An Overview of the Science of Aging and Longevity

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Associate Professor of Medicine
University of Massachusetts Chan Medical School

January 21, 2022

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Objectives

- Provide an overview of the current state of the science on the aging process.
- Review the current hallmarks (drivers) of aging.
- What interventions can one leverage in their lives to improve health span and lifespan?
- What does the future hold in the field of aging, longevity and rejuvenation medicine?

2

Questions for consideration:

- How long can humans actually live?
- Is getting old always synonymous with poor quality of life?
- What is the difference between chronologic age and biologic age?
- Is aging a disease?
- If so, can it be "treated"?
- As age is most strongly correlated with all advanced chronic diseases, should we focus on treating diseases or treating aging?
- Can age be regressed?

3

Gilgamesh: An Ancient story of the timeless pursuit of immortality

The **Sumerian Epic of Gilgamesh** dates back nearly 5,000 years and is thought to be perhaps the oldest written tale on the planet. It is a story of the mythological hero-king of Uruk and his dangerous quests and adventures in search of the secret of immortality.

4

"First you forget names, then you forget faces. Next you forget to pull up your zipper and finally, you forget to pull it down."

George Burns
1896 - 1996

5

"Everybody needs a passion. That's what keeps life interesting. If you live without passion, you can go though life without leaving any footprints."
—*From her book,* If You Ask Me (And Of Course You Won't)

Betty White
1922-2021

6

Jeanne Louise Calment was a French supercentenarian and the oldest human whose age is well-documented, with a lifespan of 122 years and 164 days. The oldest person living today is Kane Tanaka from Japan who is 118 years old.

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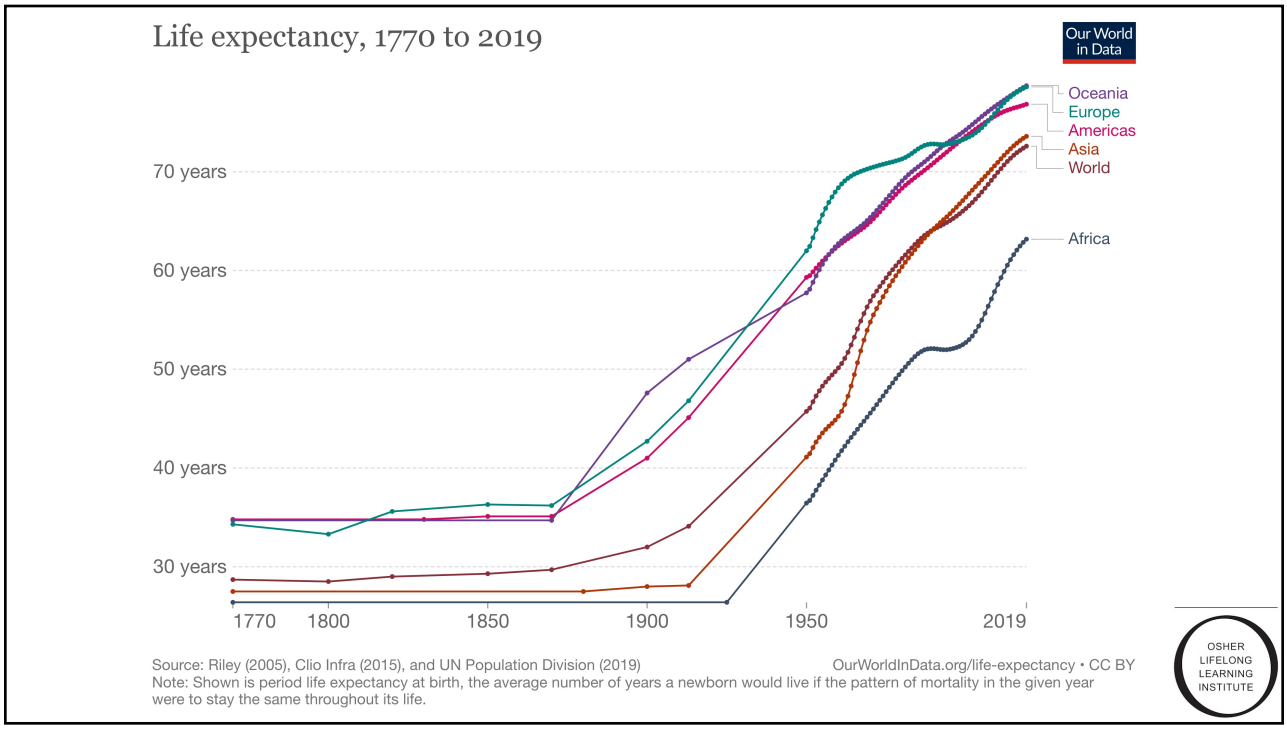

