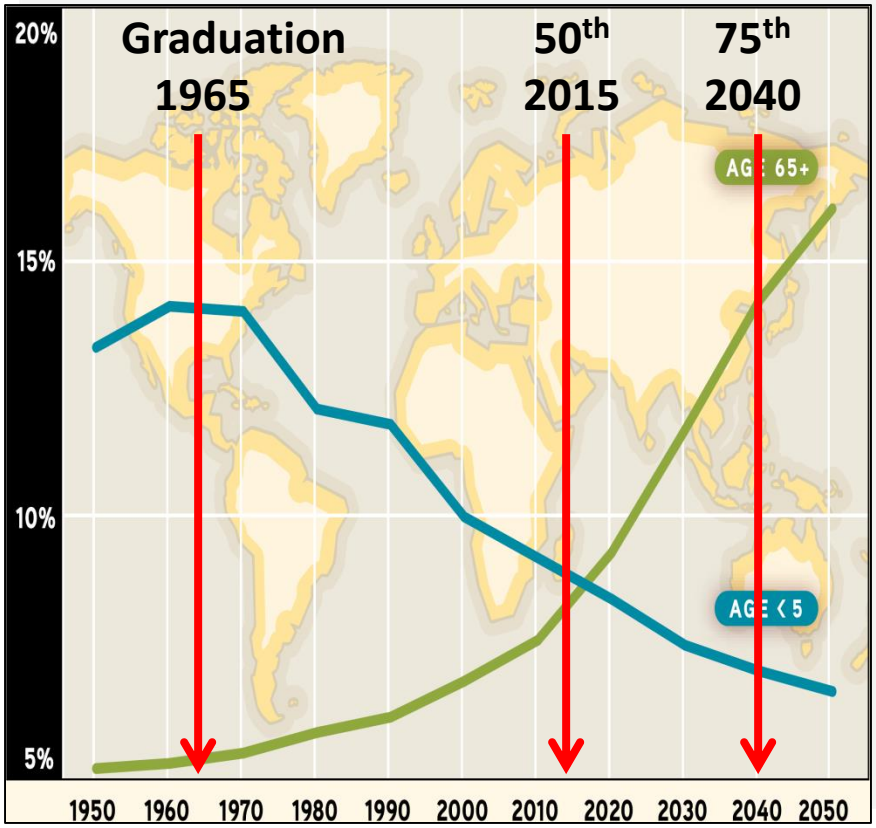
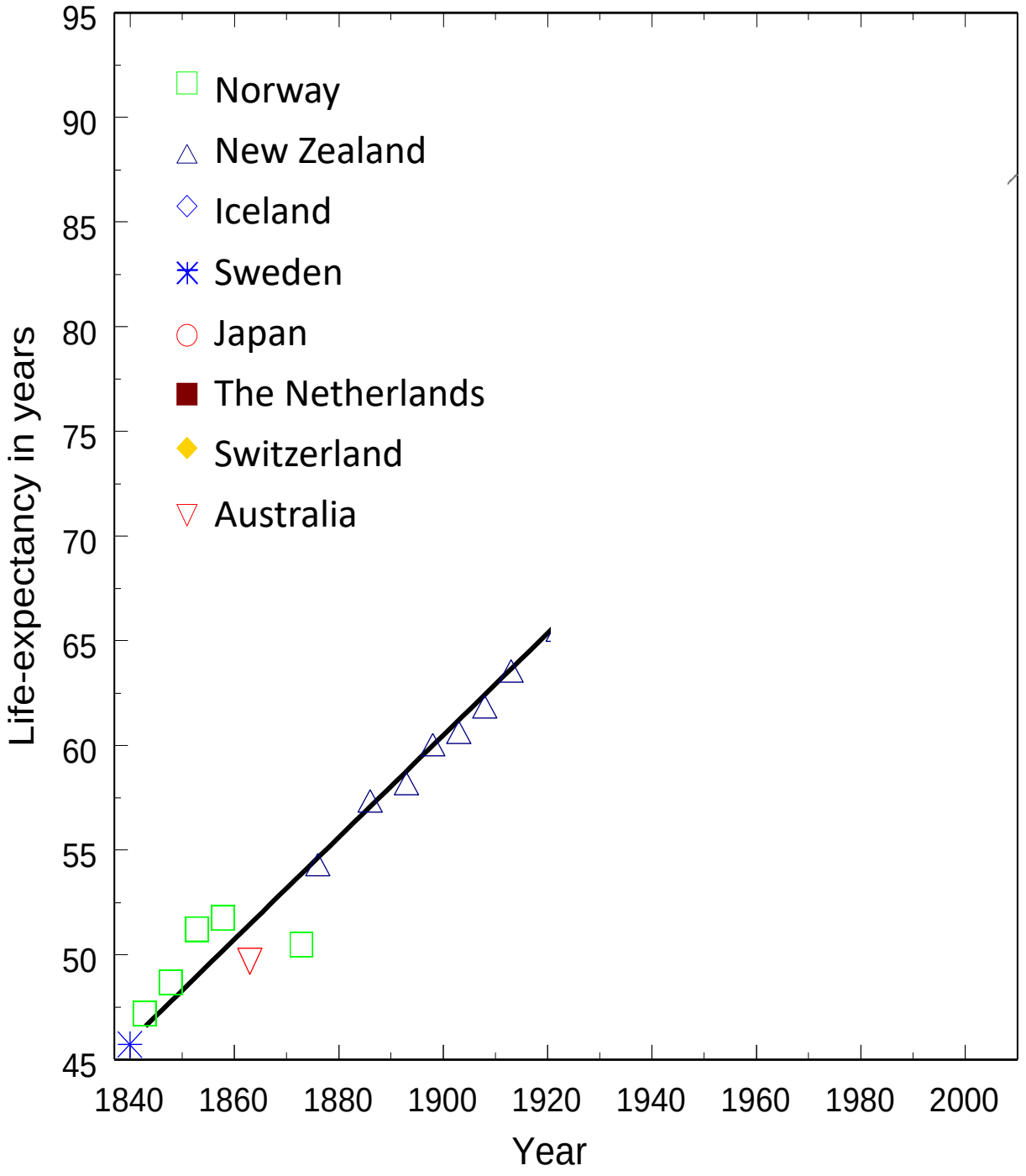
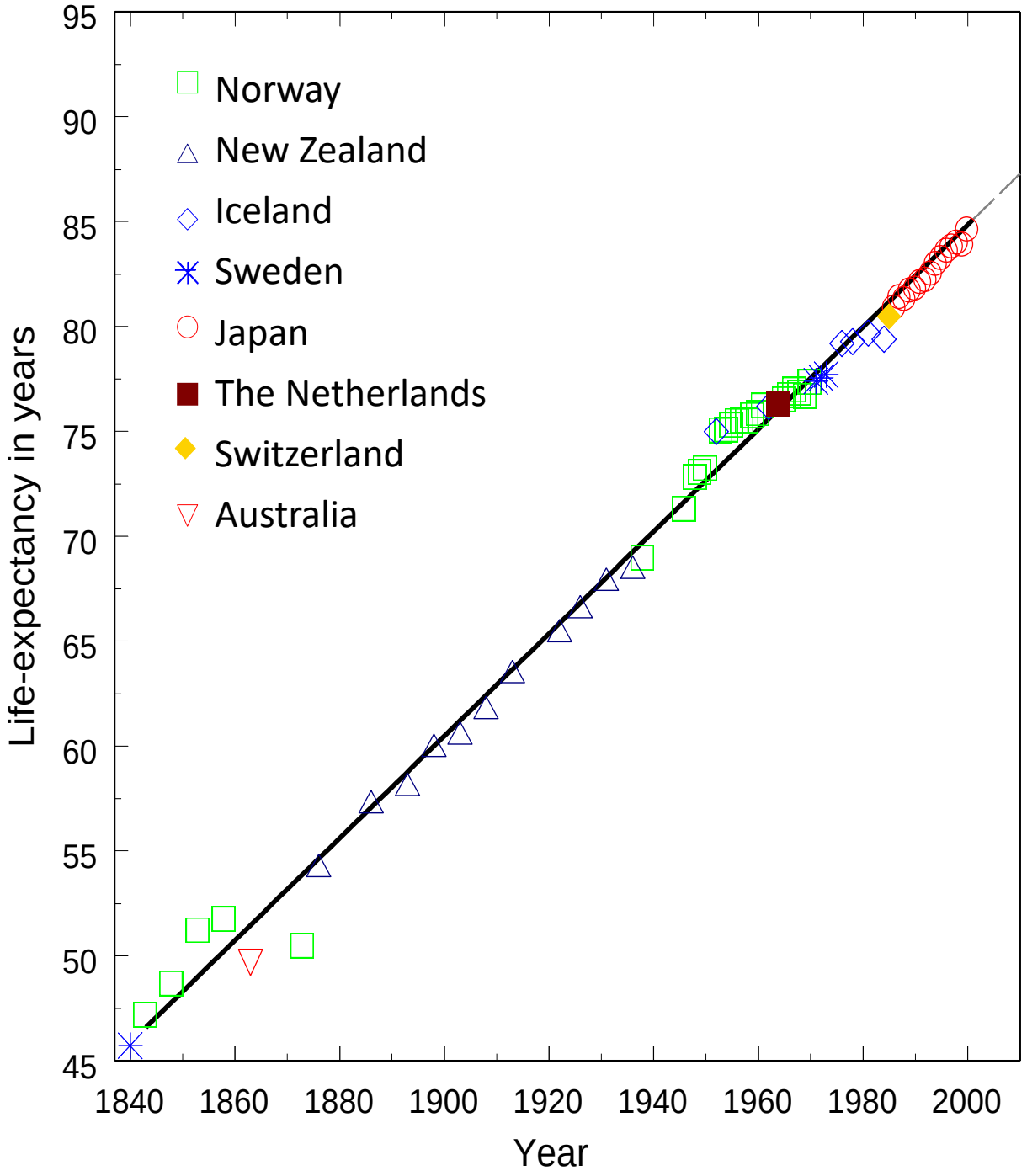


United Nation Department of Economic and Social Affairs, Population Division. *World Population Prospects. The 2004 Revision*. New York: United Nations, 2005 in *Why Population Aging Matters: A Global Perspective* at www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/GlobalAging.htm

