Longevity Leap: Mind the Healthspan Gap

Secilia Salem

Lifespan vs. Healthspan

Lifespan

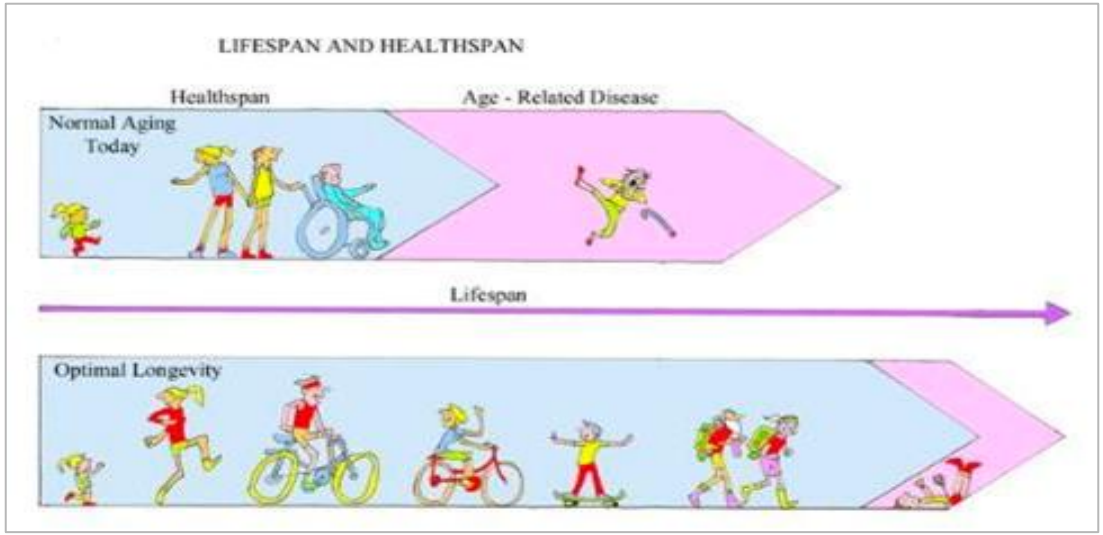
The period of time between the birth and death of an organism.

Healthspan

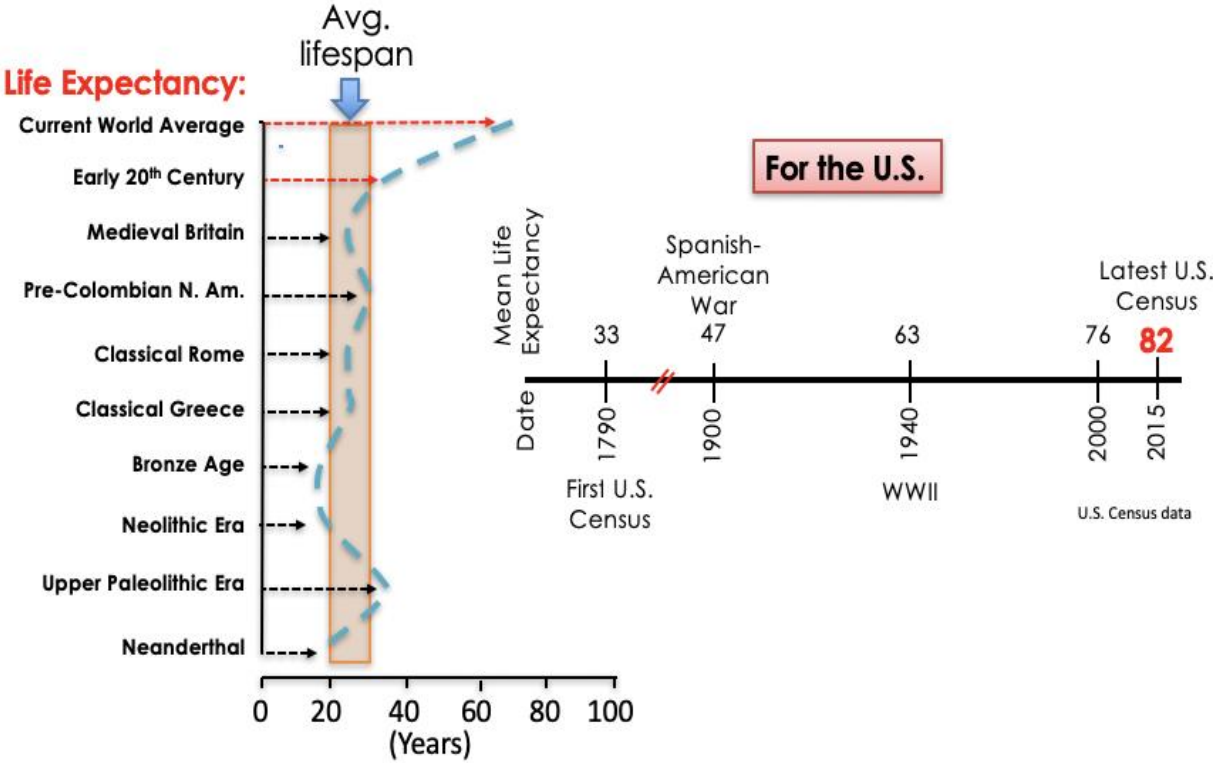
The period of time in life when one is free from disease and disability.

Average in US:

77.28 years (2020)



Why should we care about healthspan?