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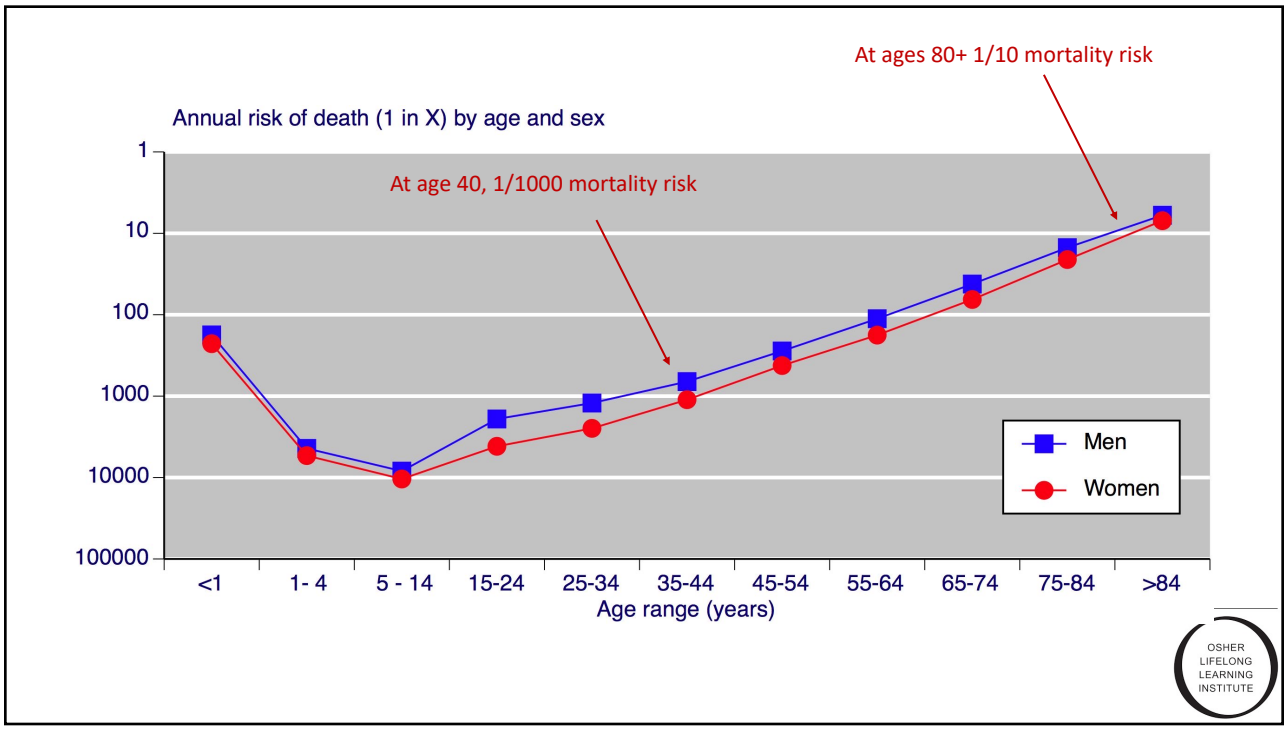