Female life expectancy in the record-holding country

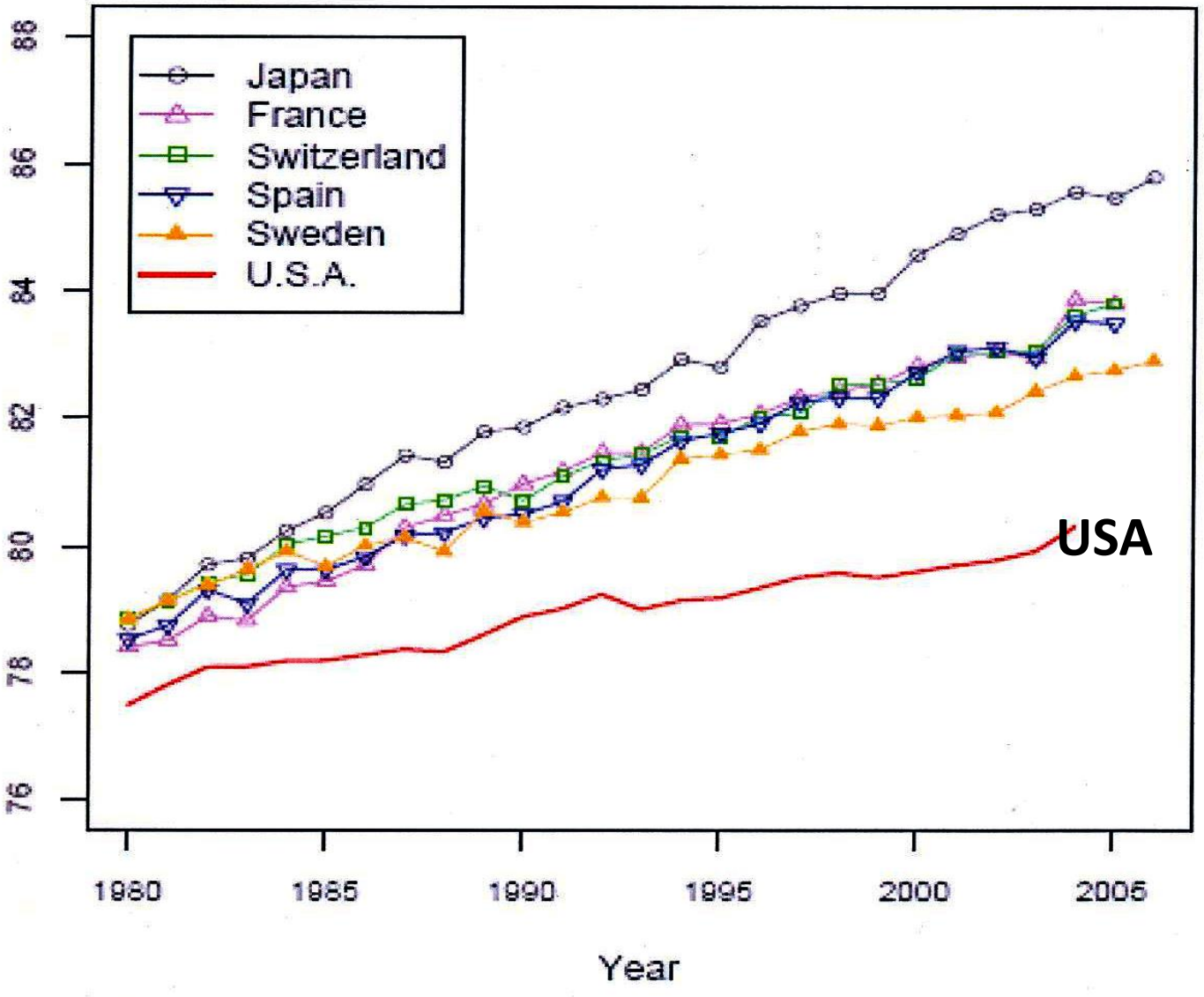


Female life expectancy in the record-holding country from 1840 to 2000

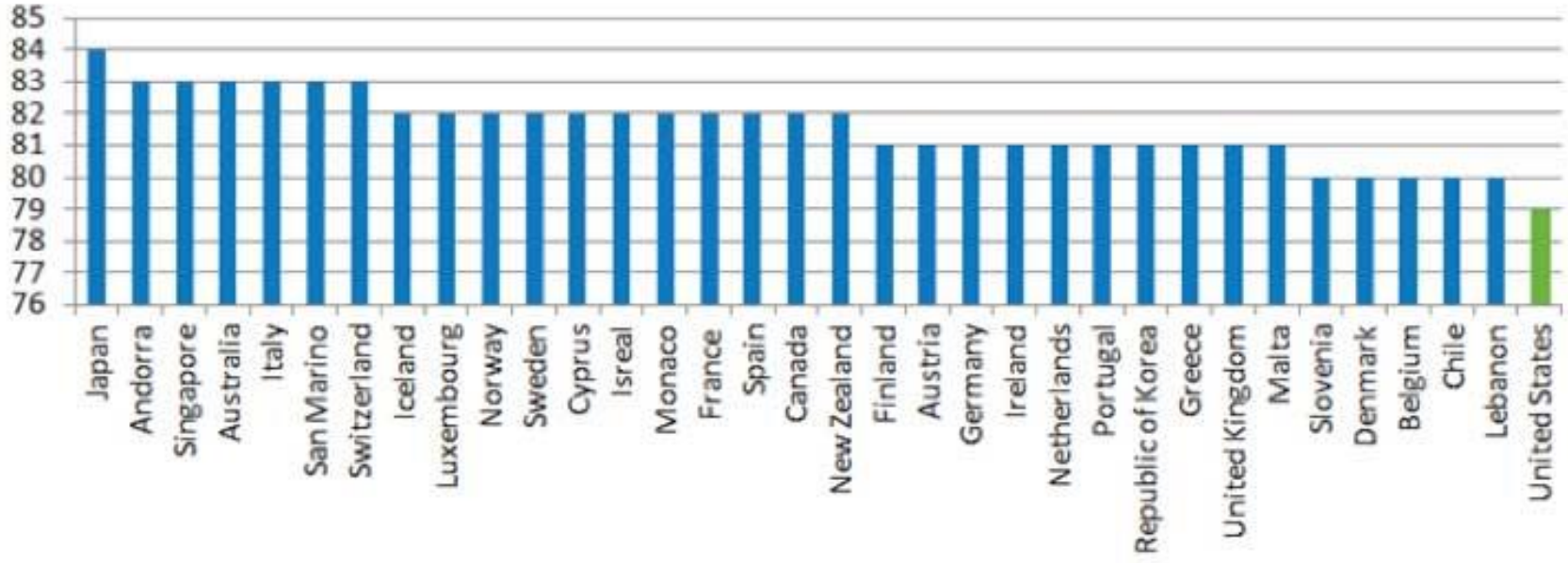


Oeppen & Vaupel, 2002

United States Lagging in Life Expectancy
Females, 1980-2005

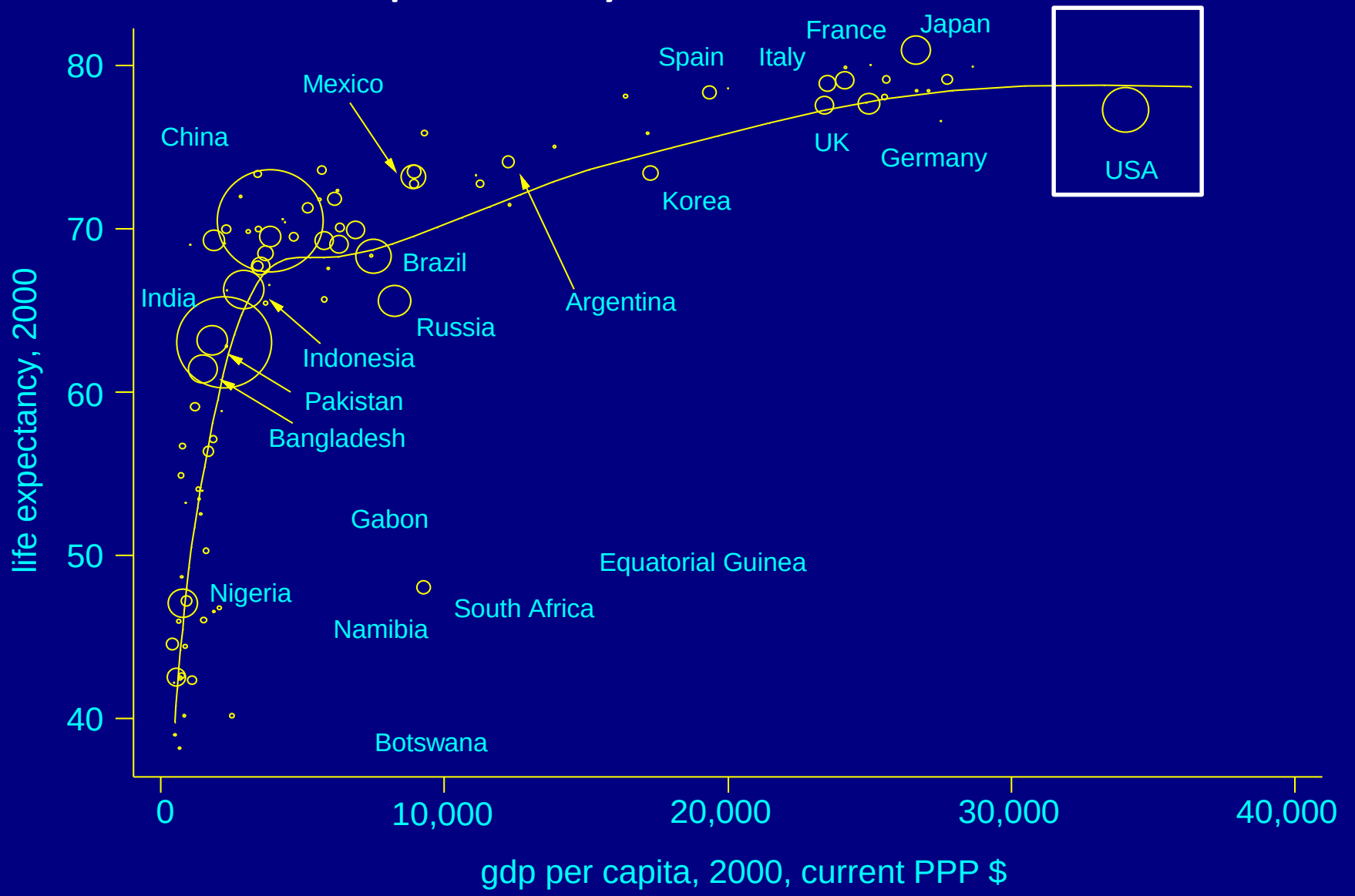


U.S. ranks 34th in life expectancy at birth



Source: America's Health Rankings, 2014

Life Expectancy and National GDP

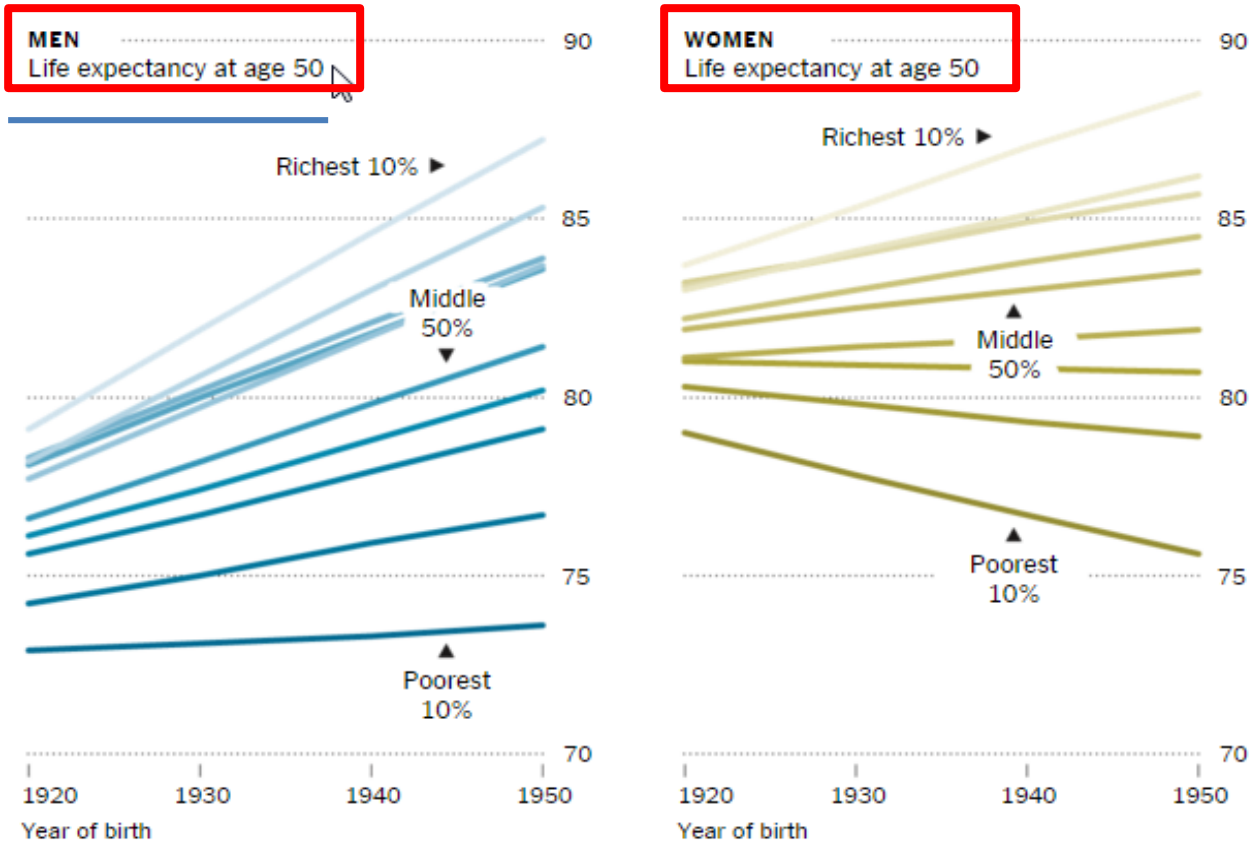


Life expectancy falling for the poor, rising for the rich in USA

HEALTH | Disparity in Life Spans of the Rich and the Poor Is Growing

An Expanding Longevity Gap

Wealthier Americans tend to live longer than poorer Americans. Despite advances in medicine and education, the difference in life span after age 50 between richest and poorest has more than doubled since the 1970s.

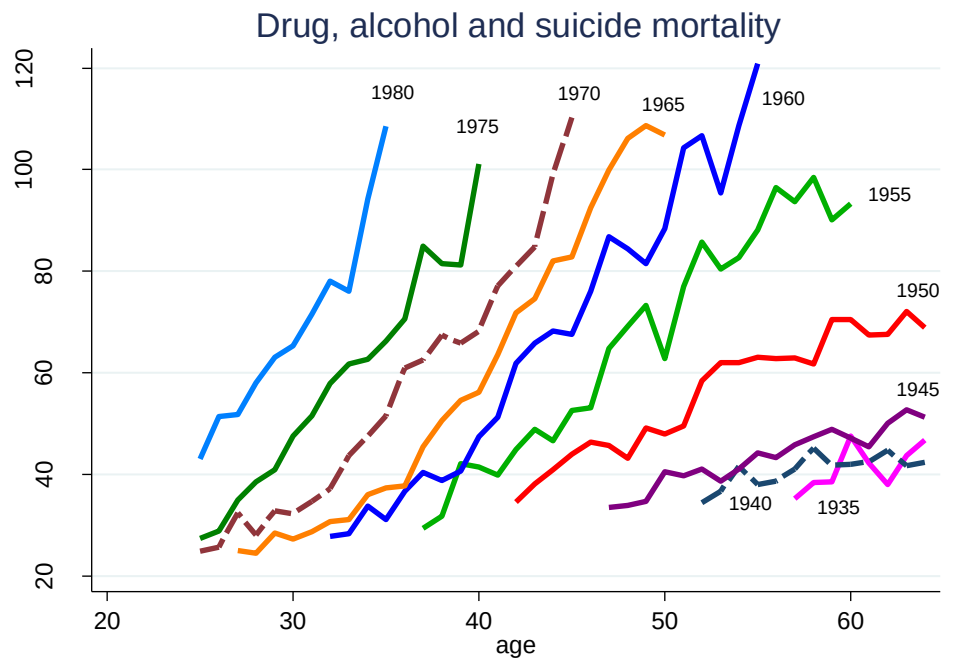


Sources: Brookings Institution; U. of Michigan Health and Retirement Study

By The New York Times

Drug, alcohol and suicide mortality white non-Hispanics by birth cohort

Less than BA (undergraduate degree)