Medicine Has Extended Our Life Expectancy

Better Sanitation

Antibiotics

Dramatically decreased mortality from infectious diseases

Pre- & post-natal care

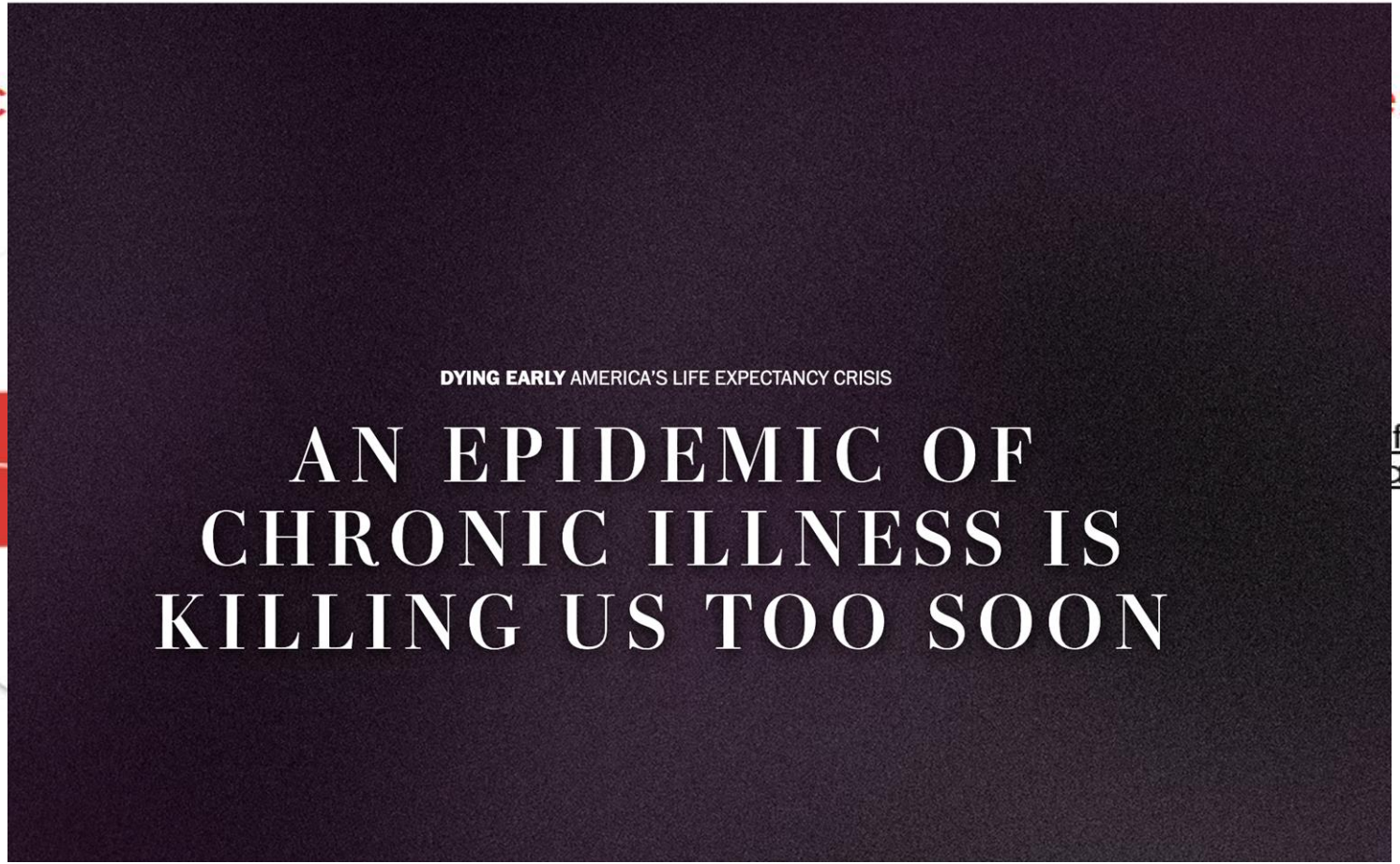
Lowered mortality in childbirth & infant mortality

Drugs

Has made otherwise lethal diseases "chronic" in nature

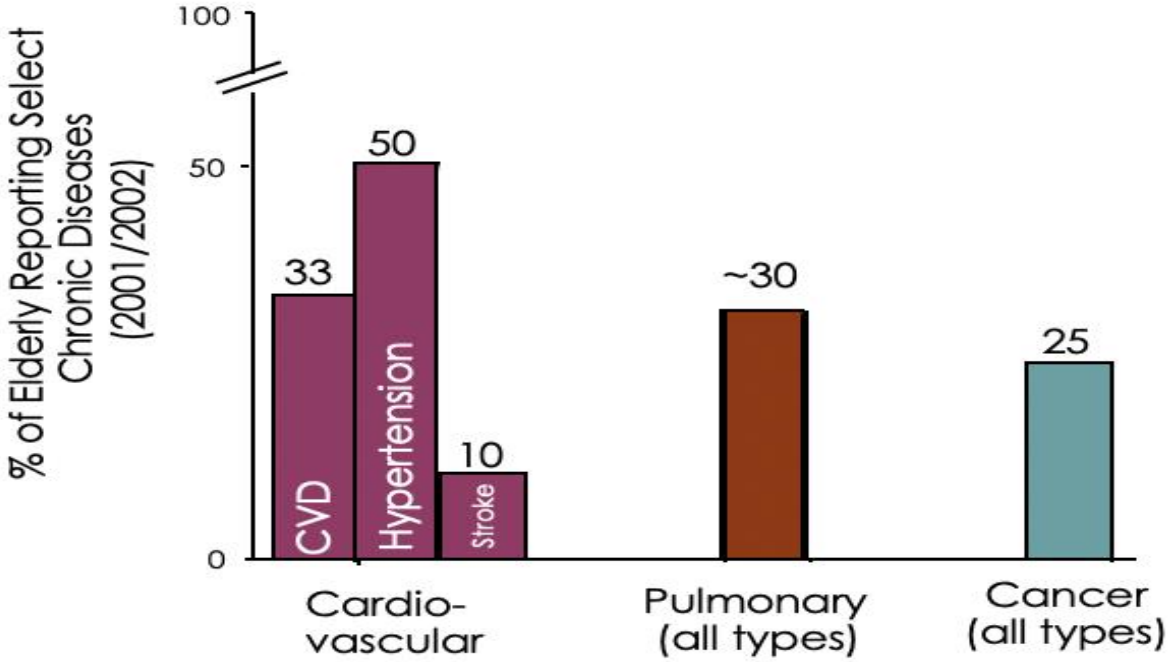
"Assist" Devices

Compensates for loss of physiological function


The Washington Post
Democracy Dies in Darkness
DYING EARLY AMERICA'S LIFE EXPECTANCY CRISIS
AN EPIDEMIC OF CHRONIC ILLNESS IS KILLING US TOO SOON

Older Adults are at High Risk for Chronic Disease

80% of Americans >65 yrs of age have at least 1 chronic disease



Source: CDC, National Center for Health Statistics, National Health Interview Survey

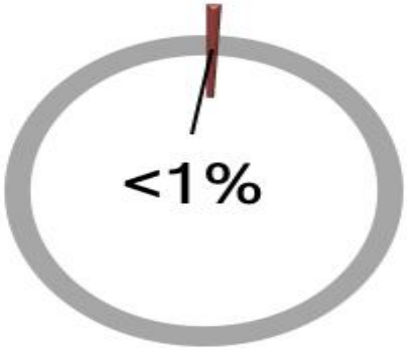
Age-related Loss in "Activities of Daily Living" (ADL)

Characteristic	% of those ≥ 65 years
Weight loss	17.5
Exhaustion	15.5
Low Energy	27.0
Slowness	43.2
Weakness	21.8

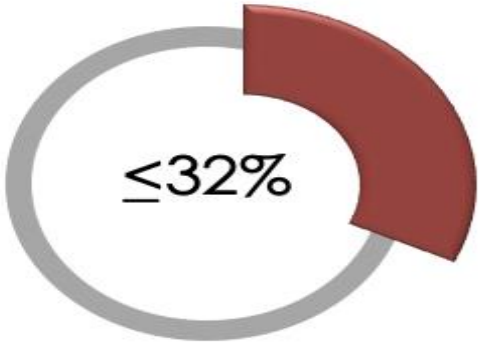
J Gerontol A Biol Sci Med Sci (2007) 62: 738-743.