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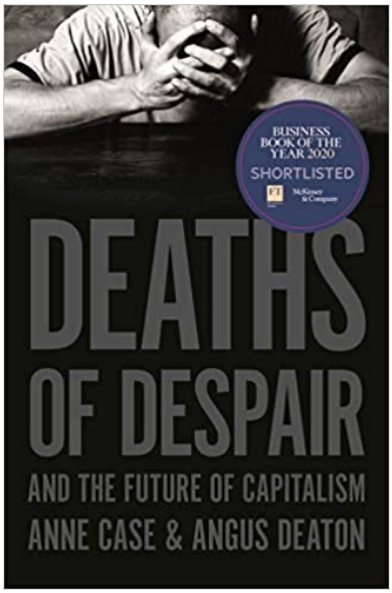

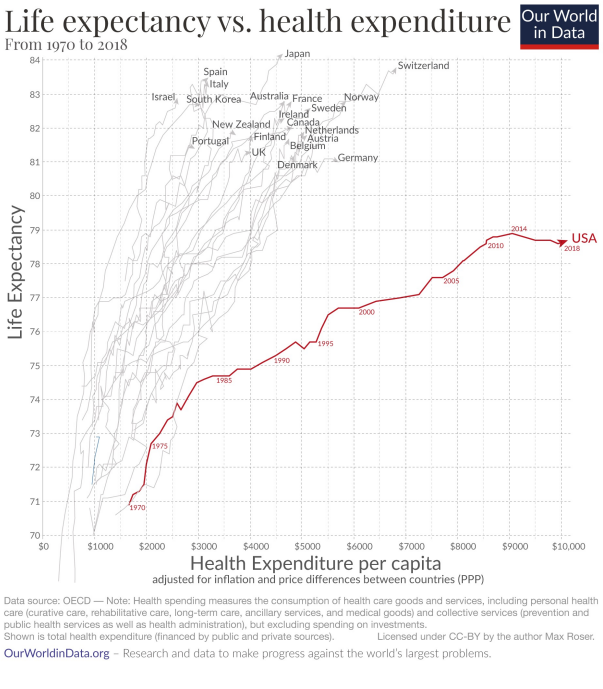

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Life Expectancy in U.S. Declined 1.8 Years in 2020, CDC Says

Covid-19 was the nation's third leading cause of death last year, behind heart disease and cancer, new figures show

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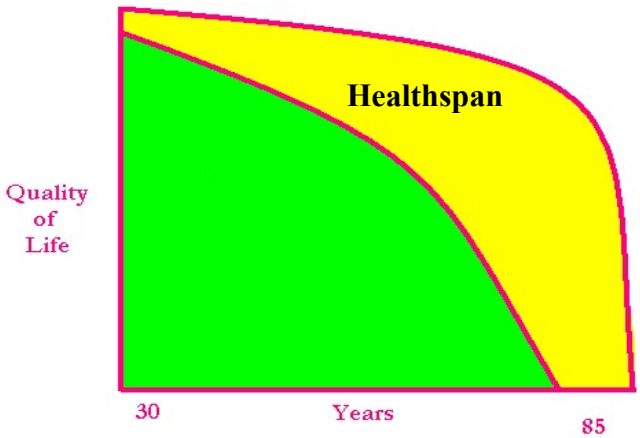
SPECIAL ARTICLE ARCHIVE

Aging, Natural Death, and the Compression of Morbidity

James F. Fries, M.D.