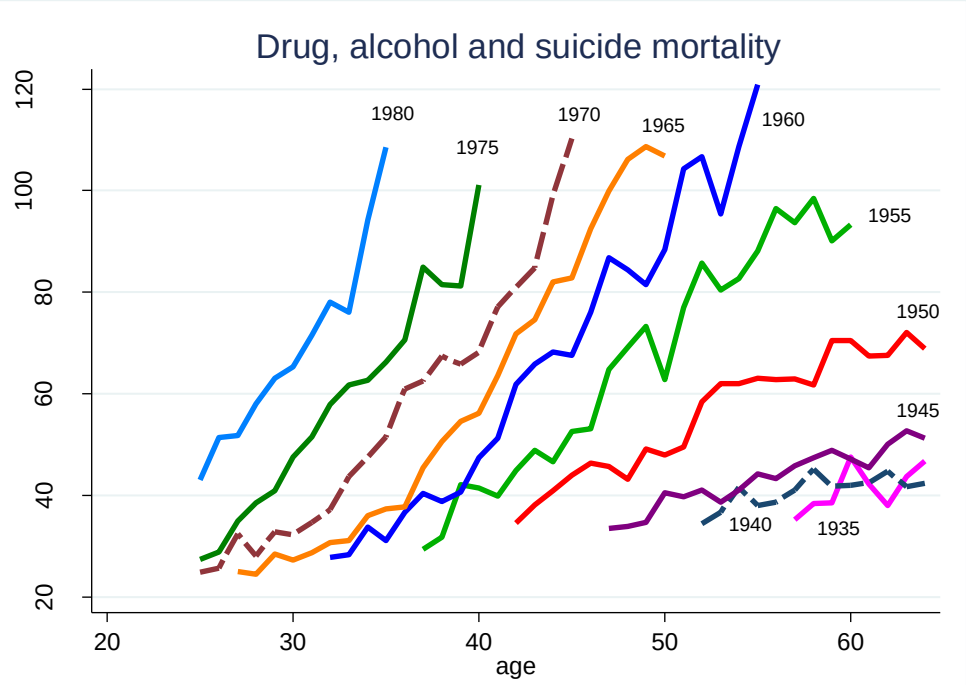
TWO AMERICAS

With worse outcomes for younger birth cohorts

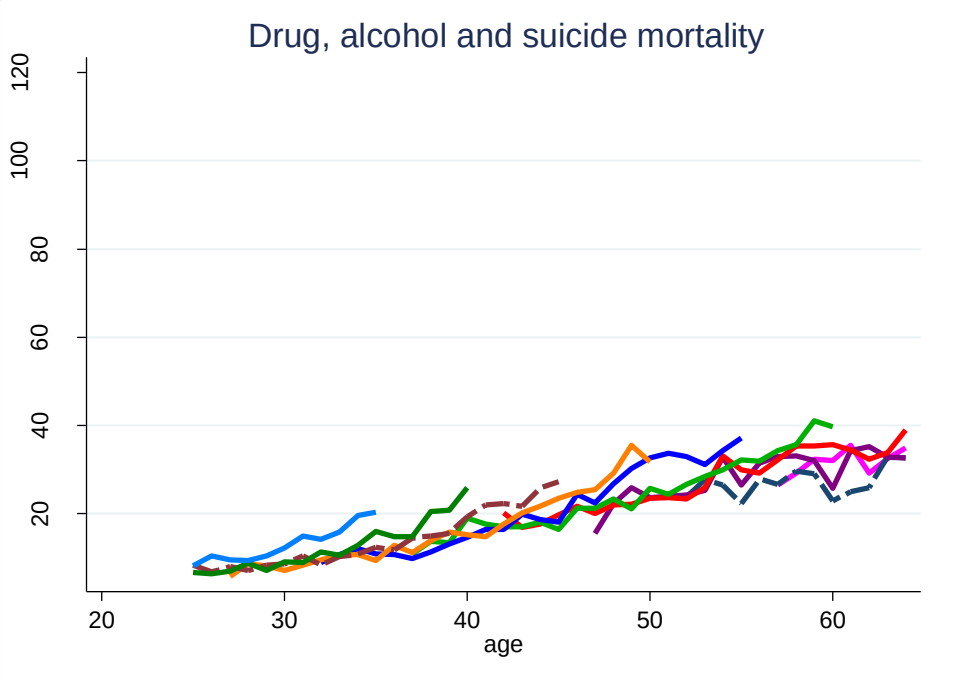
Case and Deaton

Drug, alcohol and suicide mortality white non-Hispanics by birth cohort

Less than BA



BA or more

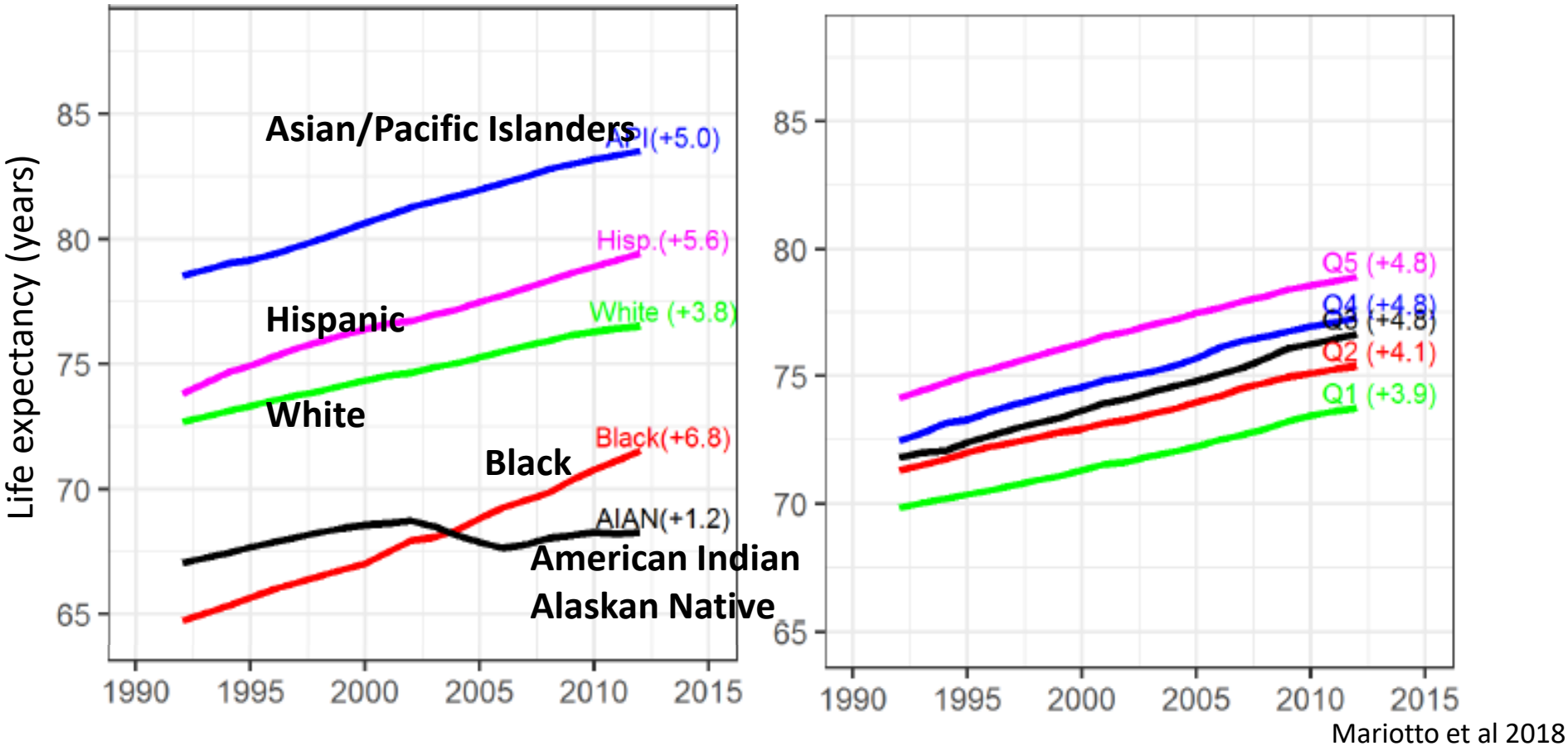


TWO AMERICAS

With worse outcomes for younger birth cohorts

Case and Deaton

Male life expectancy by race/ethnicity and SES

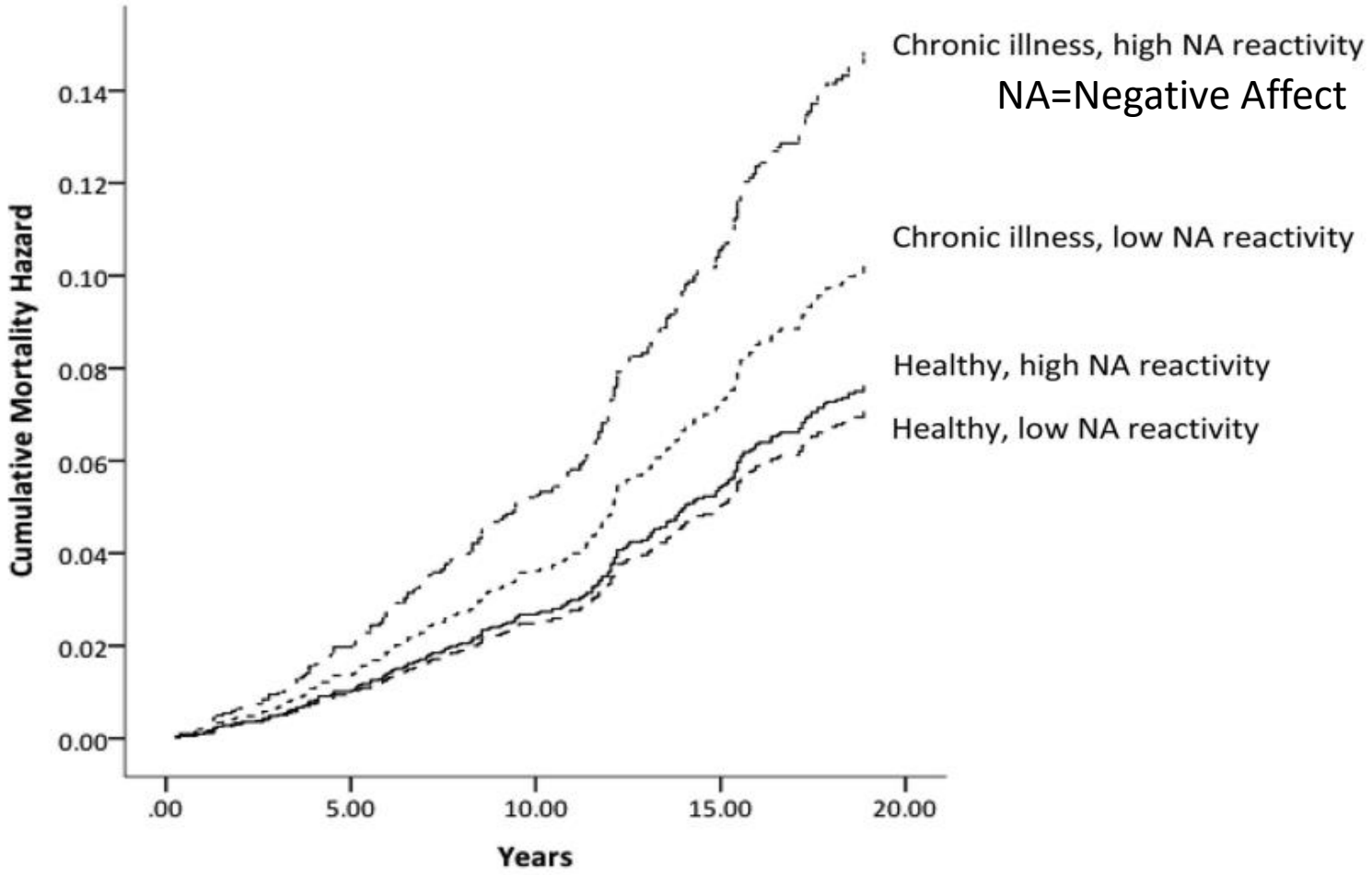


Mariotto et al 2018

What can be done to improve healthspan?

Correlations and Clinical Trials

Attitudes Concerning Daily Stress Can Affect Mortality Risk
A Correlation

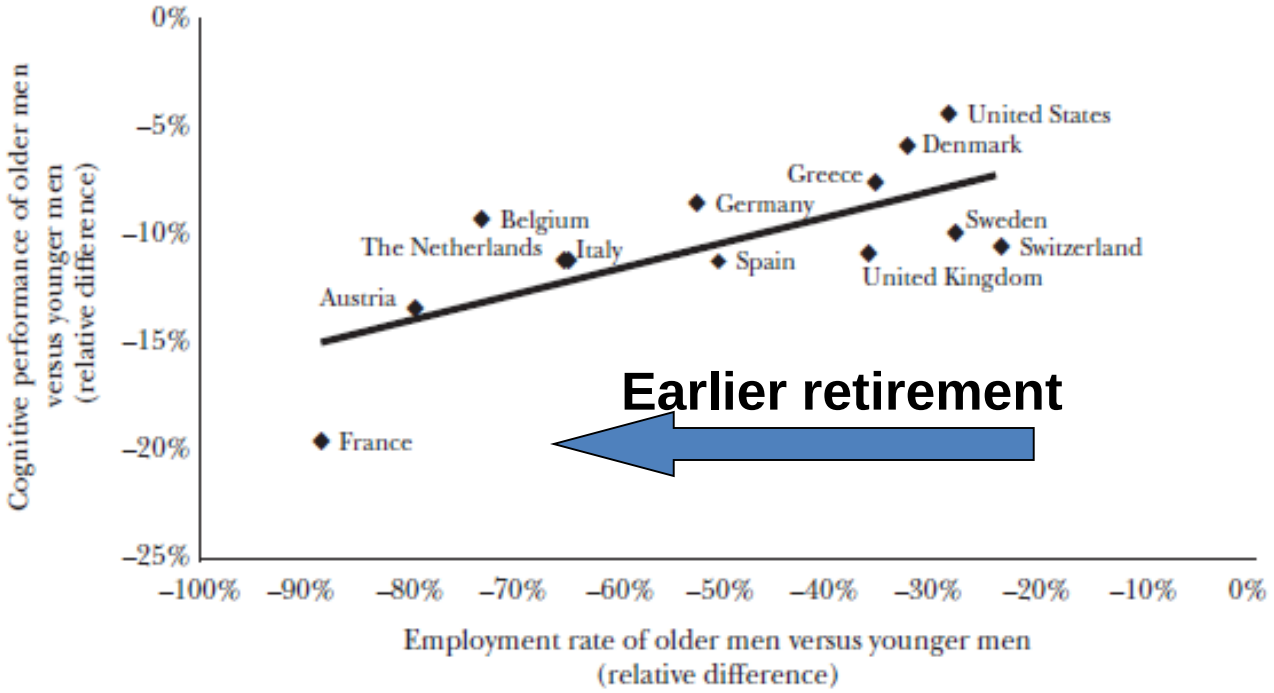


Chiang et al. (2018). *Health Psychol 37*(2):170.

Cross-Country Correlation of Early Retirement and Decreased Cognitive Performance
A "Natural Experiment"

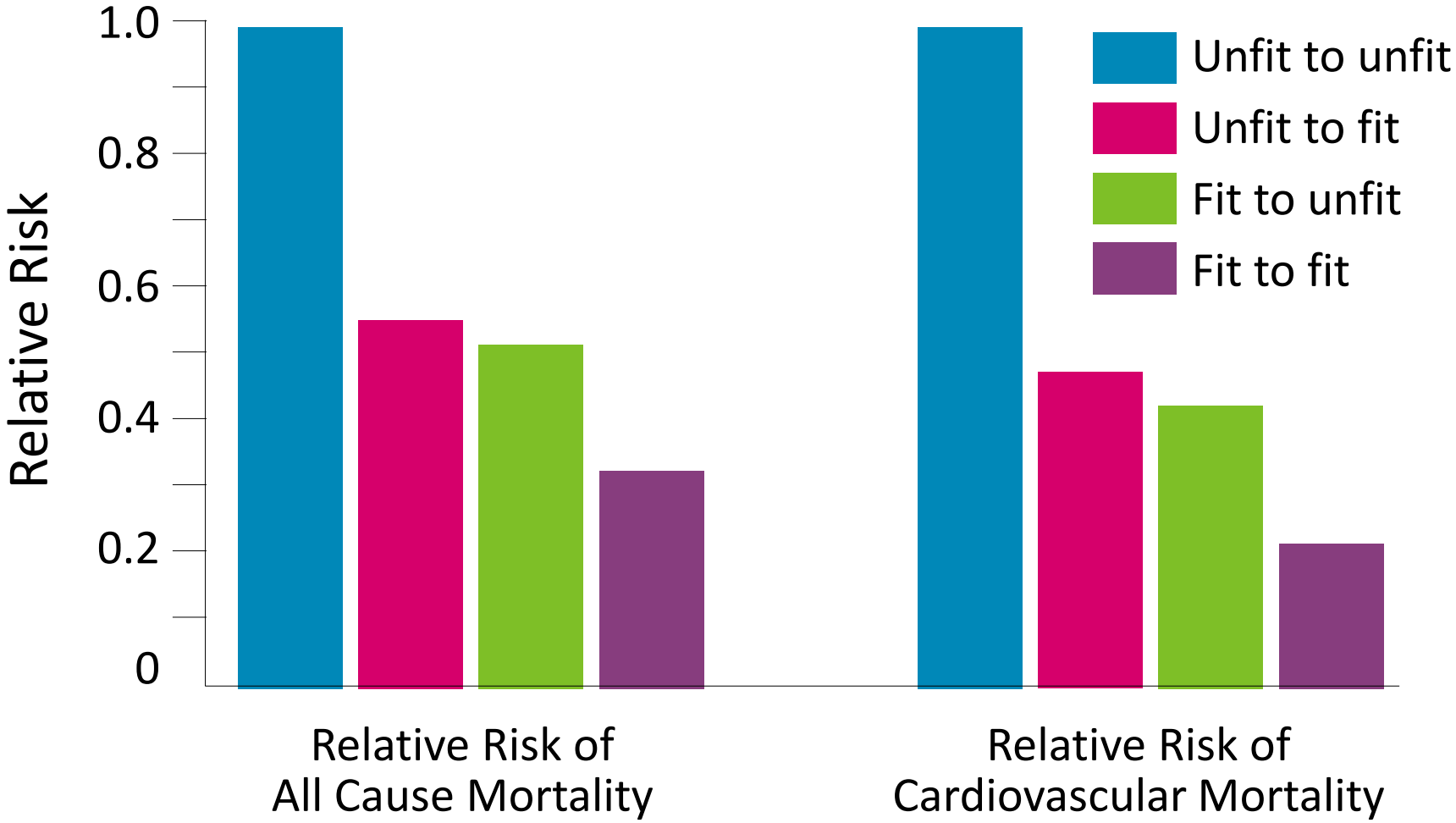
Decreasing Cognition

Drop in Cognitive Performance as a Function of Drop in Employment Rate between Men 50–54 and 60–64 Years Old



Source: Adam, Bay, Bonsang, Germain, and Perelman (2007). Reproduced with permission. Data drawn from ELSA for England, HRS for the United States, and SHARE for other countries for 2004.

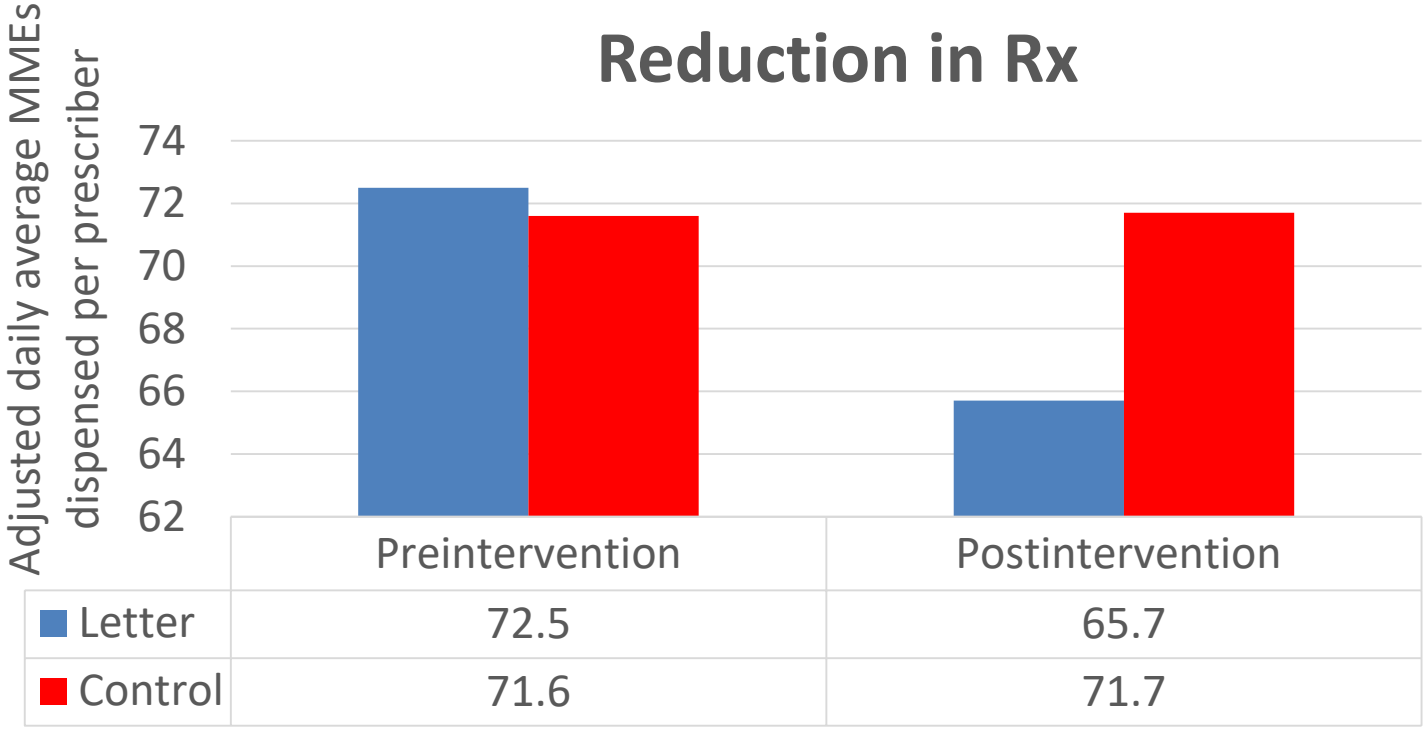
Becoming Physically Fit Reduces Mortality
An Observational Correlation



1000 men aged 20-82 5 year follow-up

Source: Blair et al. *JAMA* 1995

Notification of Patient Overdose Deaths Reduces Clinician Opioid Prescriptions A Randomized Clinical Trial – A "nudge"