Dementias Become Increasingly Common With Age

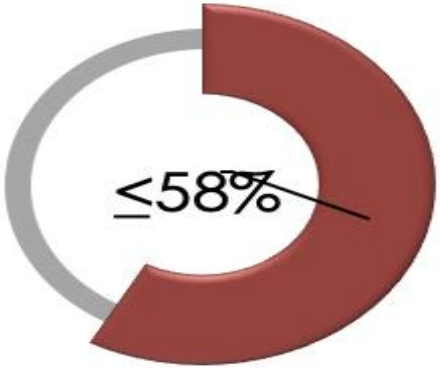
Alzheimer's Disease:



Under 65 years



80 to 89 years

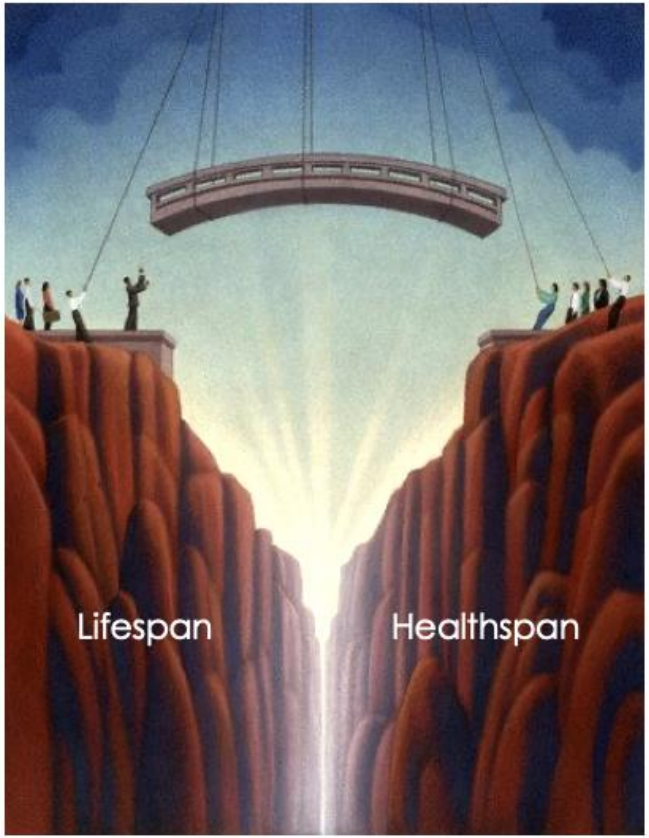


90 to 95 years

…Mild cognitive impairment is even more widespread with age:

Beydoun et al. BMC Public Health 14: 643, 2014

Is There a Way to Bridge the Gap Between Lifespan and Healthspan?

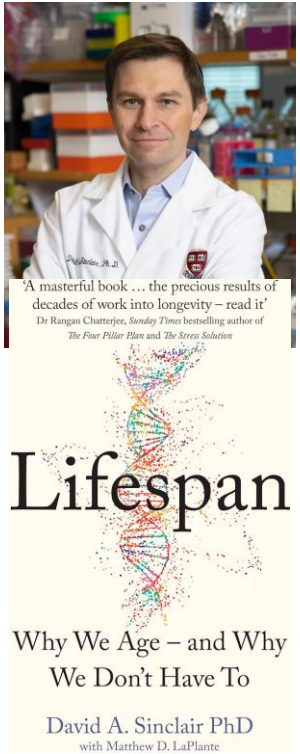


Additional Benefits to Life- and Health-span Will Now Likely Come From a Better Understanding Of the Basic Biology of Aging

Senescence:

The biological processes of aging that lead to increased risk for mortality

Is Aging a Disease?



- Sinclair lab hypothesis: the loss of epigenetic information is likely the root cause of aging. By analogy, if DNA is the digital information on a compact disc, then aging is due to scratches.
- Sinclair's approach is based on a broad view that links diseases of age such as cancer, diabetes, Alzheimer's, and heart failure to common cellular processes.

The Hallmarks of Aging

Your Genetic Make-up Influences Life Expectancy

A glance at your family tree may indicate whether you have a tendency to live a long, healthy life

Family History

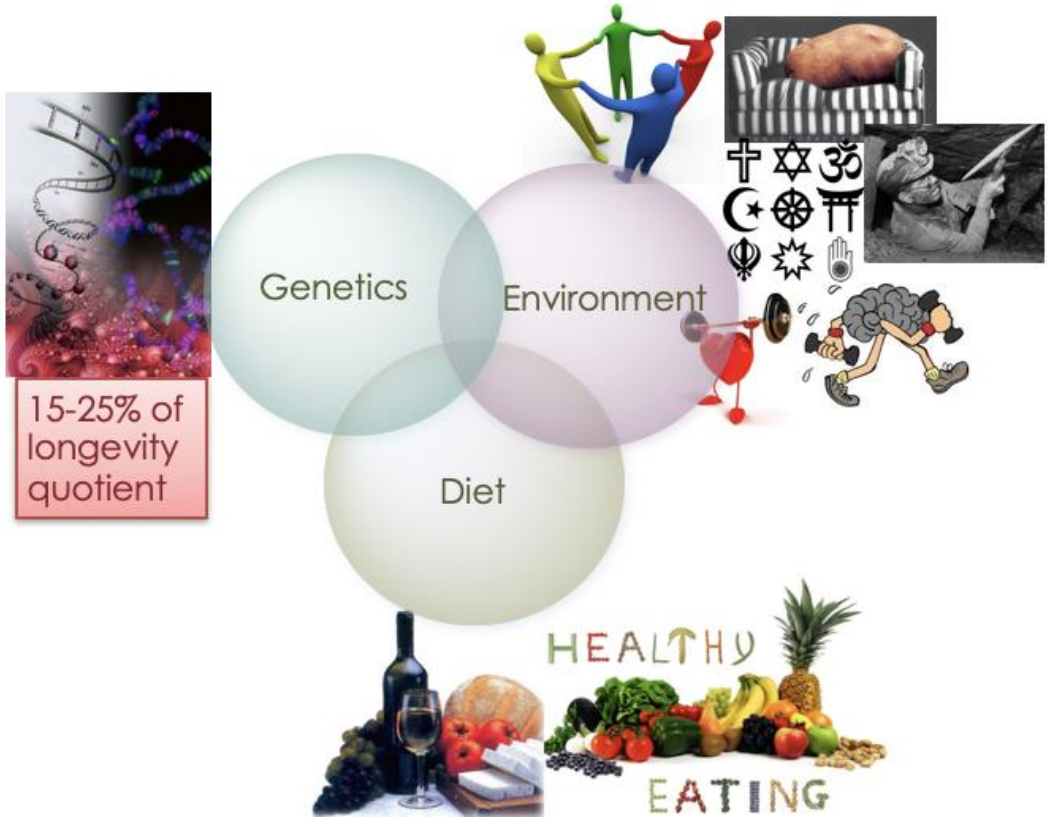
1. Exceptional longevity (1 to 3 decades longer than average) tends to run in families

2. Siblings of "super-centenarians" tend to live longer than average

What Does Genetic Analysis of Exceptionally Long-lived People Reveal About Longevity?