N Engl J Med 1980; 303:130-135 | July 17, 1980



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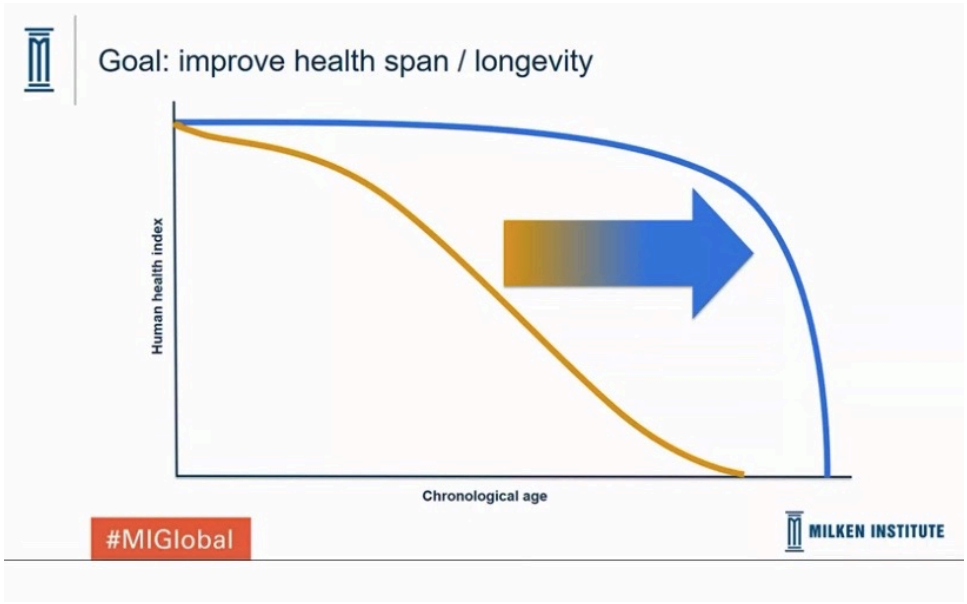

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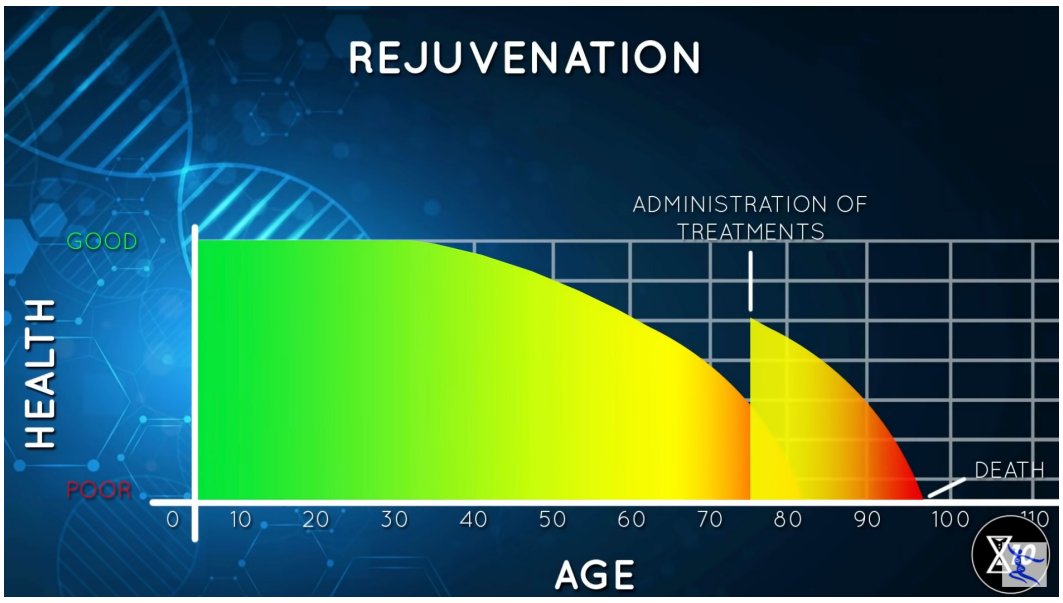