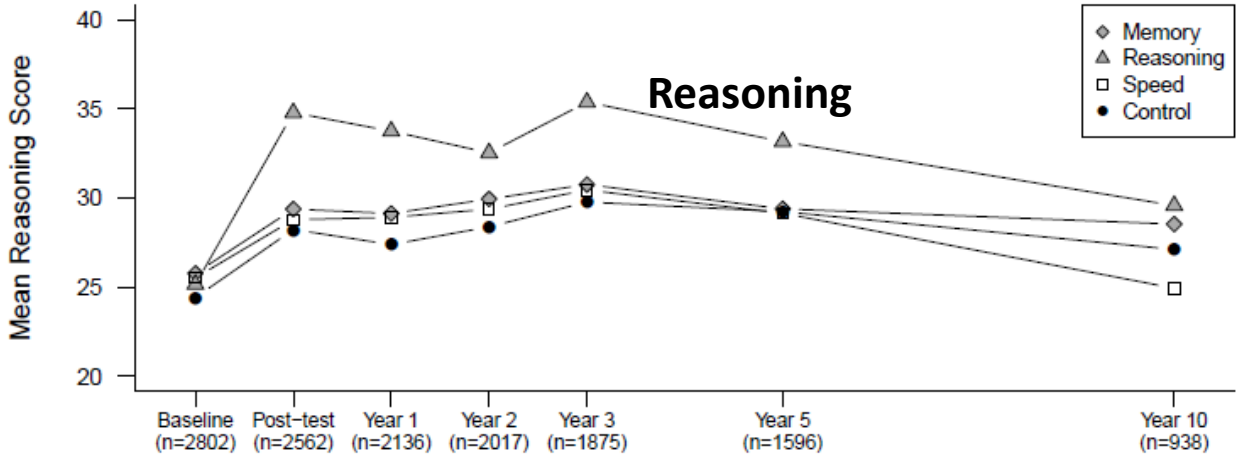


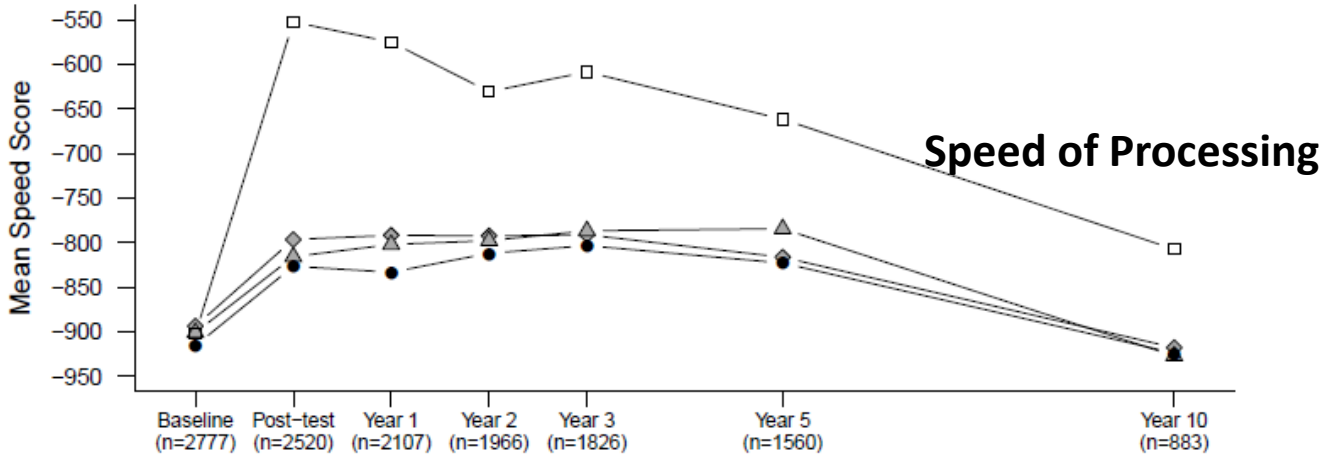
MME= milligram morphine equivalents

MMEs in Rxs of letter recipients decreased by 9.7% after 3 months

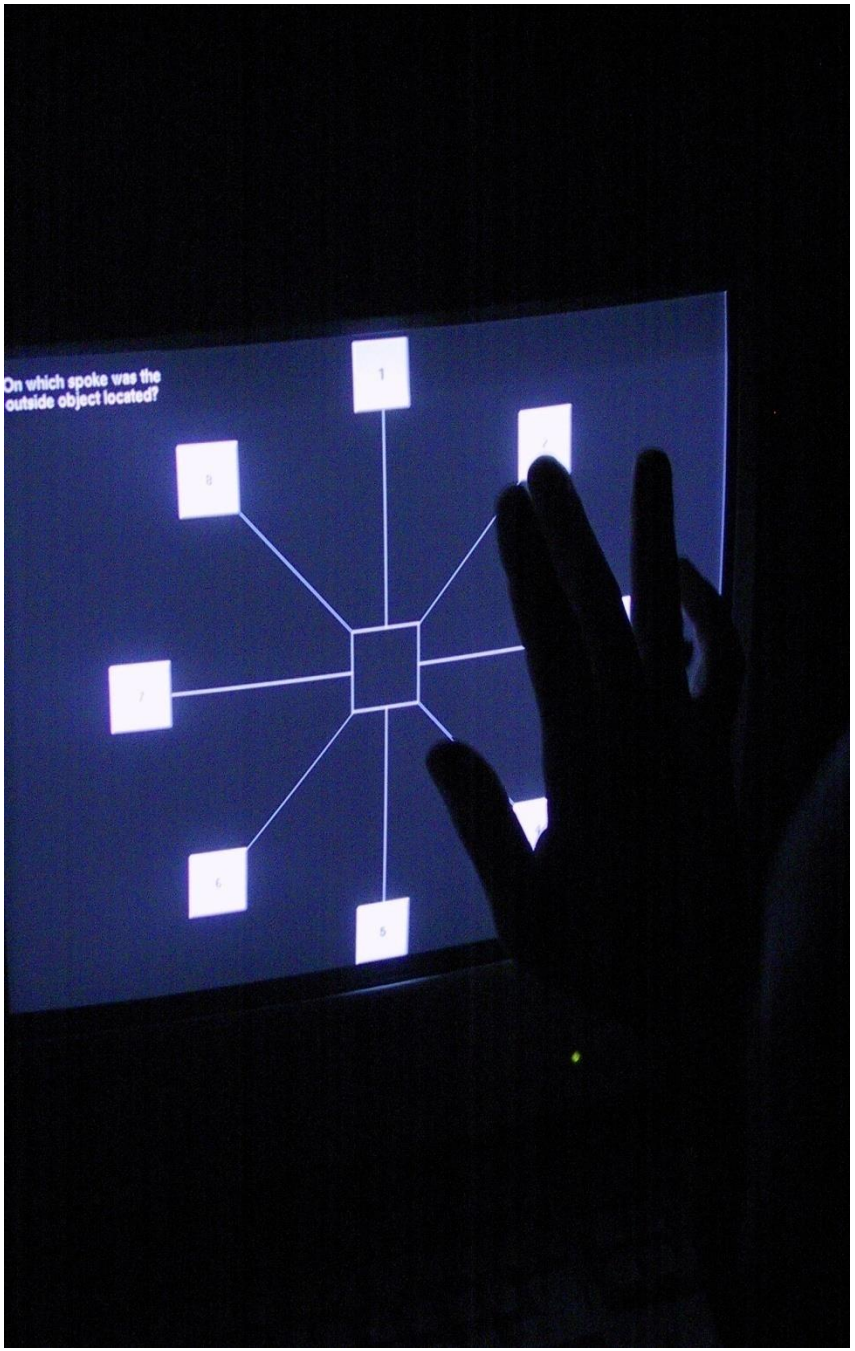
Adapted from Doctor, J et al. (2018). *Science, 361 (6402),* 588-590.

Advanced Cognitive Training (ACTIVE) Shows 10-Year Benefit in Reasoning and Speed of Processing Randomized Clinical Trial





Rebok, GW et al. (2014) *J Am Geriatr Soc* Epub Jan 13.



Useful Field of View (UFOV)

Area from which one can extract visual information at a glance without head or eye movements.

By *training* UFOV you can prospectively reduce crash rates.

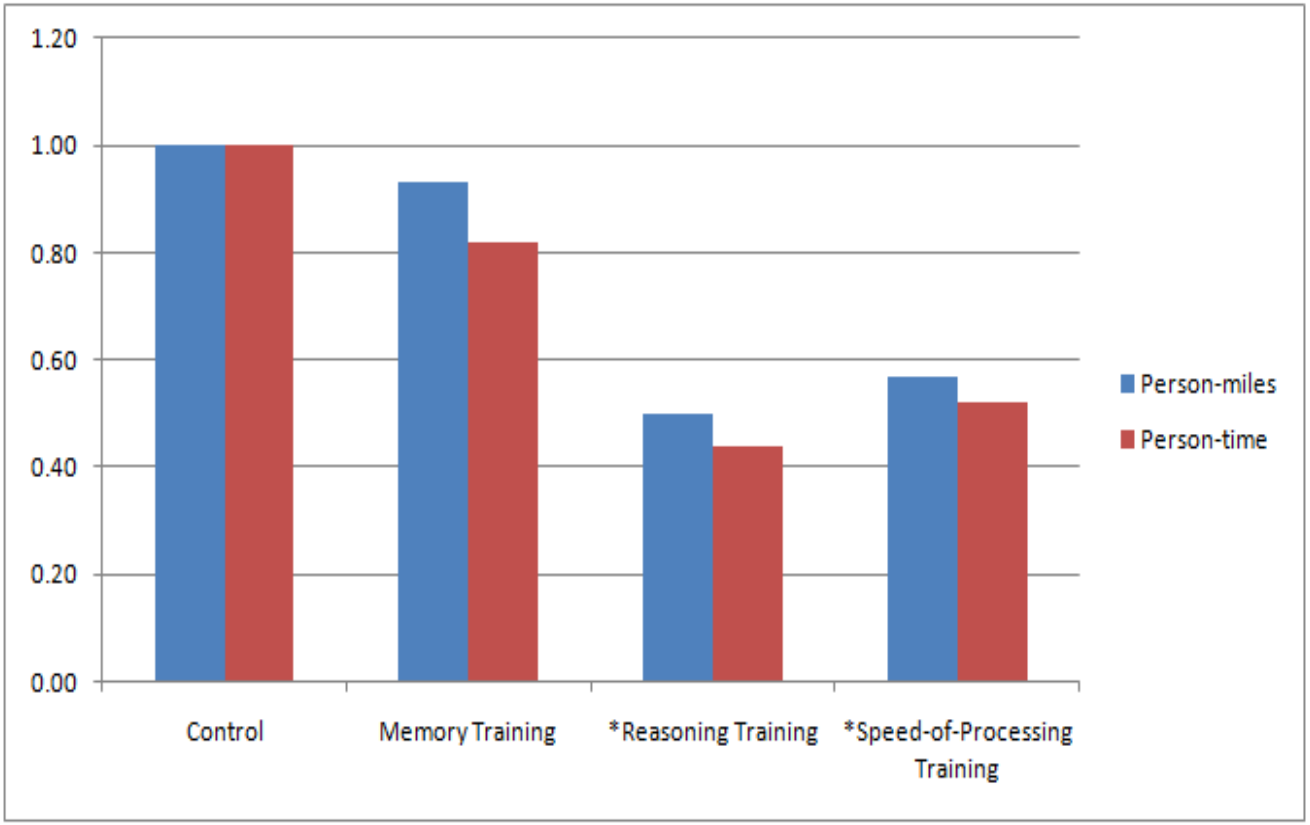
MD, CA, and FL Motor Vehicle Departments are using and testing UFOV and State Farm and All State are offering discounts with this training.

UFOV Training Outcomes

Older adults randomized to training experienced half the number of at-fault crashes

Randomized Clinical Trial

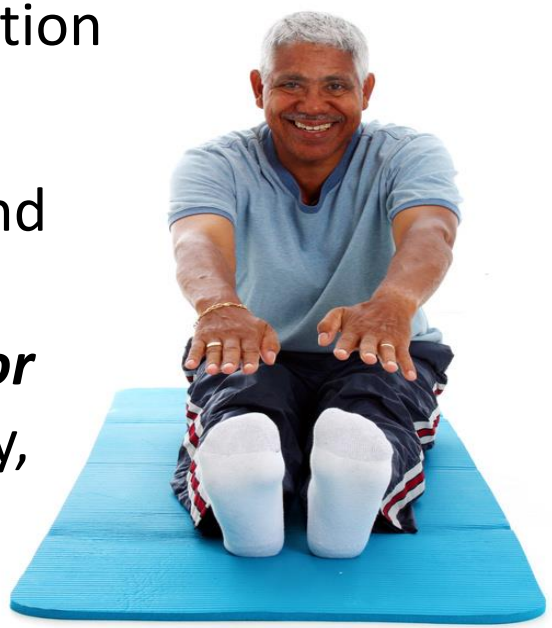
Adjusted Odds Ratio for At-Fault Crashes (5-year Crash Data)



Ball, K. et al. (2010) JAGS

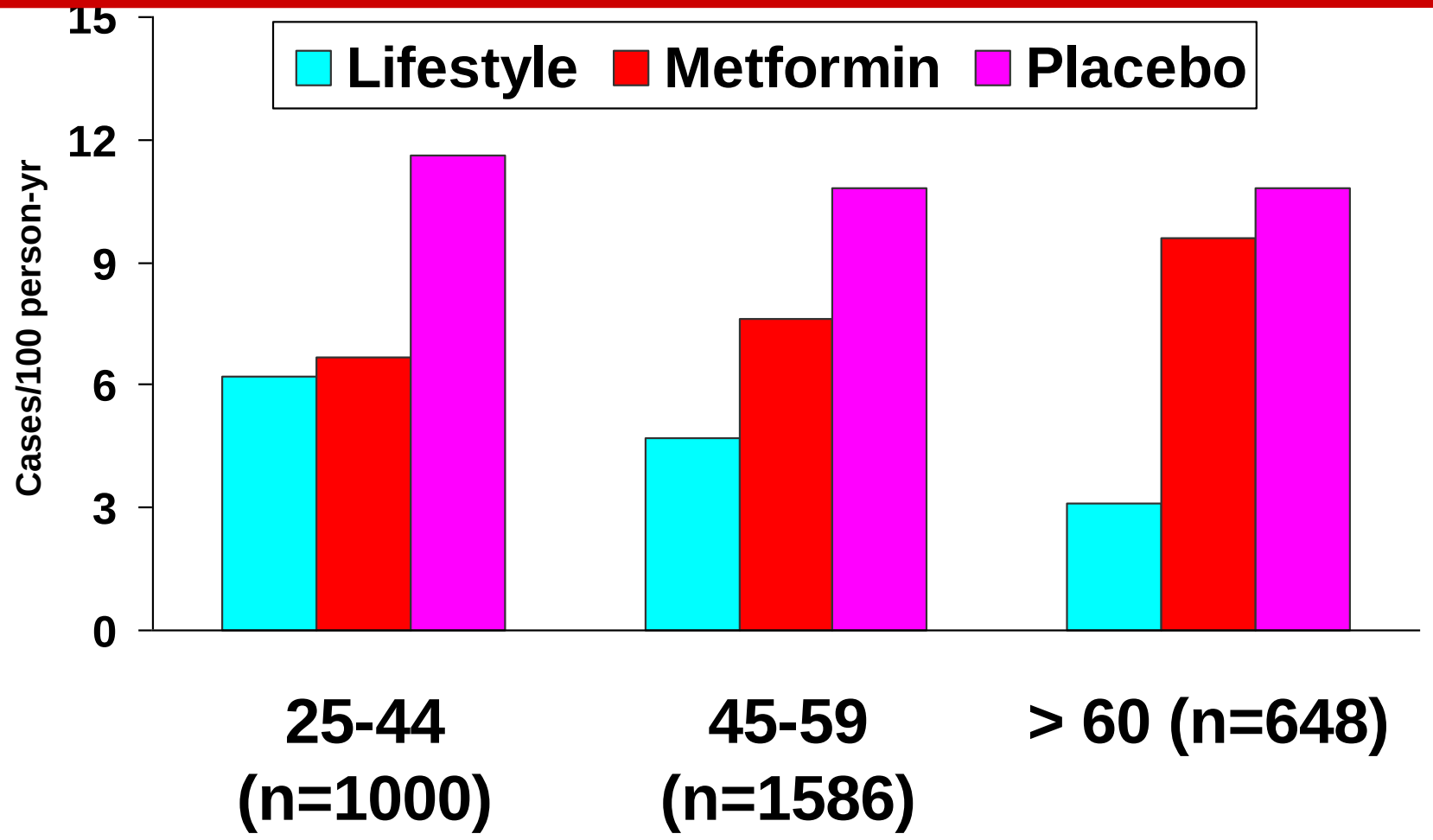
LIFE Study - RCT

- The ability to walk without assistance is critical for older people to live in a community and function well.
- The study showed that a regular, balanced and moderate exercise program followed for an average of 2.6 years ***reduced the risk of major mobility disability by 18 percent*** in an elderly, vulnerable population.
- Exercises included walking, and strength, flexibility, and balance training activities.



Pahor, M et al. (2014) *JAMA* 2014 May 27

Diabetes Prevention Trial RCT
Effects by Age

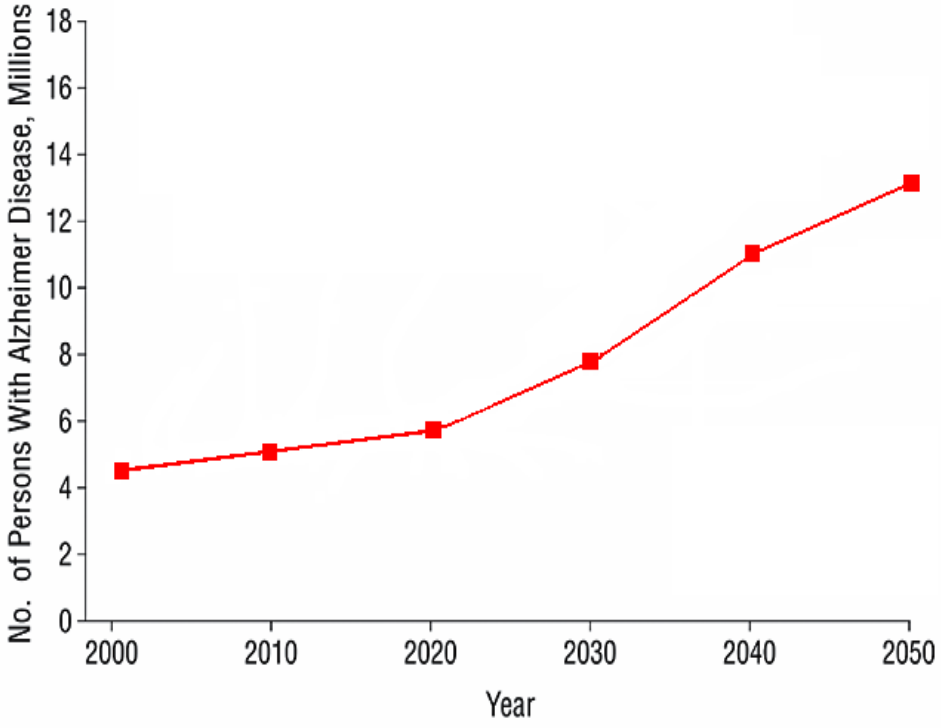


Diabetes Prevention Program, 2001

Alzheimer’s Disease

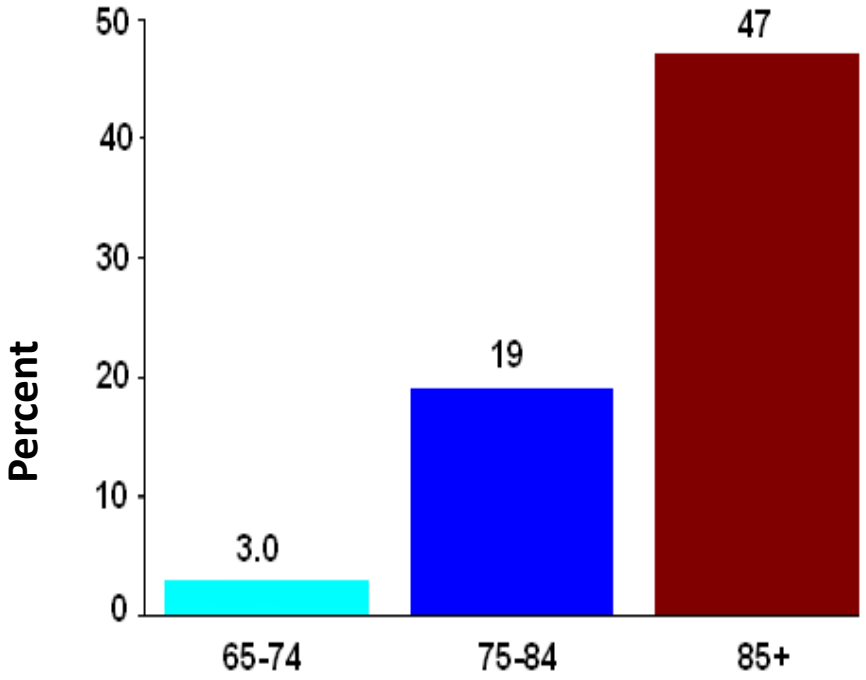
Prevalence of Probable Alzheimer's Disease In the United States

Number of Persons with AD in Millions



Evans, Arch Neurol, 2003.