There are "nodes" of exceptionally long-lived people throughout the world

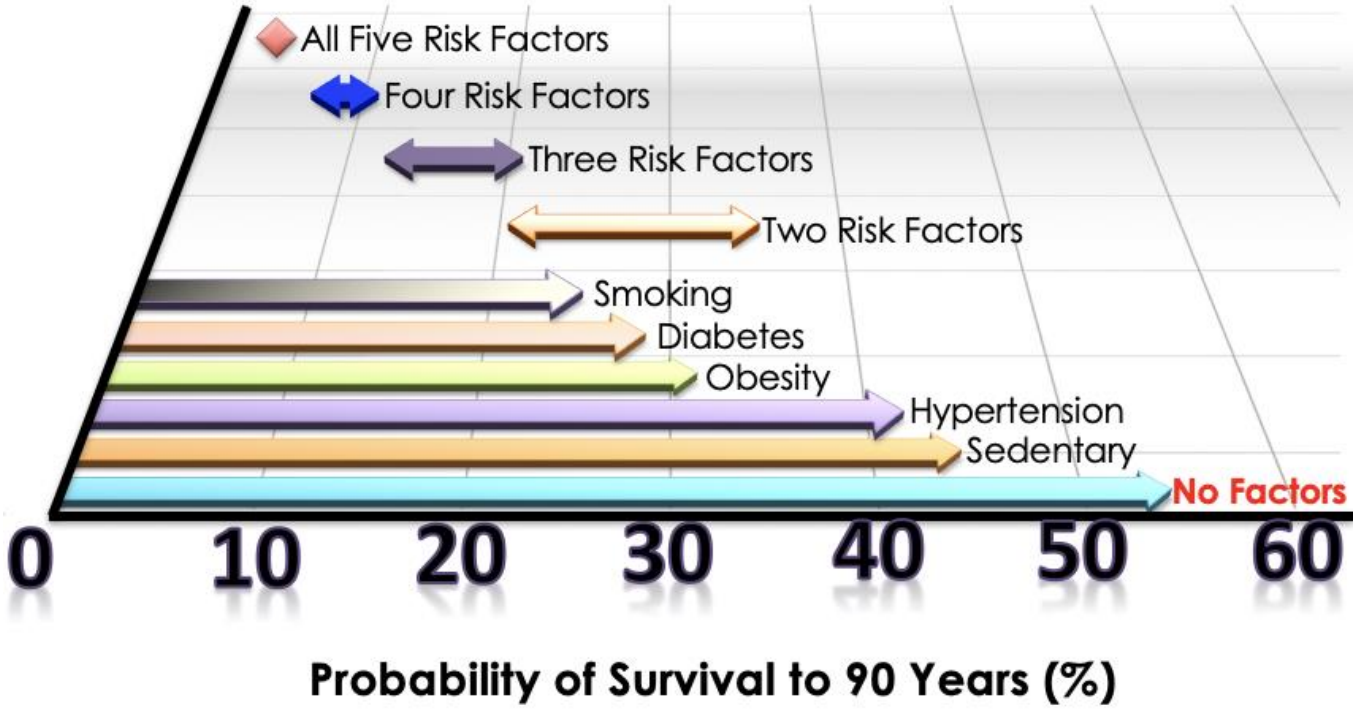
Genetic Analysis Suggests that Environment & Diet are the Major Determinants for Healthy Aging



Five Modifiable Factors Negatively Associated Life Expectancy

- **Sedentary**:
  Frailty & disuse syndromes
- **Hypertension**:
  Stroke; kidney failure; cardiovascular diseases
- **Obesity (BMI > 25)**:
  Metabolic syndrome; cardiovascular diseases; dementias; and cancers
- **Diabetes**:
  insulin resistance; cardiovascular; cognitive decline
- **Smoking**:
  Cancer; cardiovascular diseases; pulmonary diseases; and cognitive decline

Probability of 70 Year Old Men to Survive to 90 Years of Age



Yates, LB et al. Arch Internal Medicine. 168: 284-290 (2008)

Are Other Lifestyle Factors Associated with High Life Expectancy?

1	Marriage	
2	High Social Contacts	
3	Alcohol Intake	
4	Early Life Exposure to Infectious Diseases	
5	Moderate Physical Activity	

Are Lifestyle Risks Different Between Mid-life Versus Late-Life?

Lifestyle Factor	Mid-life	Late Life
BMI	High BMI = Poor Health & Shorter Lifespan	Low BMI = High Risk for Death
Hypertension	Non-survival & poor health	Non-survival & poor health
Smoking	Non-survival & poor health	Non-survival & poor health
Alcohol	≥ 3 drinks/day	>1 drink/day (15 oz/month)
Physical Activity	Not protective if stopped	Protective even if started late in life