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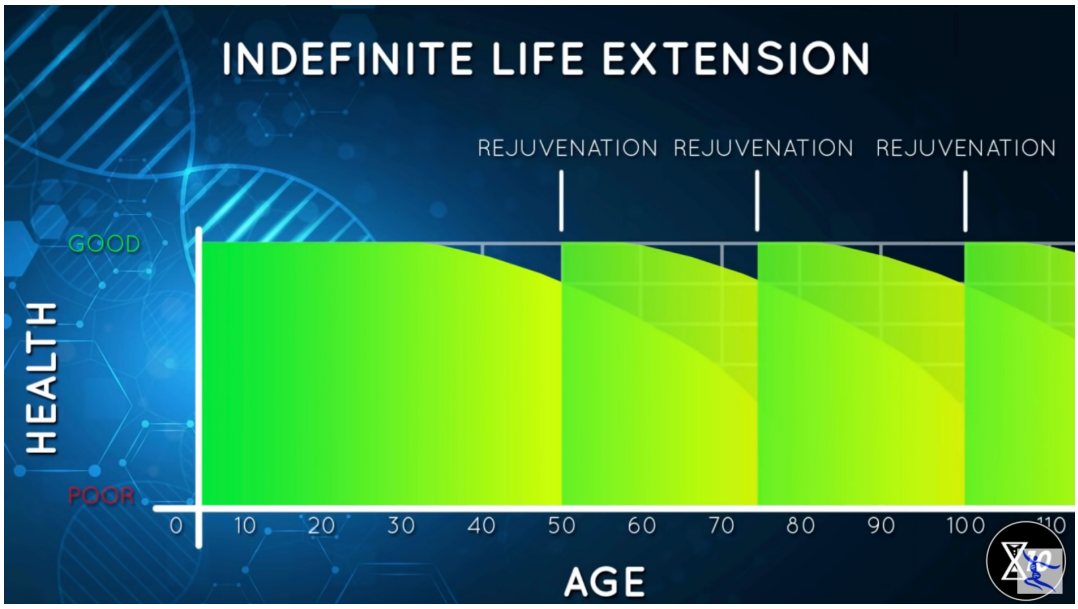

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Life span extension…

10-fold !

< 2-fold

5-25%

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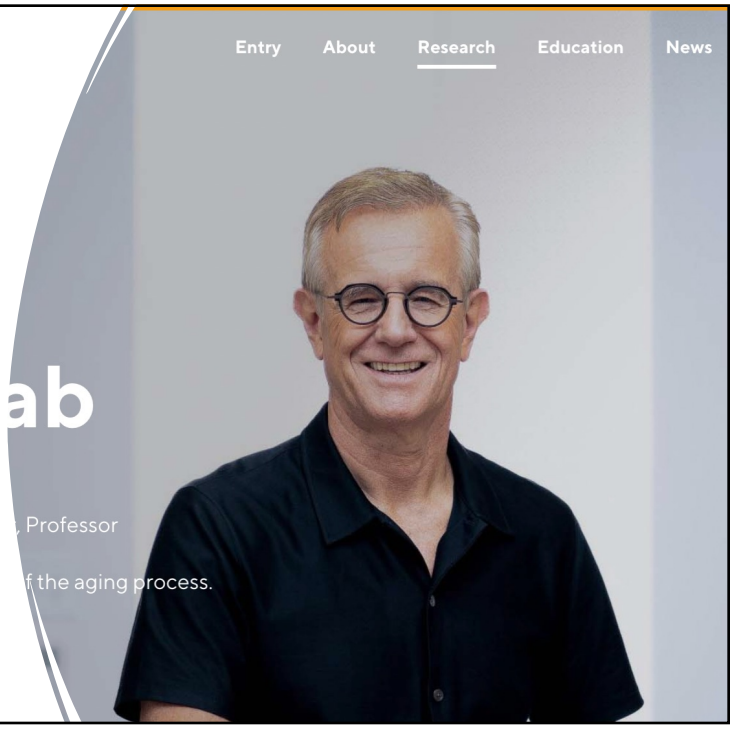
"Less than 10% of what contributes to longevity can be traced to genetics. Over 90% of what contributes to longevity and healthy aging is lifestyle."

Eric Verdin MD
President and CEO, Buck Institute



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Hallmarks of Aging:

An emerging paradigm

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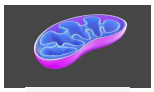
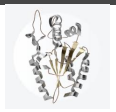
Genetics + Environment