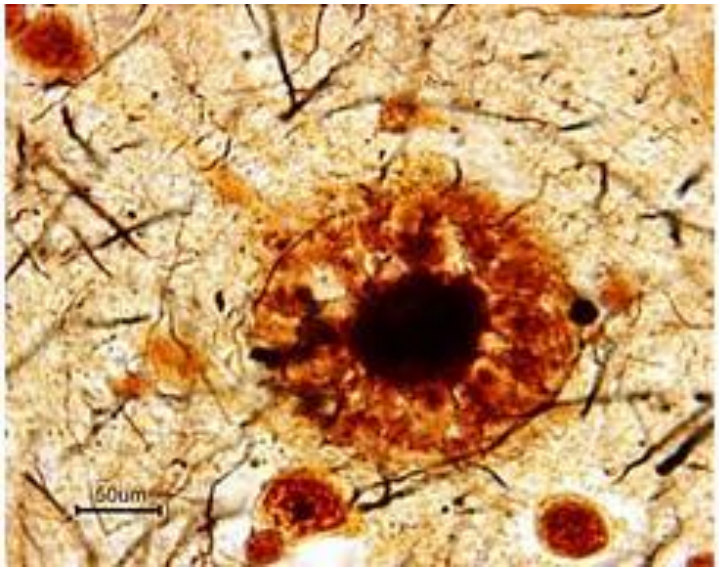
Percent of Persons with AD by Age

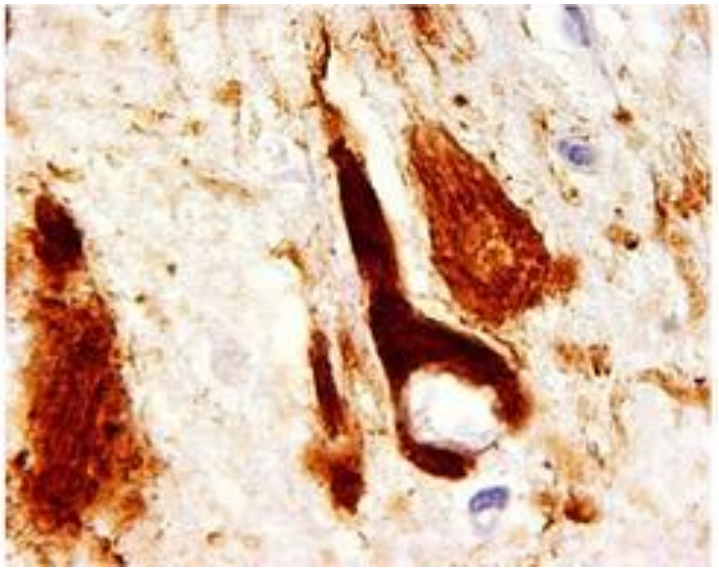


Evans, *JAMA*, 1989

Plaques (Aβ amyloid) and tangles (tau) in post-mortem brain of Alzheimer's disease

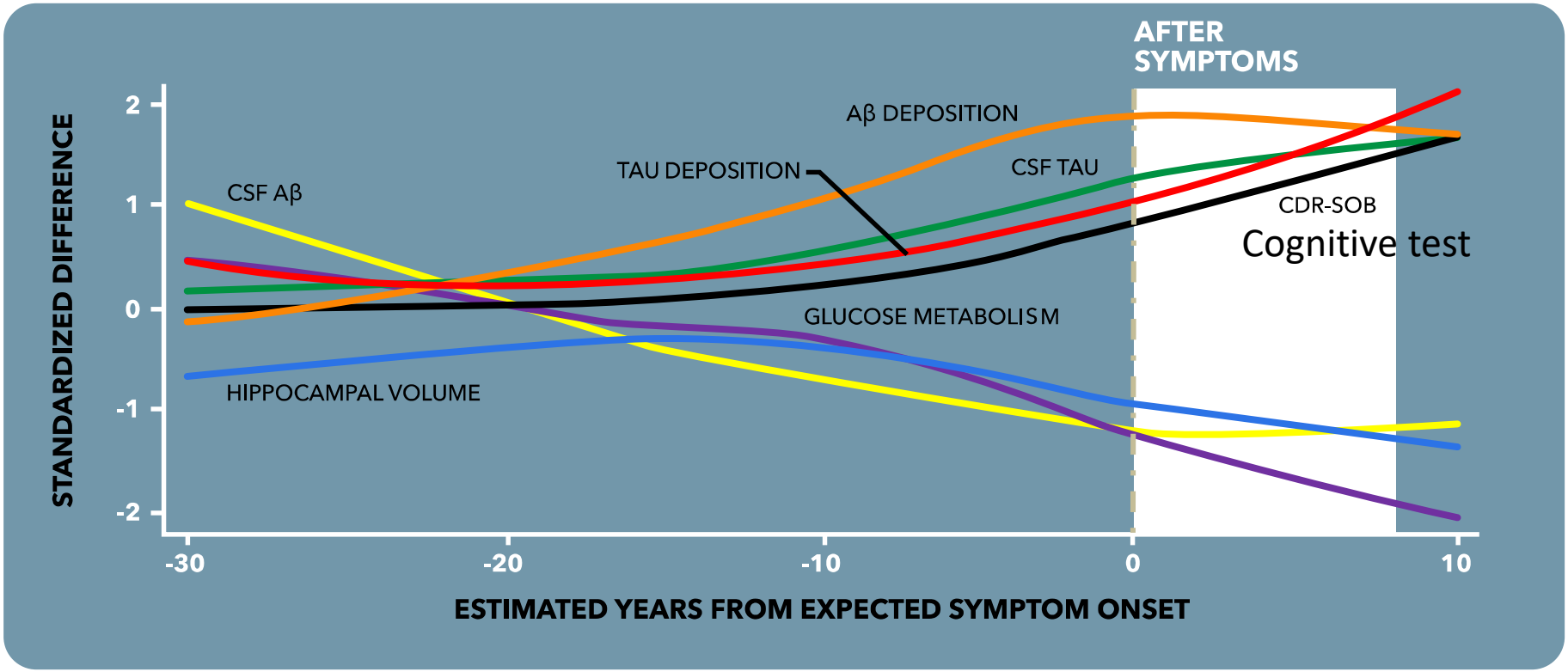
Described by Dr. Alois Alzheimer 1906





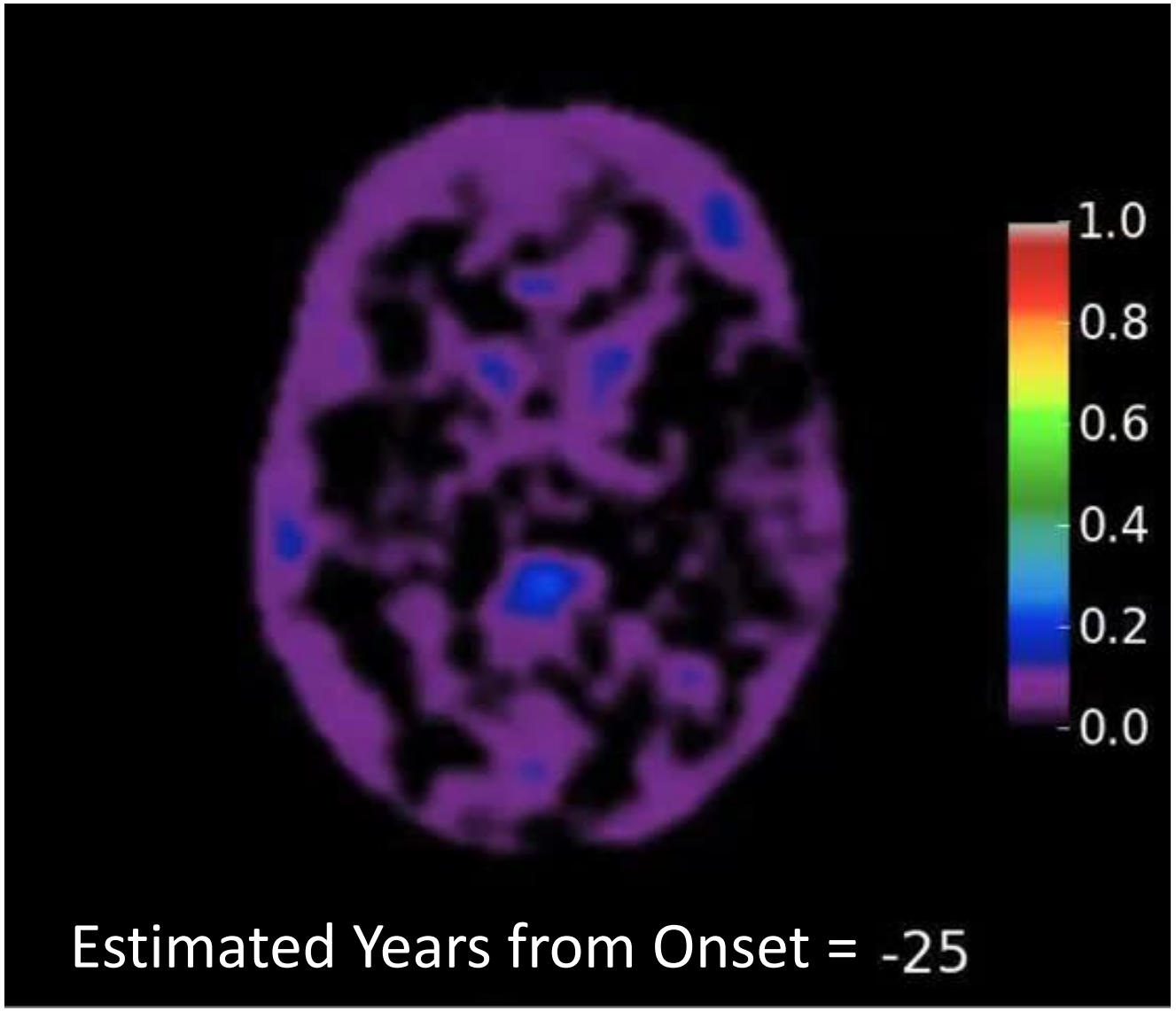
Biological Changes Years Before AD Symptom Onset

How early can we intervene?



Adapted from Bateman RJ et al. (2012) *N Engl J Med*; Aug 30; 367:795-804

Aβ Deposition in Autosomal Dominant AD
Years before Expected Clinical Symptoms



Courtesy of Tammie Benzinger; Bateman, R et al. (2012) *N Engl J Med* 367(9):795-804.

Biological Changes Years Before AD Symptom Onset

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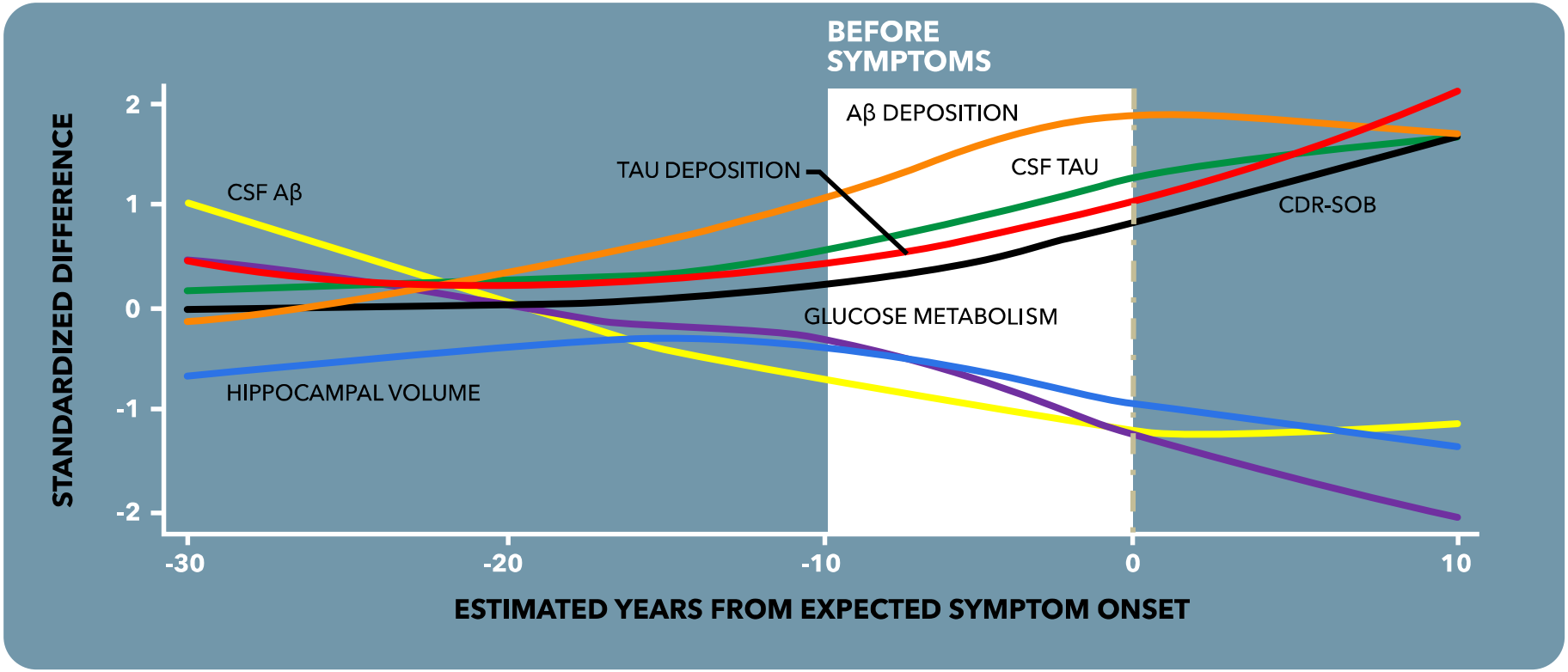
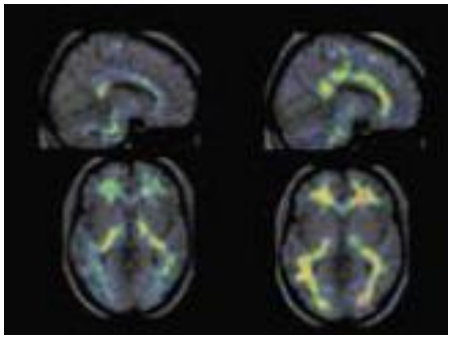


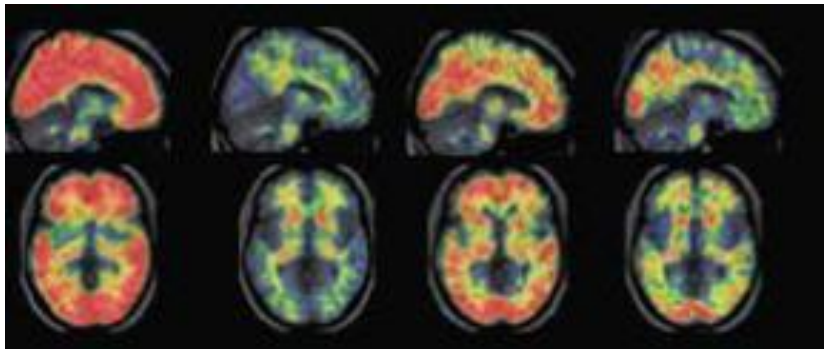
Adapted from Bateman RJ et al. (2012) *N Engl J Med*; Aug 30; 367:795-804

Early Intervention May Be Possible –
Thanks to Trial Volunteers from a Colombian Family

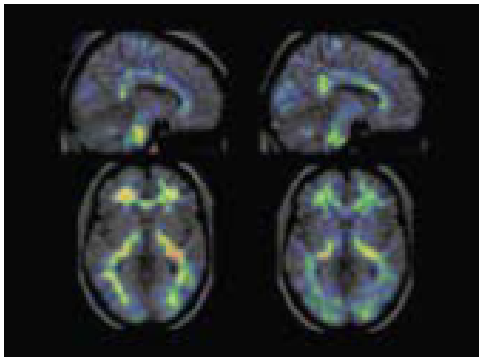
Non-Carriers, late 30's



Gene Carriers, late 30's



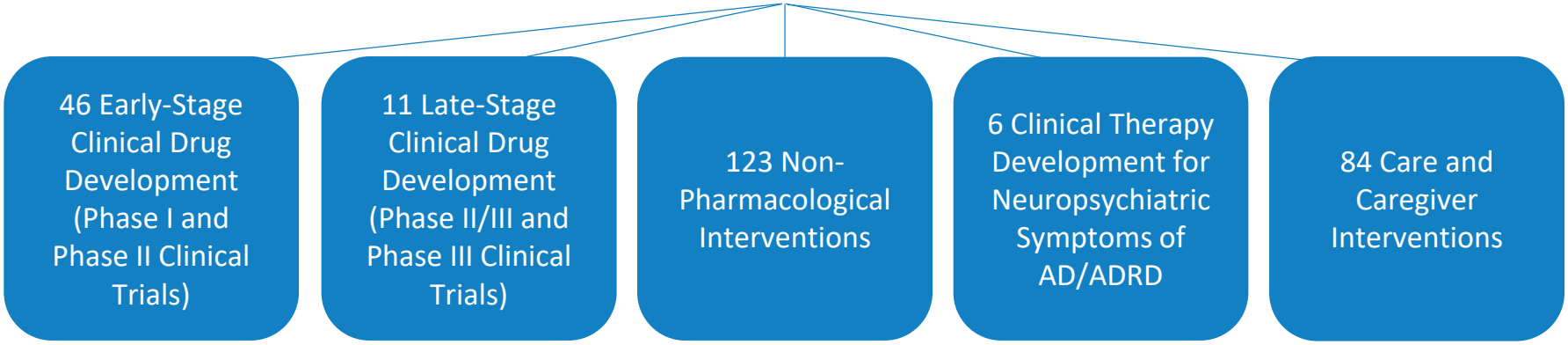
Beta-amyloid, late 20's



Dementia onset is in late 40's

Fleisher, AS, Reiman, EM and colleagues (2012). *Lancet Neurology*

Active NIA AD/ADRD and Related Intervention and Prevention Trials (~270)



Amyloid (11)
Receptors (2)
Sleep (1)
Growth factors and Hormones (2)
Inflammation (3)
Metabolism and Bioenergetics (2)
Multi-target (2)
Neurogenesis (2)
Oxidative stress (3)
Synaptic Plasticity/ Neuroprotection (6)
Vasculature (2)
Other (10)

Amyloid (7)
Synaptic Plasticity/ Neuroprotection (2)
Tau (1)
Vasculature (1)

Assistive Tech/Device (13)
Cognitive Training (18)
Combination Therapy (11)
Decision-Supportive (5)
Diagnostic Tools (8)
Diet/Supplements (7)
Exercise (27)
Light Therapy (1)
Neurostimulation (14)
Sleep (6)
Other (13)

Pharmacological (4)
Non-Pharmacological (2)

Improving Care for PWD (43)
Improving Family or Informal Caregivers (41)

https://www.nia.nih.gov/research/ongoing-AD-trials

Possible Environmental and Lifestyle Factors Affecting Alzheimer's Disease

- Age
- Head Injury
- High Blood Pressure
- Cholesterol
- Homocysteine
- Diabetes
- Education/Brain Reserve/Occupation
- Exercise
- Social Contacts

NASEM (National Academies) Findings Strength of Evidence for Interventions

- Insufficient evidence to justify a public health information campaign to encourage adoption of specific interventions
- Three interventions supported by encouraging, but inconclusive evidence
  - Cognitive training
  - Blood pressure management for people with hypertension
  - Increased physical activity
- All have minimal risk of harm, and two known to be beneficial for other conditions

2017

SPRINT-MIND Research Question

SPRINT Memory and Cognition in Decreased Hypertension

Does intensive blood pressure control compared with standard control reduce the occurrence of dementia?