Being a bit overweight is not so risky

High risk at all ages

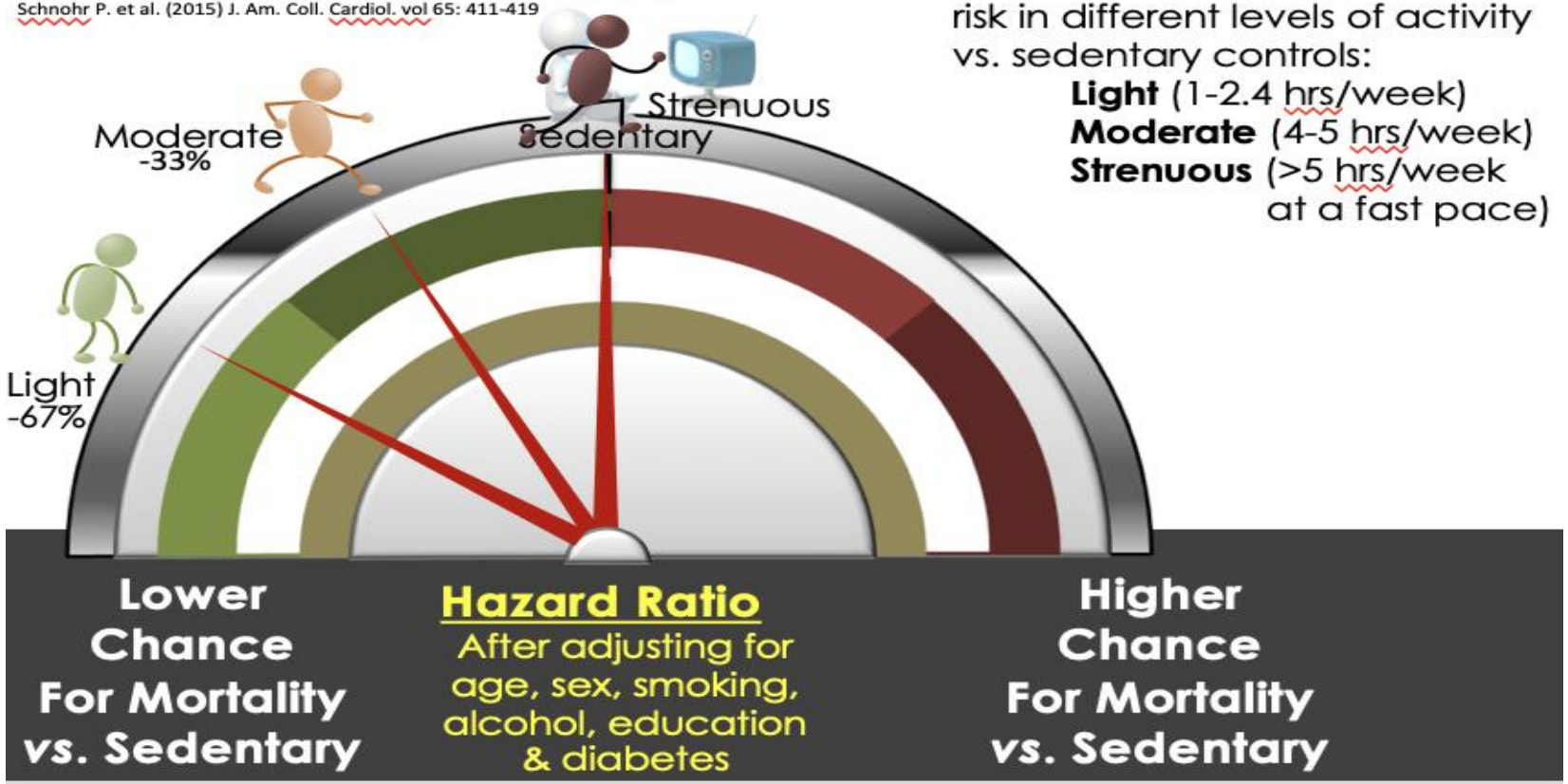
Increasing risk with age

Jogging & Mortality

- Followed joggers & non-joggers since 2001
- Ages: 25 to 90 years
- Looked at all-cause mortality risk in different levels of activity vs. sedentary controls:
  - **Light** (1-2.4 hrs/week)
  - **Moderate** (4-5 hrs/week)
  - **Strenuous** (>5 hrs/week at a fast pace)