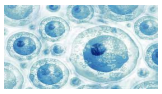
Epigenetic Regulation

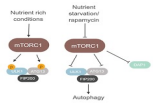

Genomic Instability


Telomere attrition


Mitochondrial Bioenergetics


Loss of Proteostasis


Stem cell depletion


Deregulated Nutrient Sensing


Altered Intercellular Communication


Cellular Senescence

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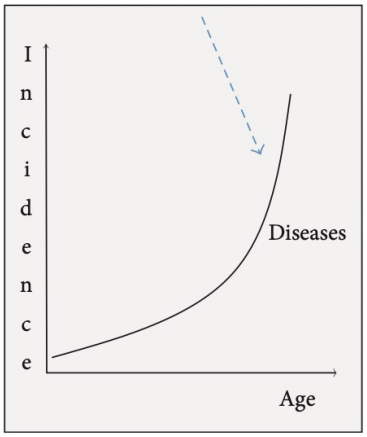
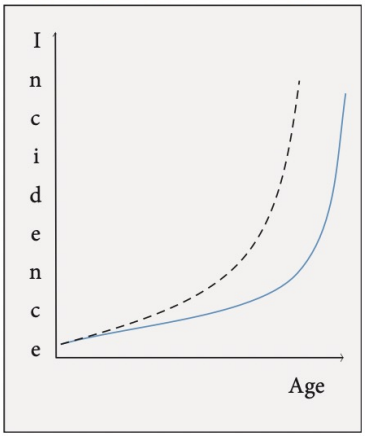
Treating Diseases vs. Treating Aging

Age-related diseases raise exponentially:
This is not a coincedence!



Treat aging

Prolonging the healthy years of life:
Improving lifespan and healthspan!



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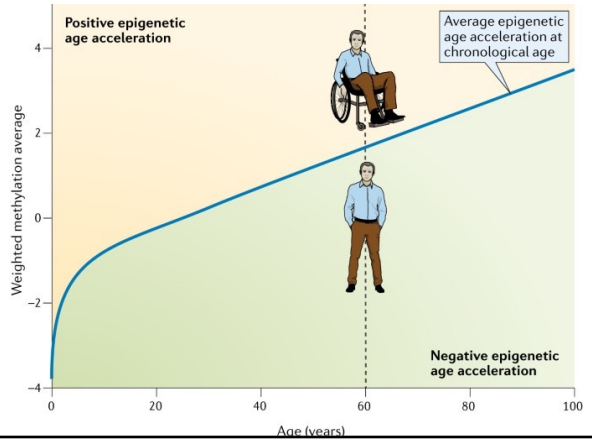
Review Article | Published: 11 April 2018

EPIGENETICS

DNA methylation-based biomarkers and the epigenetic clock theory of ageing

Steve Horvath & Kenneth Raj



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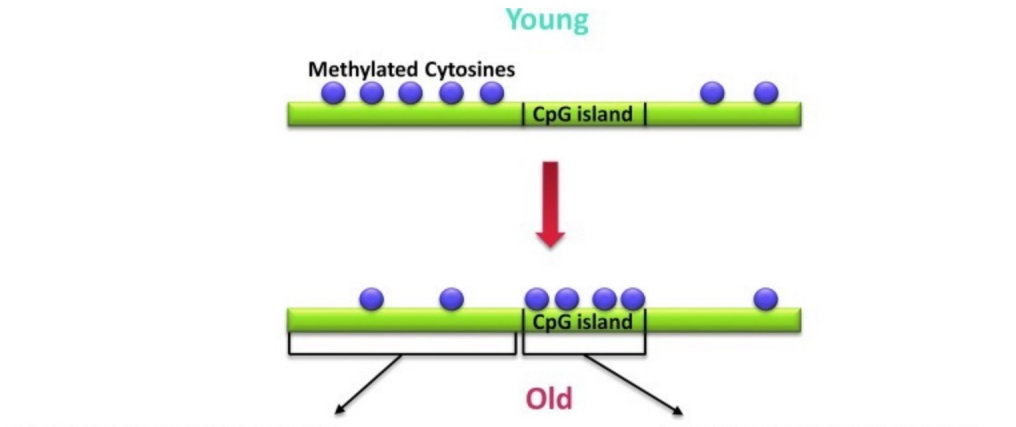