Randomized Controlled Trial Target Systolic Blood Pressure

Intensive Treatment
Goal SBP < 120 mmHg
(n= 4,278)

Standard Treatment
Goal SBP < 140 mmHg
(n= 4,285)

SPRINT
Systolic Blood Pressure Intervention Trial

The SPRINT MIND Investigators for the SPRINT Research Group (2019). *JAMA, 321*(6):553–561.

SPRINT-MIND: Secondary Cognitive Outcomes

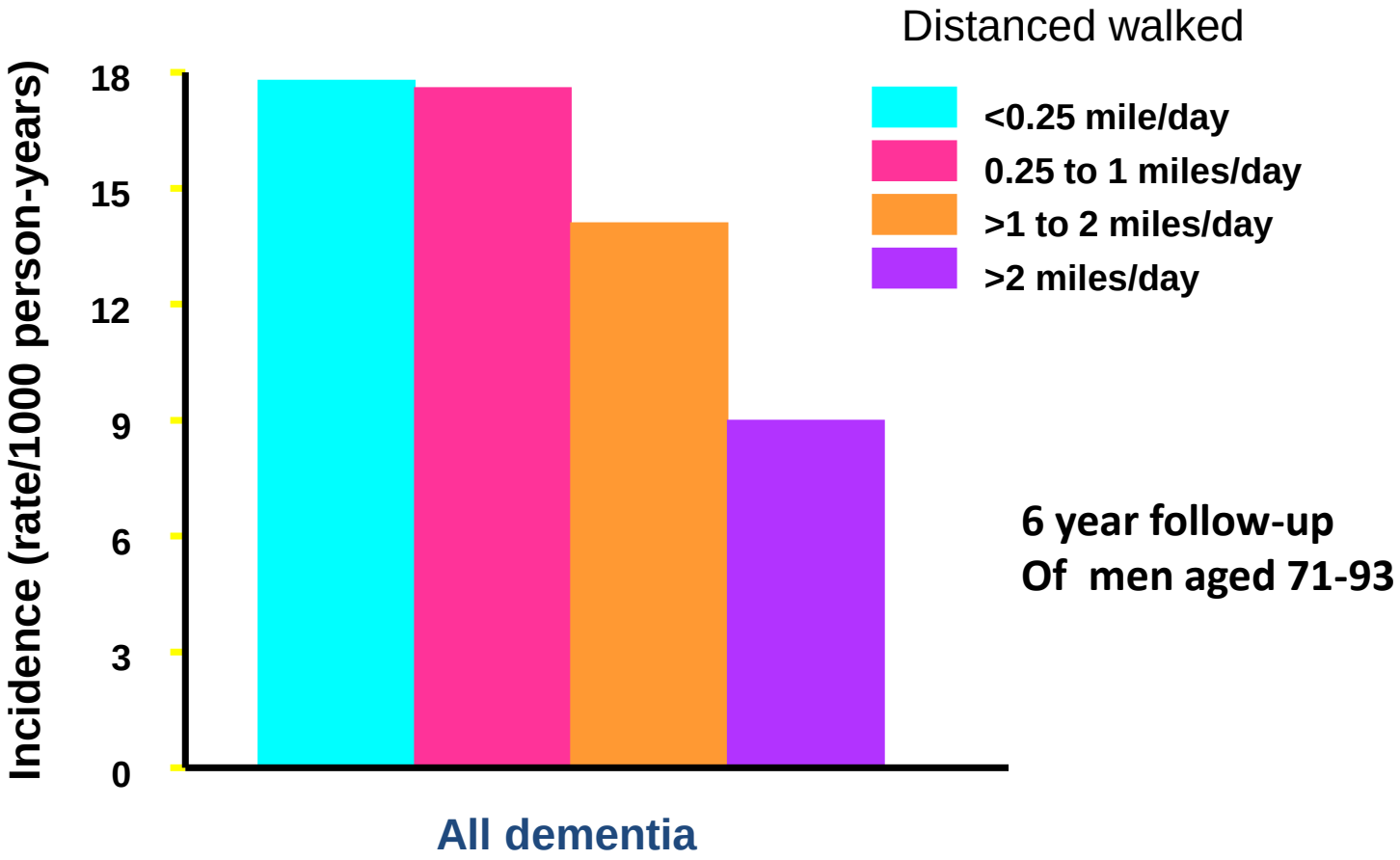
- 19% reduction in the rate of developing MCI
- 15% reduction in the rate of composite MCI and probable dementia

The SPRINT MIND Investigators for the SPRINT Research Group (2019). *JAMA, 321*(6):553–561.

Is Fitness Good for Your Brain?

NY Times, 2007/11/08

Age-adjusted Incidence of Dementia According to Distance Walked
An Observational Study



Significant excess vs men who walked >2 miles/day ($p<0.05$)

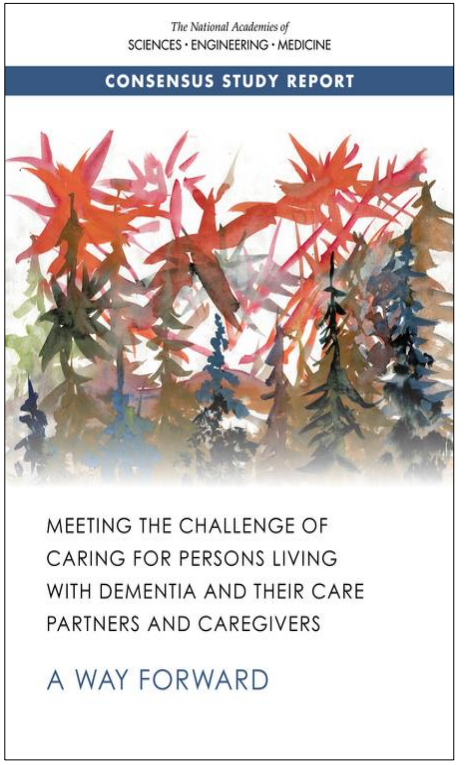
Abbott et al., JAMA, 2004 Honolulu-Asia Aging Study

National Academies Recommendations on Dementia Care & Caregiving

Key Messages from NASEM Synthesis:

Expert committee **report outlining a set of recommendations** on the readiness of interventions for broad dissemination and implementation, **and research gaps** in the field –***February 2021***

- Most caregiving interventions were not assessed in the study because they had small sample sizes, were pilots, or had high risk of bias
- Two types of interventions demonstrated low-strength evidence of benefit in clinical trials:
  - **Collaborative Care**
  - **Resources for Enhancing Alzheimer's Caregiver Health (REACH) II**
- The report recommends broader implementation of these programs in real-world settings that allow for continual monitoring, evaluation, and quality improvement



https://www.ncbi.nlm.nih.gov/books/NBK567818/

Introducing the new Alzheimers.gov!

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DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

Biology of Aging

Aging as a Risk Factor for Multiple Diseases/Conditions

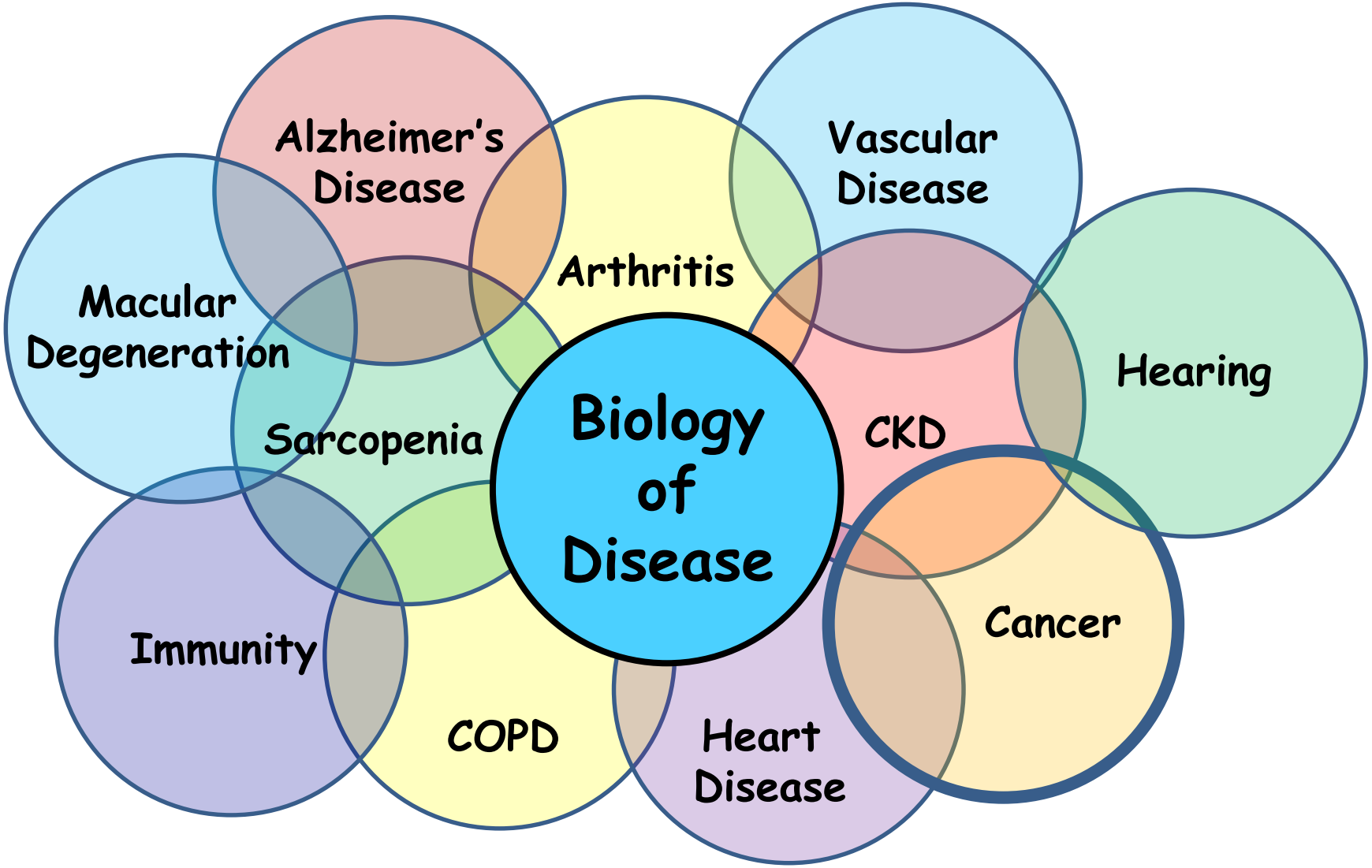
Leading Causes of Death, Adults 65+ Years, 2014

Rank	Cause of Death
1	Heart Disease
2	Cancer
3	Chronic lower respiratory diseases
4	Stroke
5	Alzheimer's disease
6	Diabetes
7	Accidents (unintentional injuries)
8	Influenza and pneumonia
9	Kidney disease
10	Septicemia

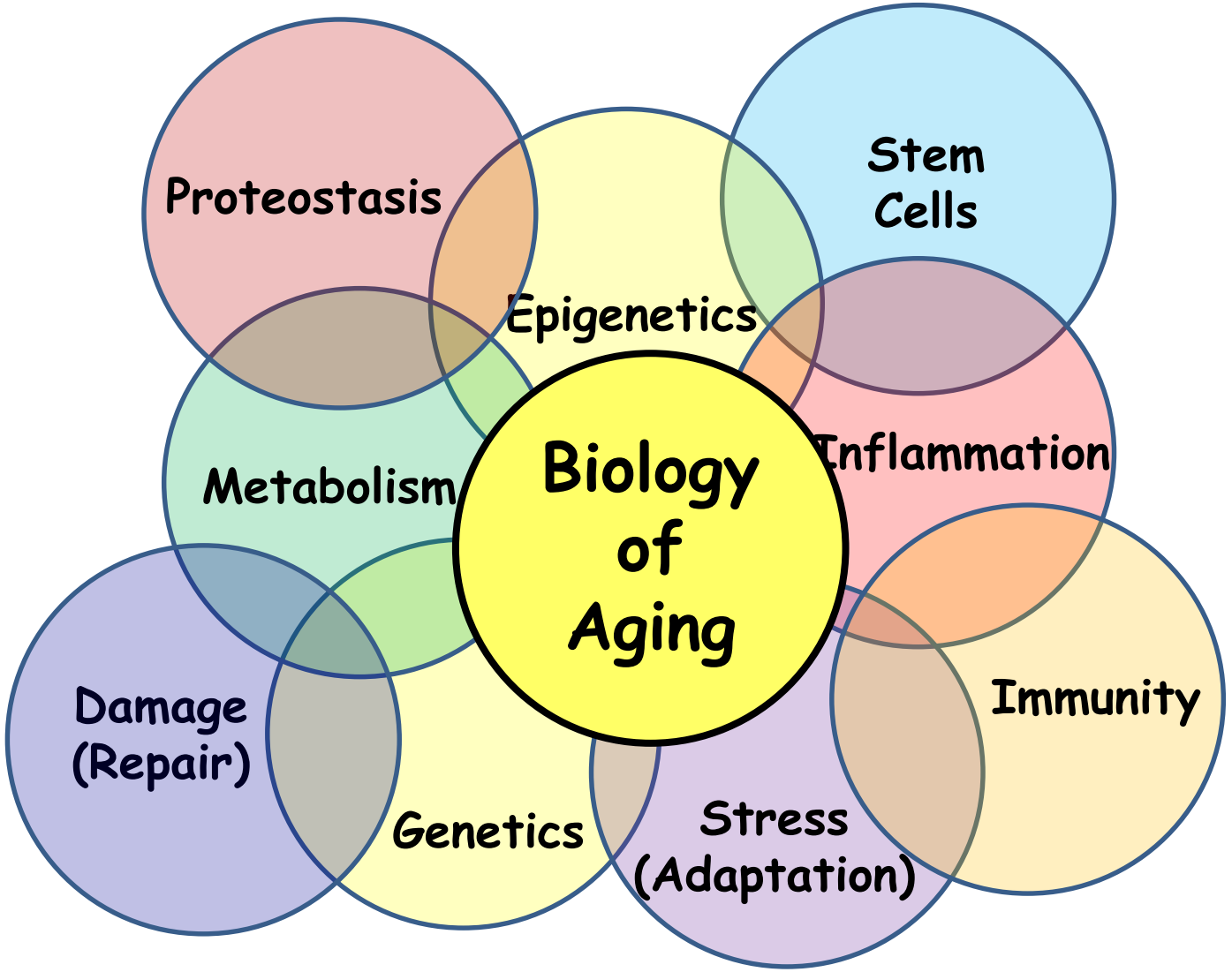
Many diseases and conditions "of aging" may be tractable if we can intervene in the aging process itself

SOURCE: CDC/NCHS,. Public-use 2014 Mortality File. Deaths: Final data for 2014. National vital statistics reports . Available from: http://www.cdc.gov/nchs/data/dvs/lcwk3_2014.pdf

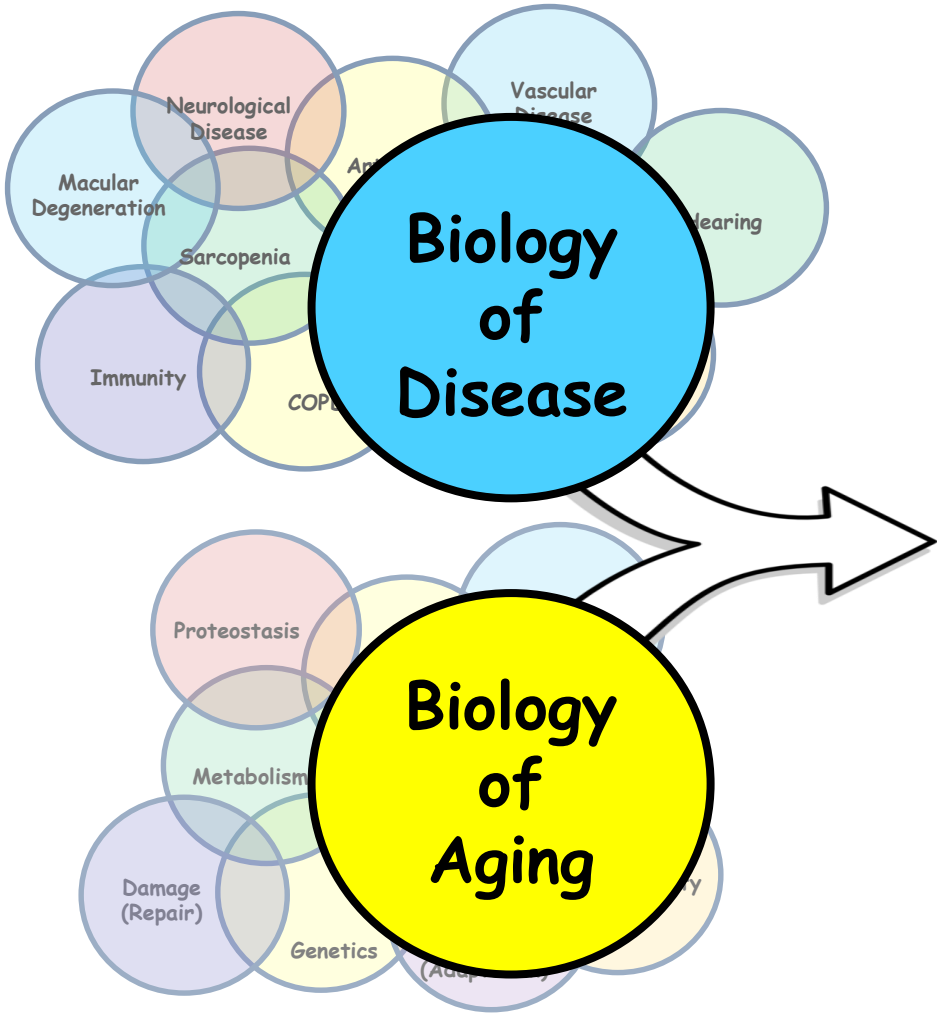
Many Chronic Diseases are Studied Individually