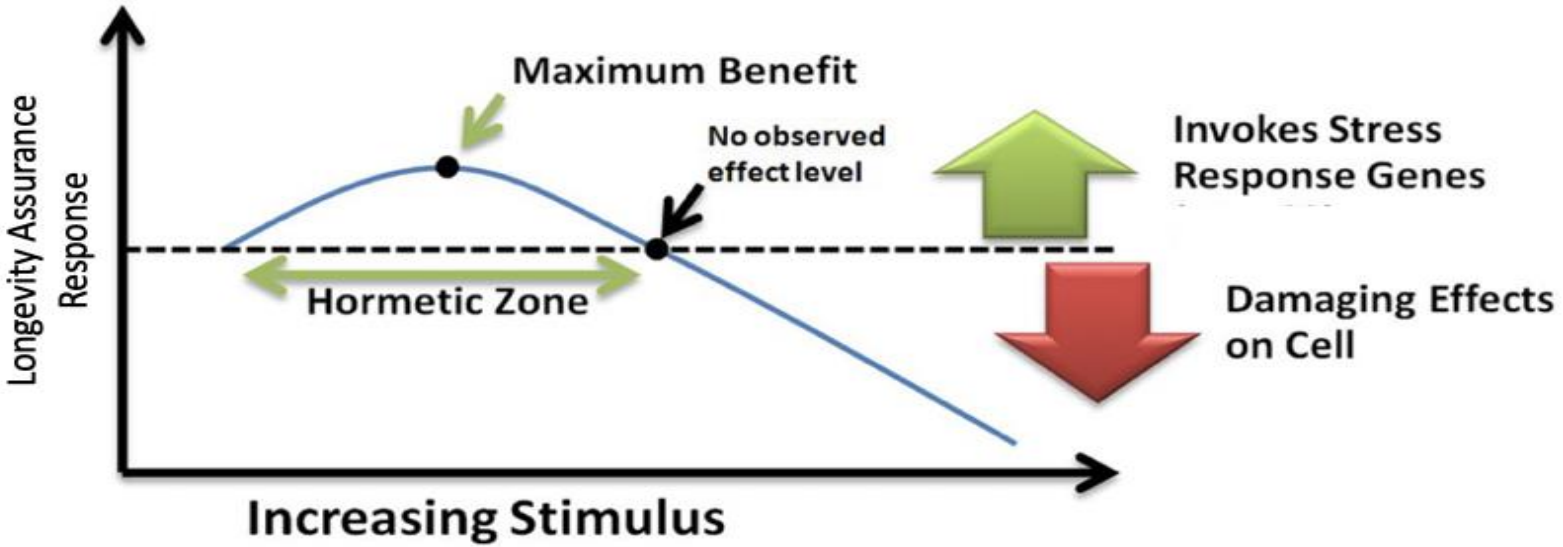
-The Copenhagen City Heart Study

Schnohr P. et al. (2015) J. Am. Coll. Cardiol. vol 65: 411-419

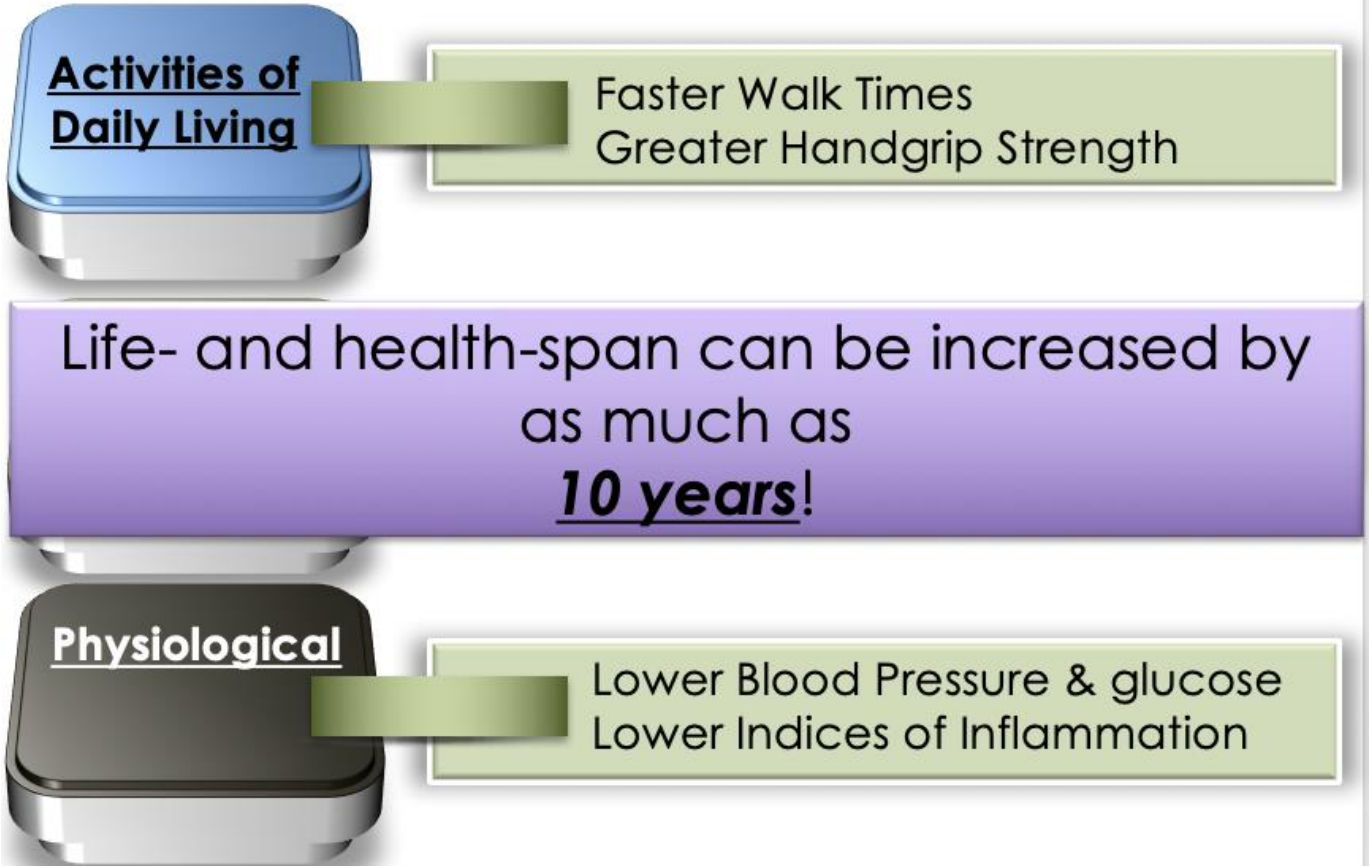


The Benefits Exercise is an Example of "Hormesis": Low to Moderate Stress is Beneficial

Hormesis

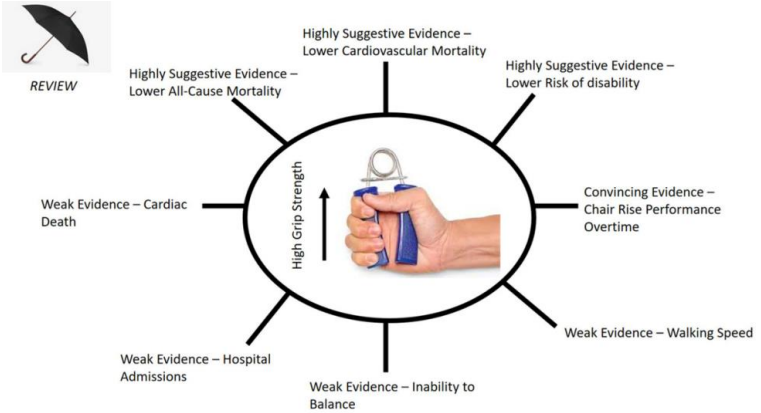


Accentuating Positive Lifestyle Factors & Eliminating the Adverse Ones Promotes Healthy Aging

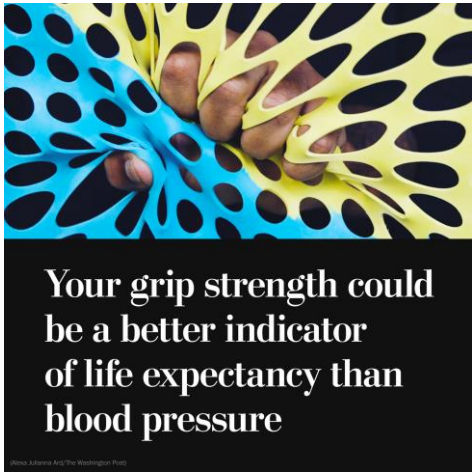


Grip Strength

- Use of grip strength as a biomarker of current health status is most directly supported by research showing a cross-sectional association between grip strength and the strength of other muscle actions of both healthy individuals and adults with pathology
- Grip strength is a predictor of numerous future outcomes. Mortality is probably the most widely studied outcome, with studies published as far back as the 1980s and at least 3 meta-analyses supporting the association of weak grip strength with all-cause mortality in the general population.
- Grip strength is also supported as a predictor of disease and disease-specific mortality- with much of the literature focused on cardiovascular disease and cancer. Wu et al, in a summary of 12 studies, determined that a 5kg decrease in grip strength was associated with an increased risk of cardiovascular disease (overall hazard ratio 5.98).



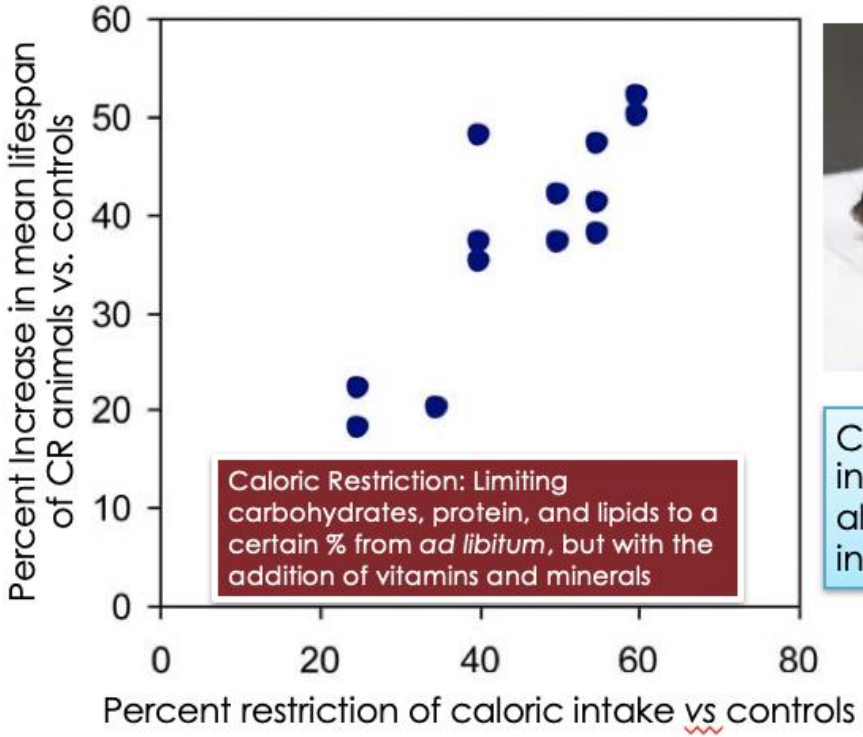
Hermoso 2018



Diet is the Largest Factor Affecting Longevity and Healthy Aging

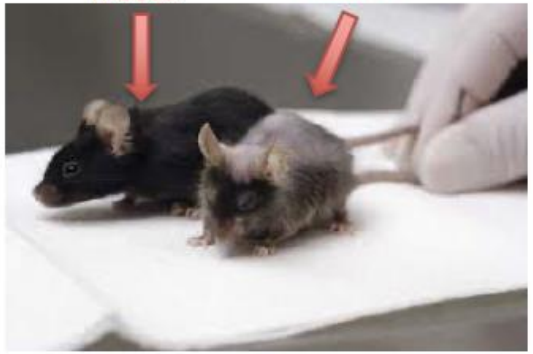
Nutrient influence on healthy aging is being extensively studied in humans and in many animal models of aging