Global hypomethylation
- Genomic instability
- Inefficient gene repression

Local hypermethylation
- Loss of expression control
- Inappropriate silencing

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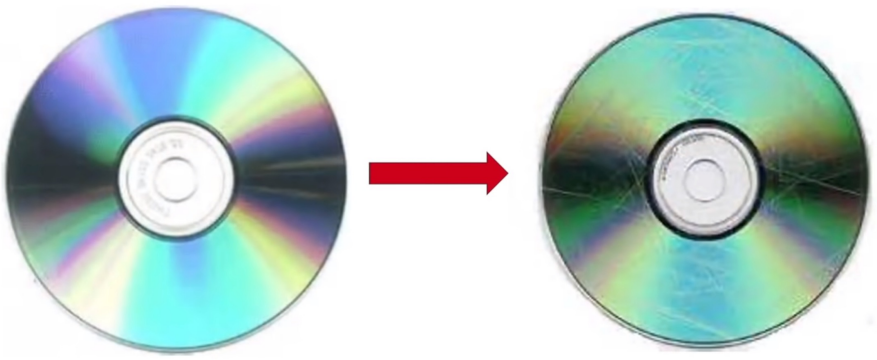

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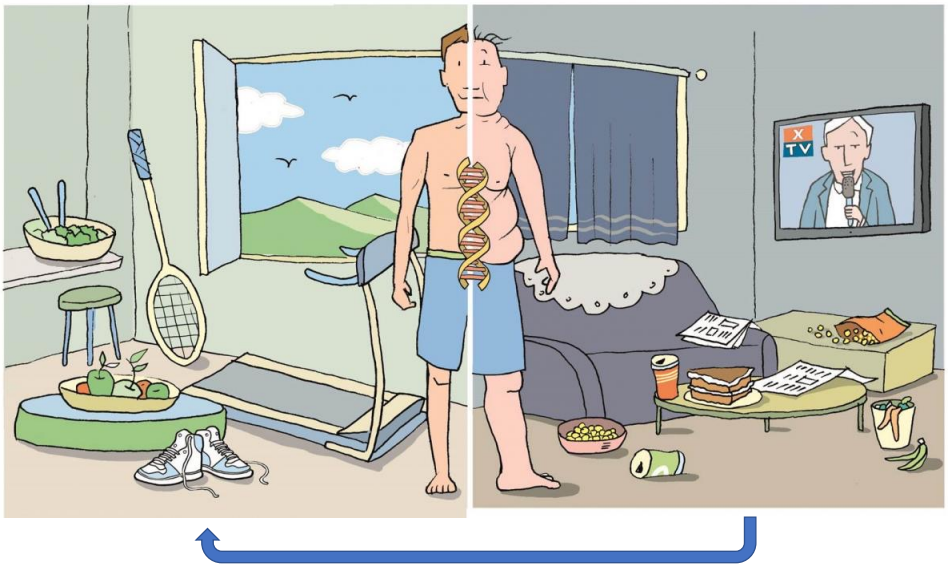

Epigenetic Reprogramming

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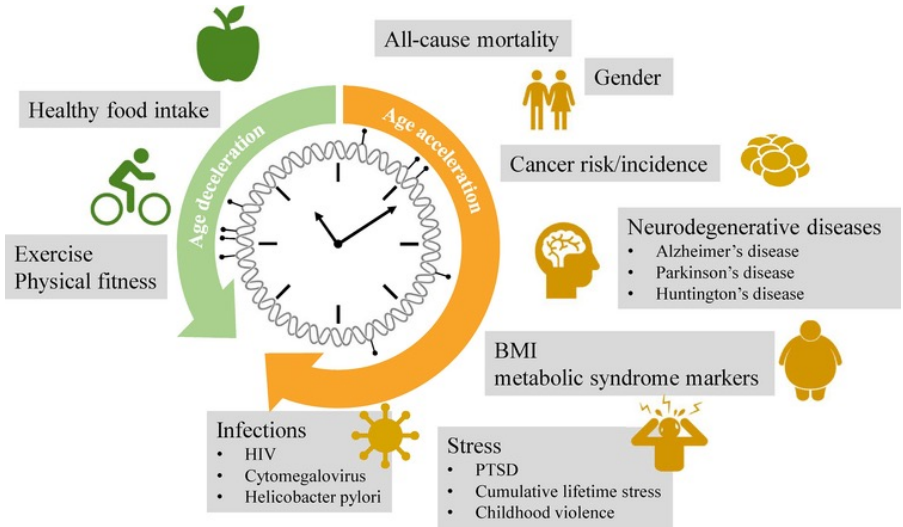