Aging is the Major Risk Factor for Most Chronic Diseases



Convergence



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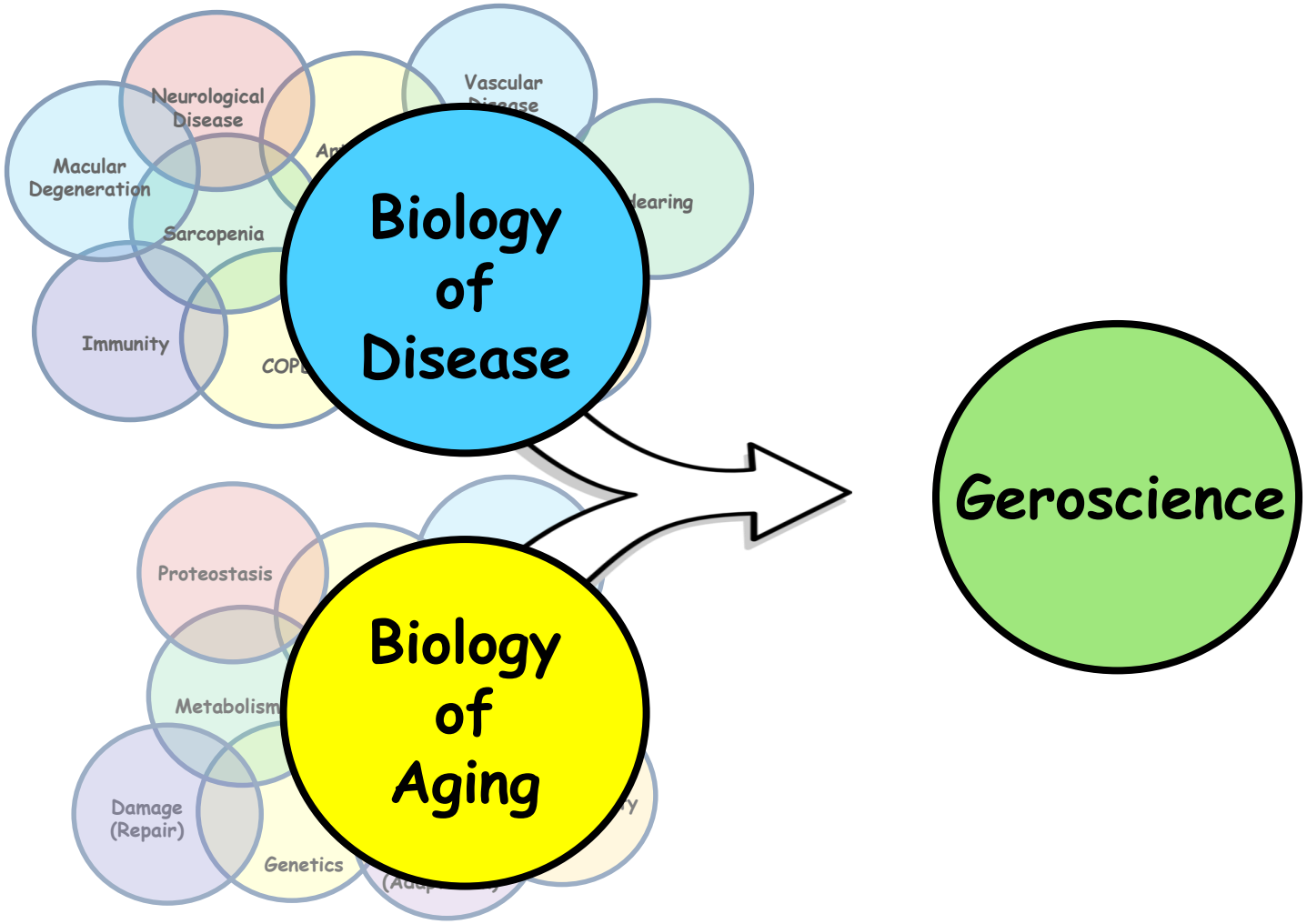

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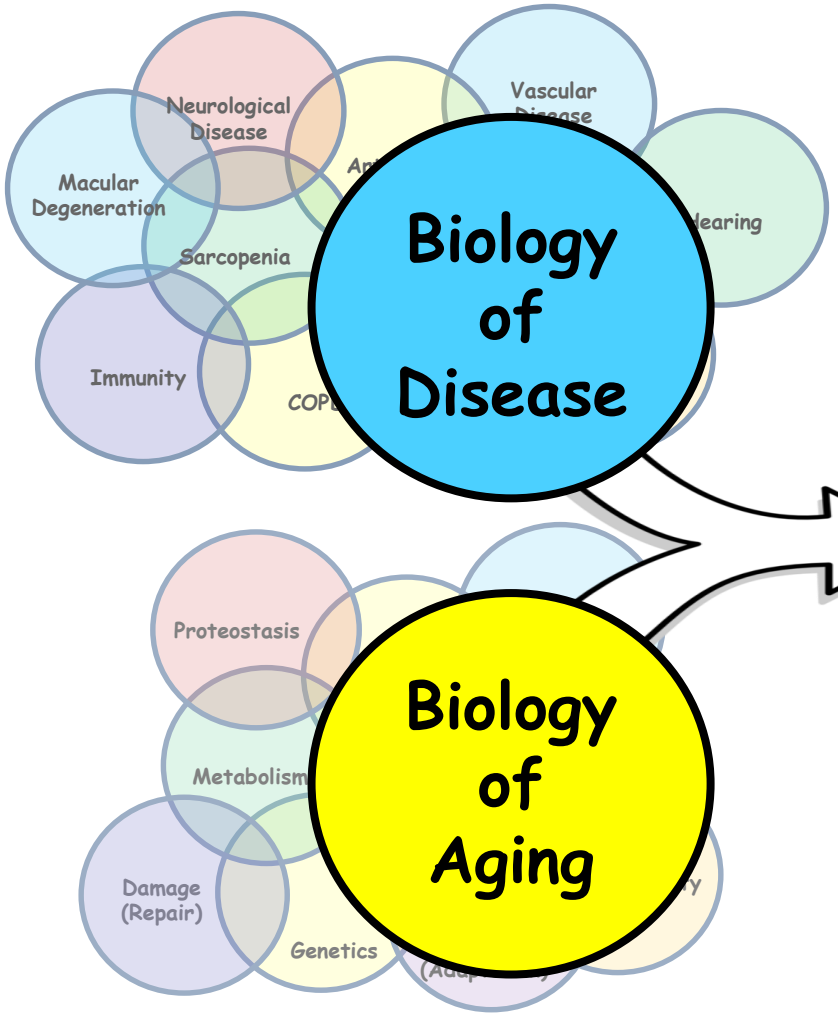
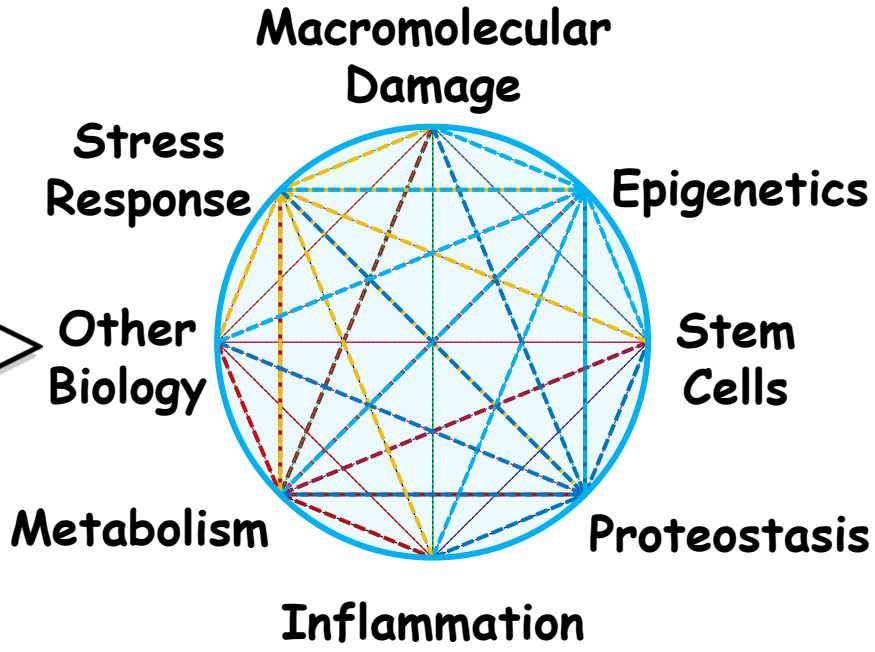




Sierra & Kohanski
J Gerontol June 2014

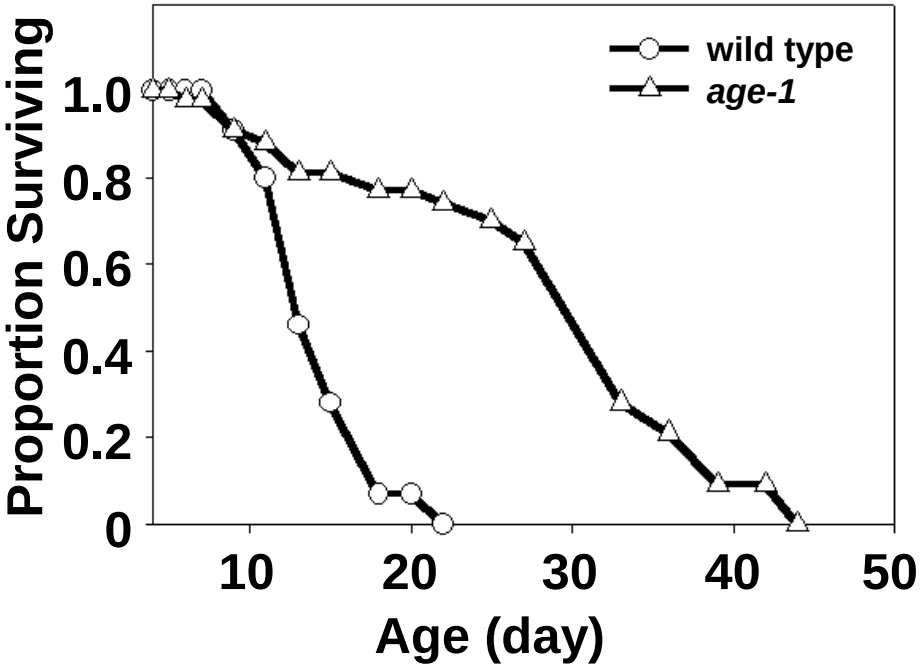
Kennedy *et al.*
Cell Nov 2014

Familial Determinants of Human Longevity

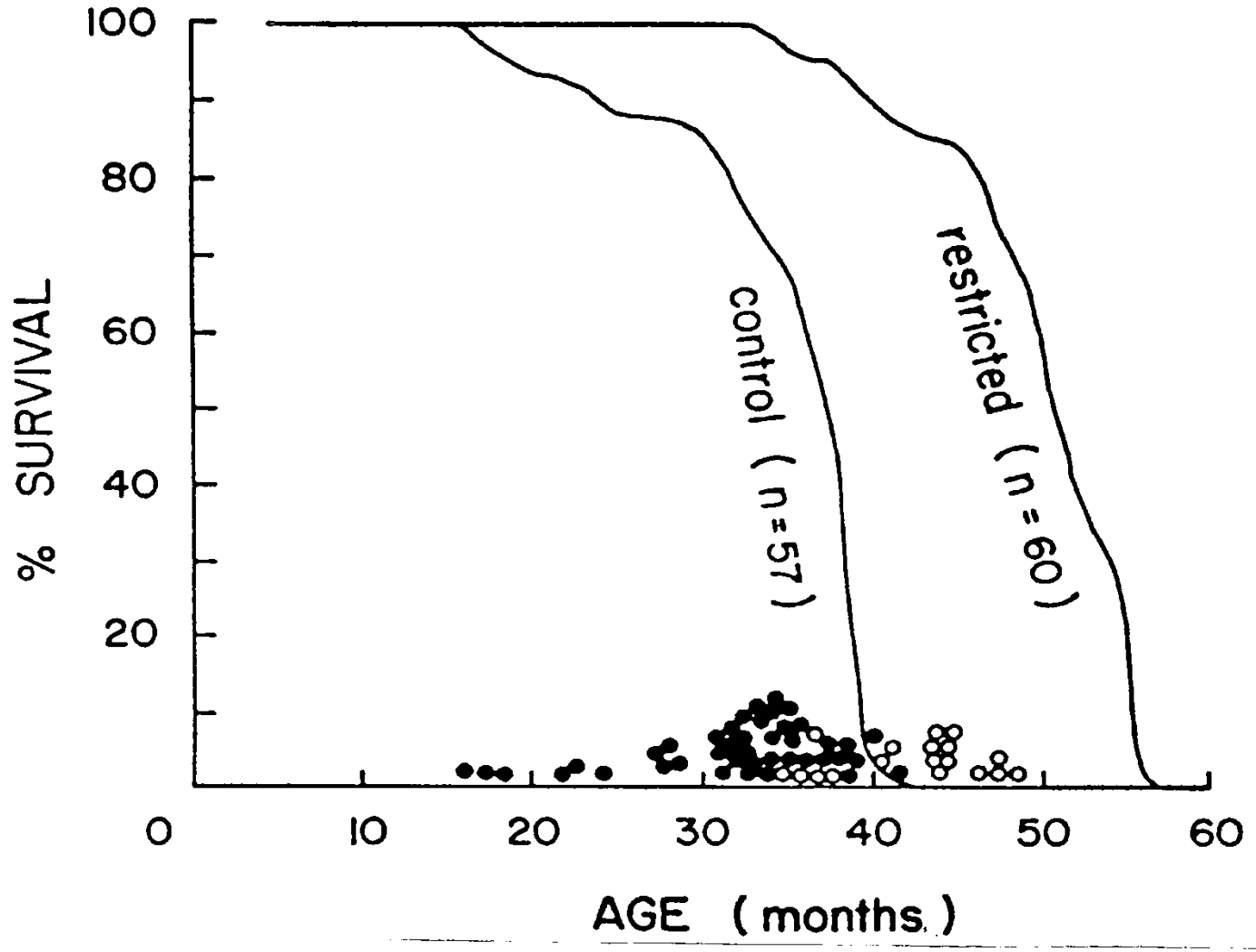
Courtesy: Dr. Nir Barzilai

Longevity Genes Across Species

Animals with a mutation in the *age-1* gene live longer than wild type



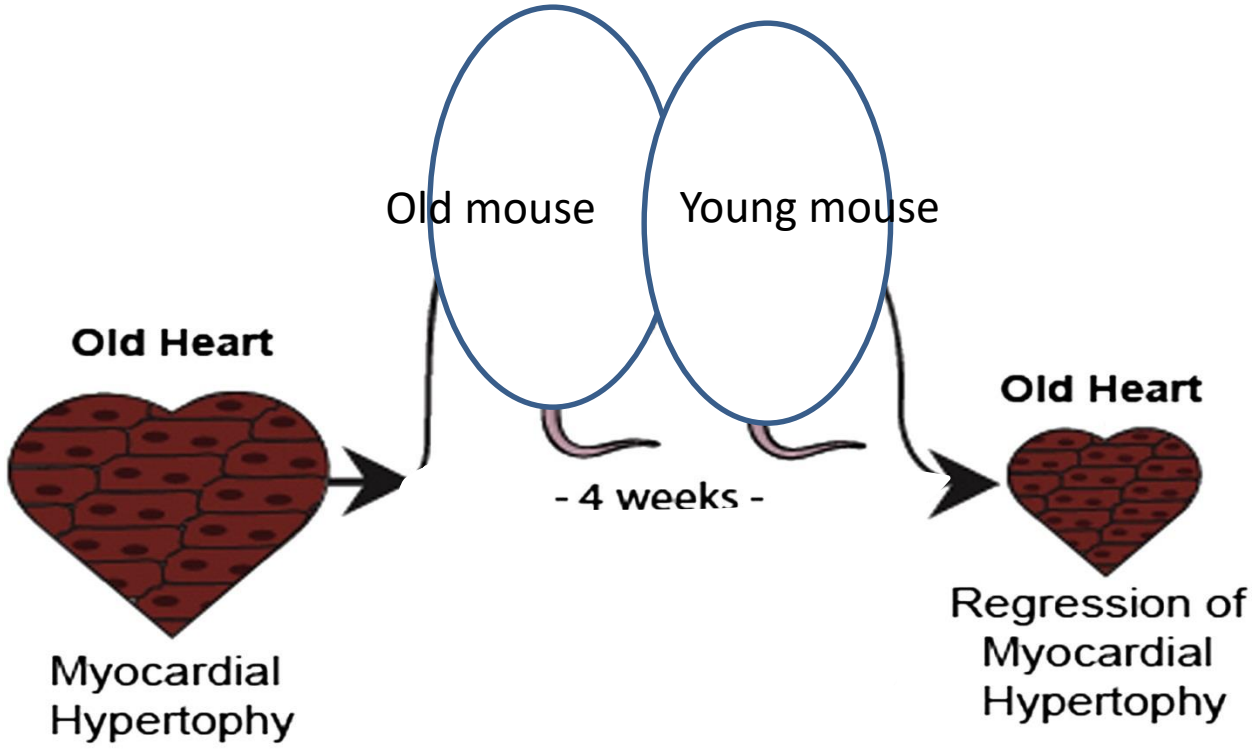
Effect of Caloric Restriction on Longevity in Rodents



Weindruch R. (1988)