A connection between nutrient energy intake and aging is best experimentally seen in "Caloric Restriction"



Calorically restricted old mouse

Ad libitum fed old mouse



Caloric restriction not only increases mean lifespan but it also extends maximal lifespan in some species!

Nature. 2011 Jan 6; 469(7328): 102–106.

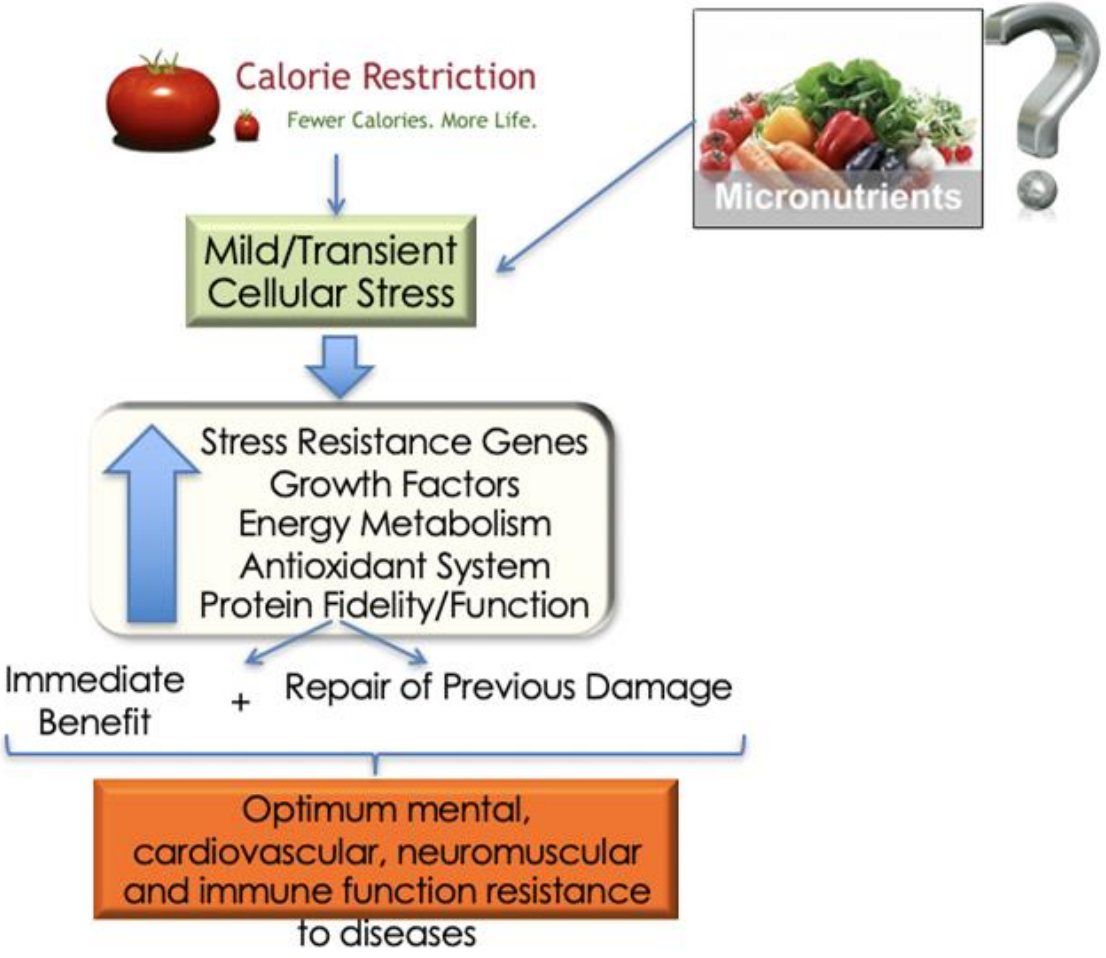
Caloric Restriction Improves Healthspan in Lab Animals

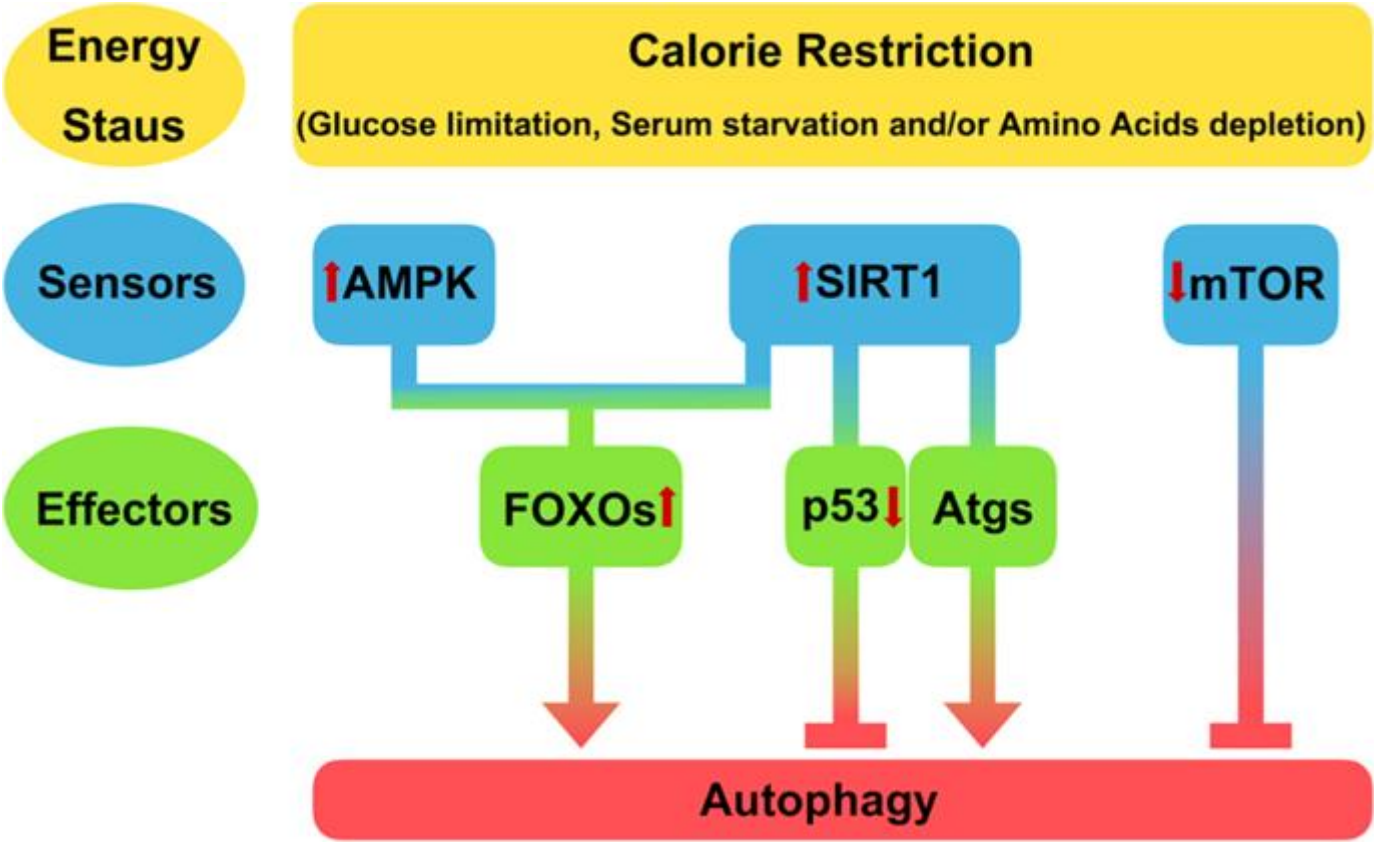
Increases

- Memory/learning
- Muscle mass
- Mitochondrial function
- Insulin sensitivity

Decreases

- Cancer
- Renal Disease
- Autoimmune Disease
- Alzheimer's Disease
- Atherosclerosis
- Sarcopenia


Calorie Restriction
Fewer Calories. More Life.
Micronutrients
Mild/Transient
Cellular Stress
Stress Resistance Genes
Growth Factors
Energy Metabolism
Antioxidant System
Protein Fidelity/Function
Immediate
Benefit
+
Repair of Previous Damage
Optimum mental,
cardiovascular, neuromuscular
and immune function resistance
to diseases


Energy Staus
Calorie Restriction
(Glucose limitation, Serum starvation and/or Amino Acids depletion)
Sensors
AMPK
SIRT1
mTOR
Effectors
FOXOs
p53
Atgs
Autophagy

Are There Micronutrients or Other Small Molecules From the Diet That Mimic Caloric Restriction?

1. Antioxidants and Phytochemicals
2. Anti-Inflammatory Compounds
3. Drugs and Small Molecules

Candidate Agents to Improve Healthspan

Over 600 candidates!

Red Wine Constituents & Alcohol

- Alcohol (1 or 2 drinks/d only!)
- Resveratrol (?)

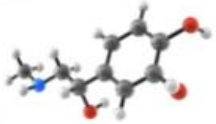
Sulfur-containing Compounds in Brassica and Onions

- Lipoic Acid
- Thioflavin T

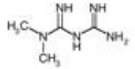
Other:

- Chocolate & coffee components

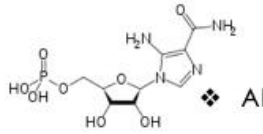
- Berries



- Rapamycin



- Metformin



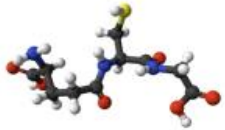
- AICAR

Optimal dosage & the long-term benefits to people (as well as potential adverse consequences) are largely unknown

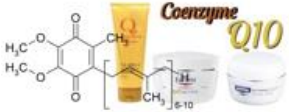
Antioxidant Supplements Fail to Significantly Improve Lifespan

Vitamin E

Vitamin C



Glutathione



Coenzyme Q

Does supplementation lower oxidative damage in older animals?

➢ Vitamin E	short-lived mice, but not humans
➢ Vitamin C	No
➢ Glutathione	No
➢ Coenzyme Q	fruit flies, but not mice

Does supplementation extend lifespan?

➢ Vitamin E	Small increase in avg. but not maximal lifespan (some mice)
➢ Vitamin C	Small increase in avg. but not maximal lifespan (mice)
➢ Glutathione	No
➢ Coenzyme Q	No

Make Sure Your Vitamin Intake is Optimal

Vitamin	RDA Men	RDA Women	LPI Recommendation
Vitamin B_{12}	*2.4 mcg/day#*	*2.4 mcg/day#*	*100-400 mcg/day of crystalline vitamin B_{12}*
Vitamin C	*90 mg/day*	*75 mg/day*	*≥ 400 mg/day*
Vitamin D	*600-800 IU/day*	*600-800 IU/day*	*2,000 IU/day from supplements; serum level ≥32 ng/ml*

Americans generally do not get enough vitamins E or D, and intake of many minerals are inadequate: magnesium, calcium, potassium, phosphorous

#Vitamin B_{12} intake should be from supplements or fortified foods due to the age-related increase in malabsorption

Why does this matter to us as Family Medicine Physicians?

- ★ FM doctors stand at a very interesting point in this new discussion of the promotion of healthspan vs lifespan.
- ★ This discussion brings up the idea of primary prevention vs primordial prevention & what our role as family medicine doctors is within it
- ★ While primary prevention is about treating risk factors to prevent chronic disease, primordial prevention refers to avoiding the development of risk factors in the first place which ultimately would lead to greater healthspan
- ★ Up to 25% of Medicare costs are spent on a patient's last year of life.

What's Next?

- The National Institutes of Health has reduced the barriers between its disease-oriented research silos, and the American Federation for Aging Research is spearheading a global effort to secure funds to launch the Longevity Dividend Initiative in 2019.
- Clinical trials designed to target aging have been approved by the US Food and Drug Administration, with the first trial set to begin in 2019.
- The National Institute on Aging has established the Interventions Testing Program to rigorously and quickly test prospective aging interventions for free. A consortium of scientists as well as public health experts and organizations has formed with the purpose of developing this new approach to extend healthspan, address the diseases of aging, and help to ameliorate the economic challenges of an anticipated rising prevalence of late-onset diseases.
- Large investments in aging biology have already begun through Google Calico and Human Longevity Inc.

Thank You!

Questions?

References

Books

- David Sinclair: Lifespan
- Tony Robbins, Peter Diamandis MD, Robert Hariri MD PhD: Life Force

Research

- https://jamanetwork.com/journals/jama/fullarticle/2703114
- https://www.cell.com/cell/fulltext/S0092-8674(13)00645-4?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867413006454%3Fshowall%3Dtrue
- https://pubmed.ncbi.nlm.nih.gov/32037449/
- https://pubmed.ncbi.nlm.nih.gov/29425700/
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3734859/
- https://jamanetwork.com/journals/jama/fullarticle/2703114

Some slides adapted from Tory Hagen of OSU Linus Pauling Institute