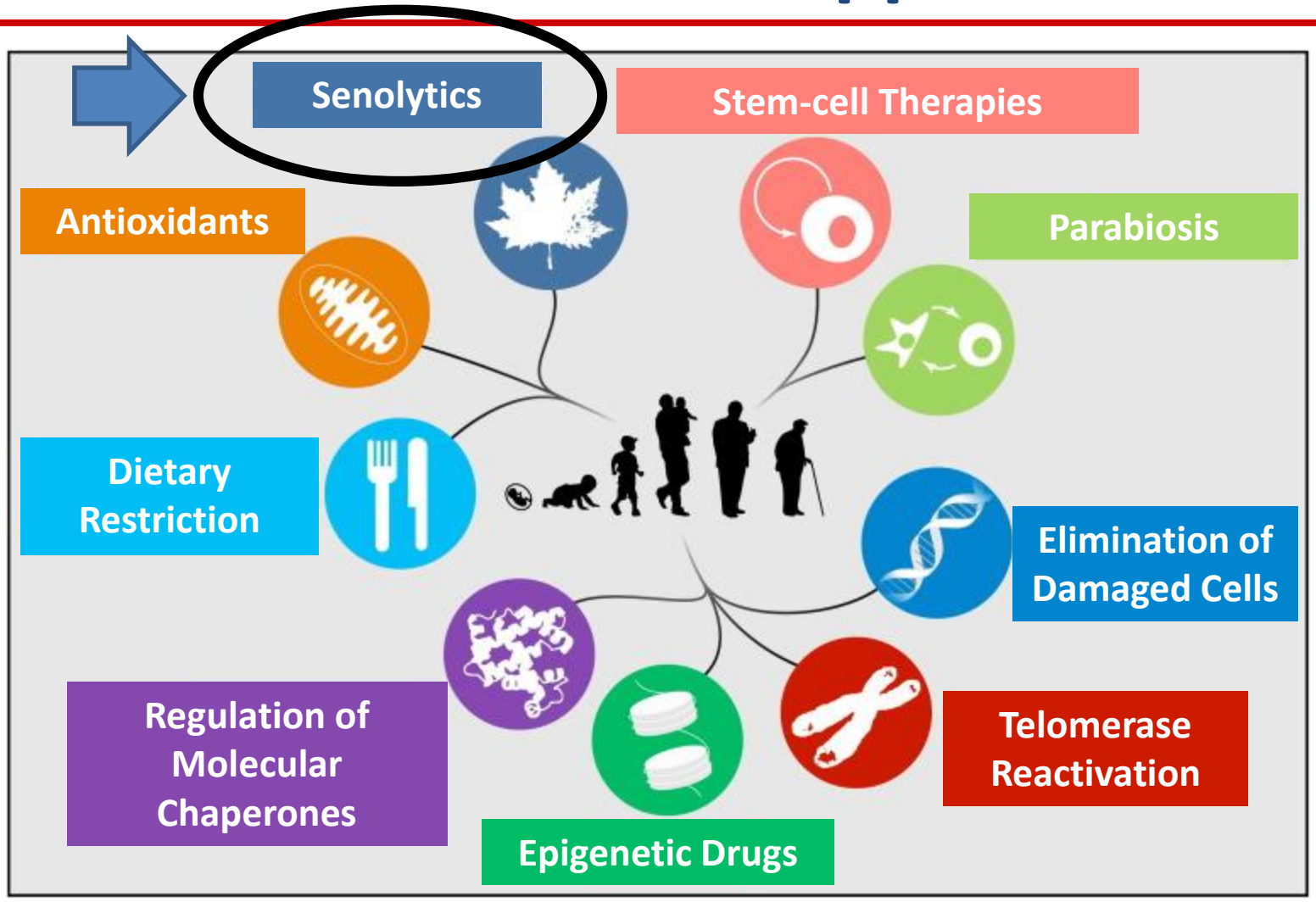
Circulating factors reverse age-related pathology

Or: How can you repair a broken heart?



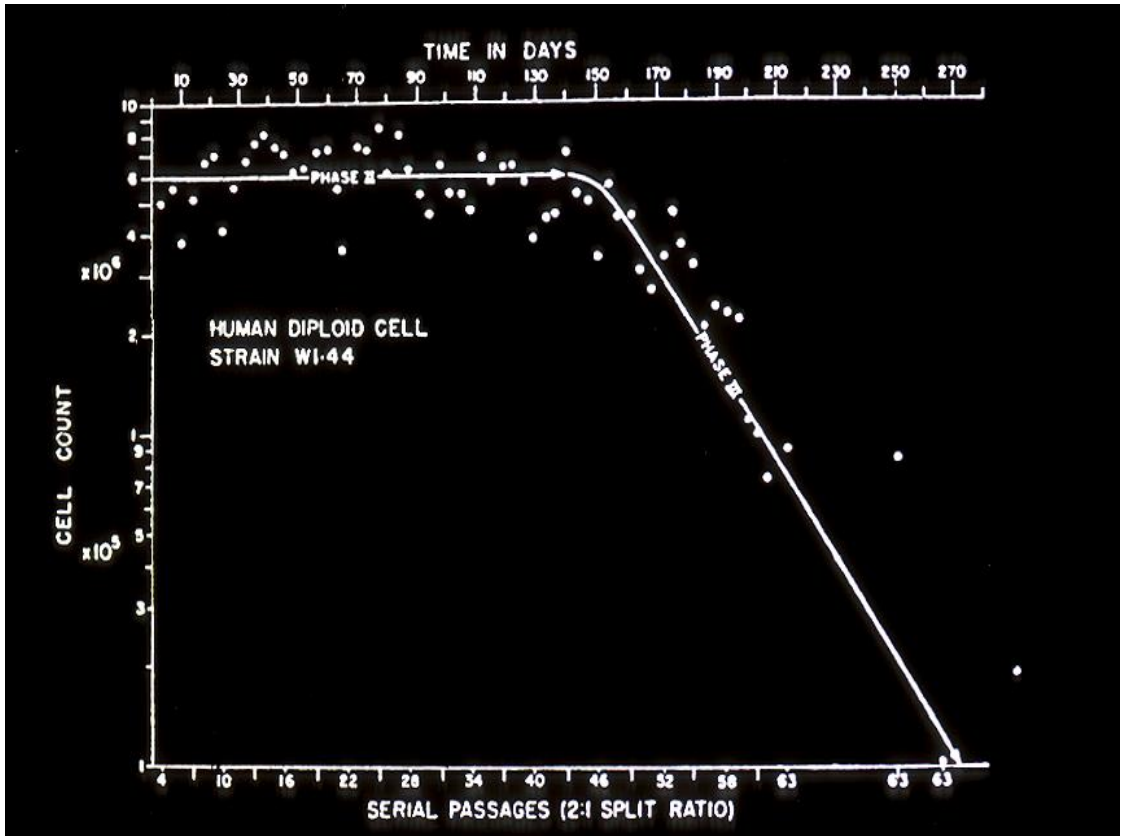
Loffredo et al. (Lee / Wagers) Cell 153:828 (2013)

Geroscience: Interventions and Approaches



Adapted from: López-Otín, C et al. (2013). *Cell* 153: 1194-1217.

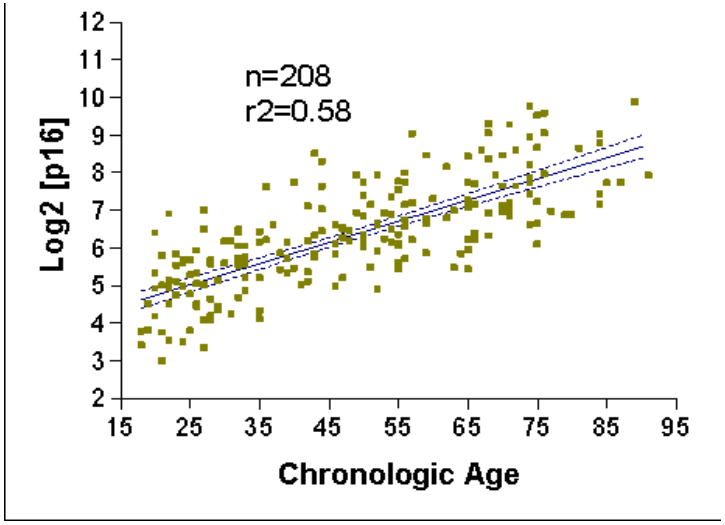
In 1961, L. Hayflick proposed that the limited replicative lifespan of cells in culture represented the phenomenon of aging at the cellular level



A cell senescence marker for aging (p16^{ink4a})

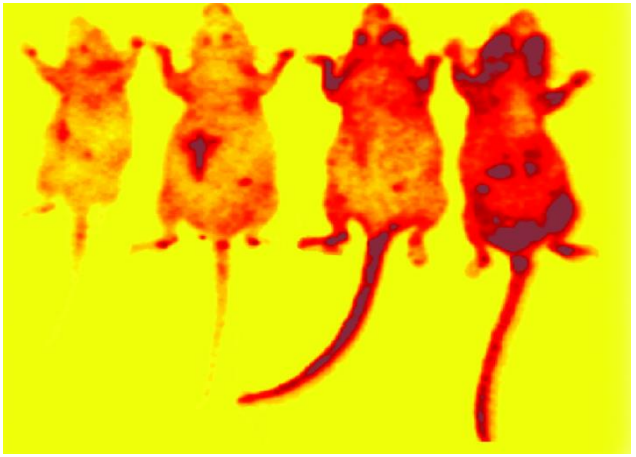
Sharpless lab, University of North Carolina

In Humans p16^{ink4}a expression in CD3+ T cells)



- **increases 1.4-fold per decade => 16-fold over 8 decade adult lifespan.**
- **Increase seen well before 'aging' is apparent.**

In Mice, a reporter of p16^{ink4} expression in all cells of the body



16 40 64 80

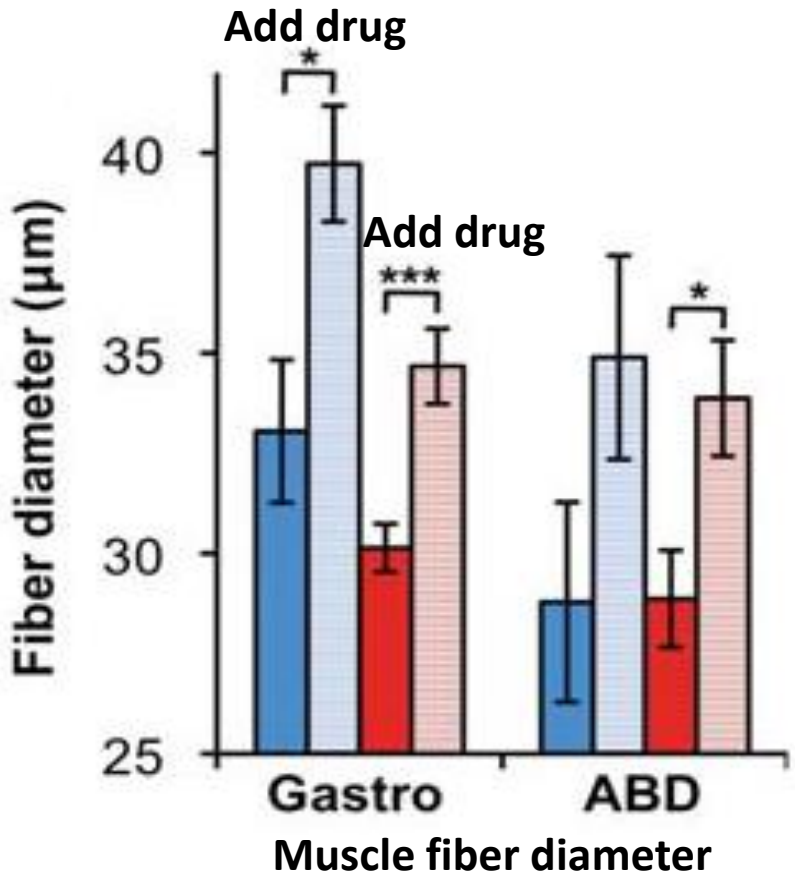
Weeks of age (one mouse)

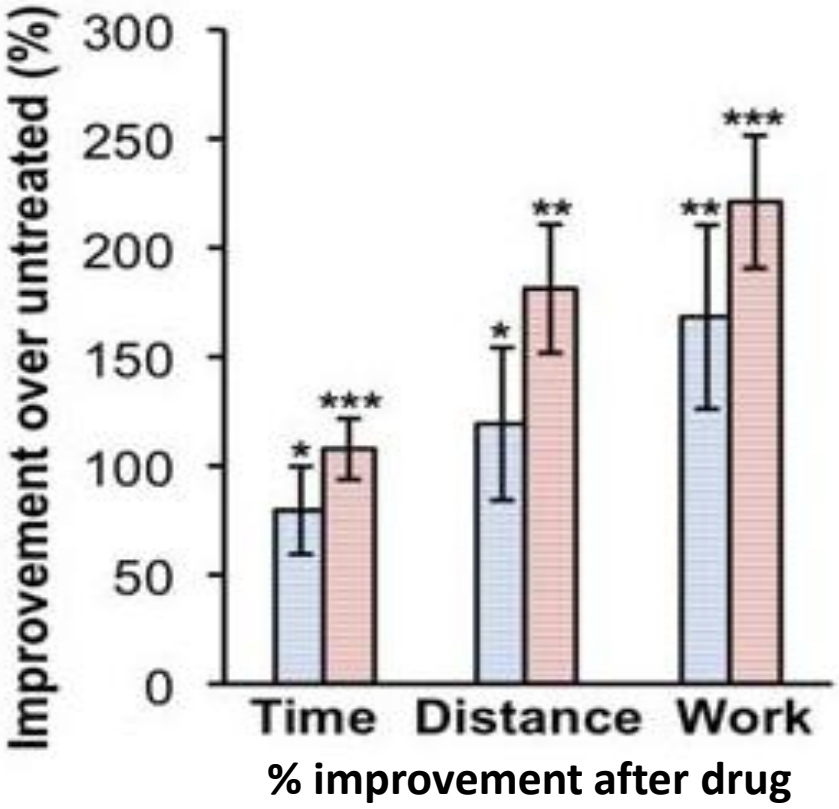
p16ink4a is a protein molecule important for regulating cell division.

Expression of this molecule increases when cells reach replicative senescence.

Adapted from
Liu et al Aging Cell 8:439-448 (2009) – human studies
Burd et al. Cell 152: 340-351 (2013) – C57BL6 mouse model

Removal of p16^{Ink4a}-positive Senescent Cells in Transgenic Mice Delays Ageing-Associated Disorders



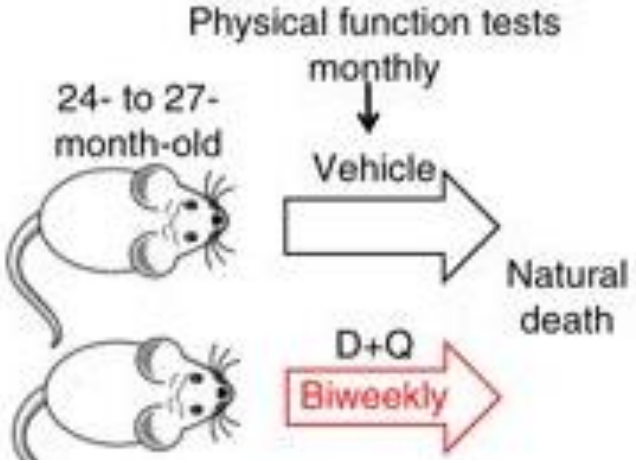


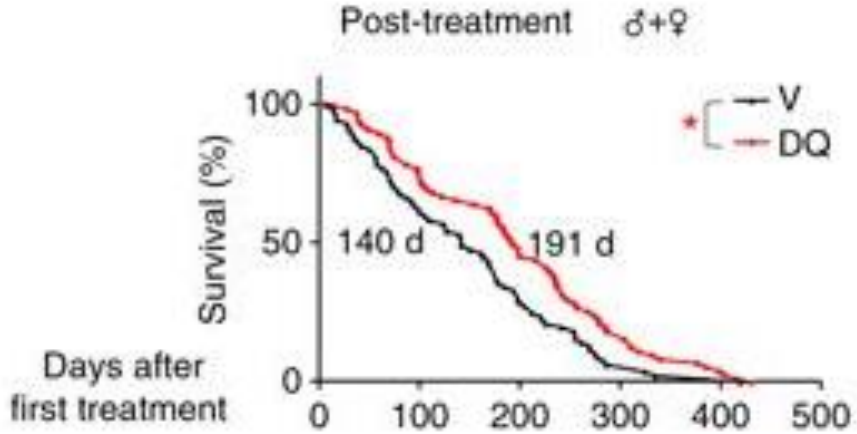
Transgenic mouse model for senescent cell elimination: p16-Ink4a promoter-dependent dimerizable caspase 8

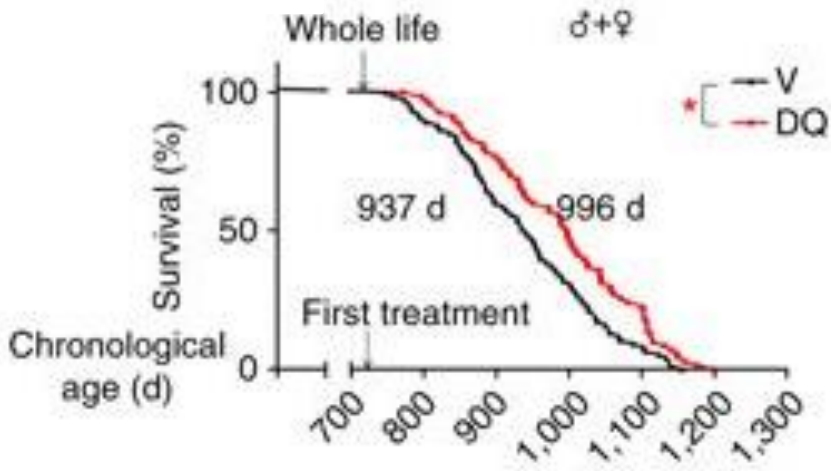
Baker *et al.*
Nature 2011

Treatment with Senolytic Drugs Extends Remaining Lifespan in Normal Older Mice

Dasatinib + quercetin
to
Disable senescent cells







Xu, M. et al. (2018*). Nature medicine*.

Jeanne Calment

(d. August 4, 1997)

Age: 122 years,
5 months,
14 days