Back to the future: Epigenetic clock plasticity towards healthy aging
•January 2018 Mechanisms of Ageing and Development DOI:10.1016/j.mad.2018.01.002

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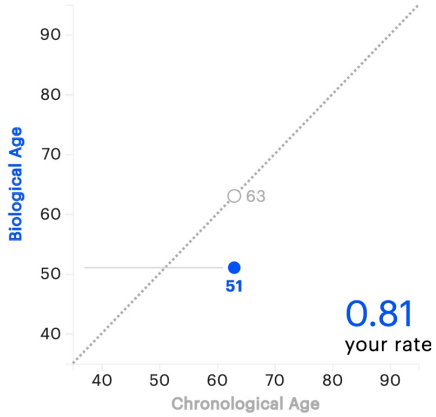
Cumulative Rate of Aging



Your cumulative rate of aging is slower than your chronological age.

Taking into your account both your chronological age and biological age, Elysium has determined your cumulative rate of aging — a personalized measure of the pace at which your body has aged for every year you've been alive.

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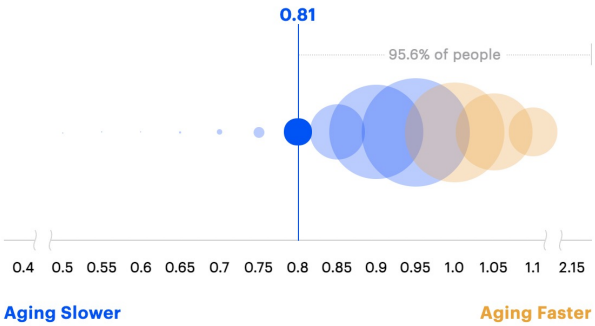
How Do You Compare?



Your cumulative rate of aging is on average slower than most of the population.

Your cumulative rate of aging is 0.81, which is slower than 95.6% of people. Your cumulative rate of aging is calculated by dividing your biological age by your chronological age.

What the graph means

The size of each bubble represents the percentage of people that fall within your personal rate of aging interval. Bubbles in blue represent the subset of the population whose cumulative rate of aging is at or below 1.0, which is optimal.

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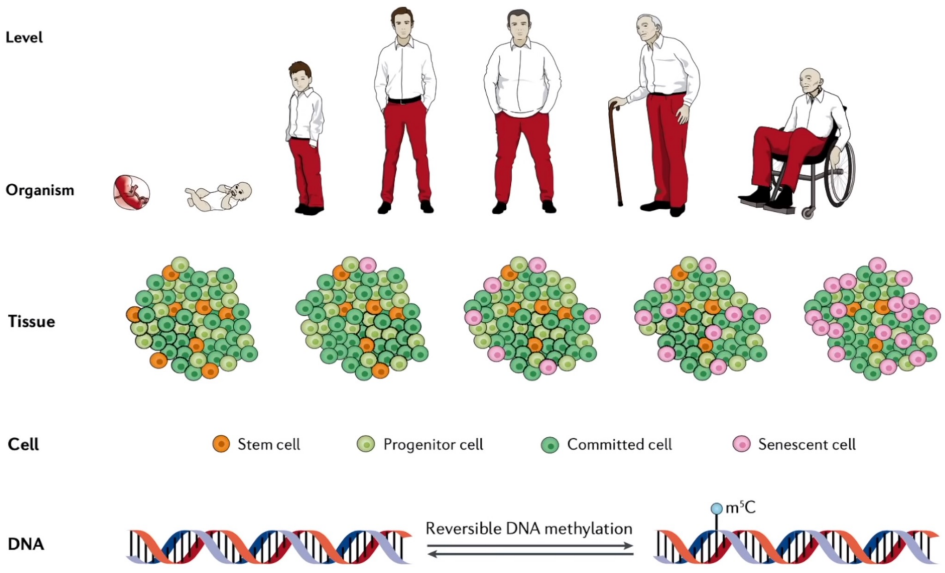

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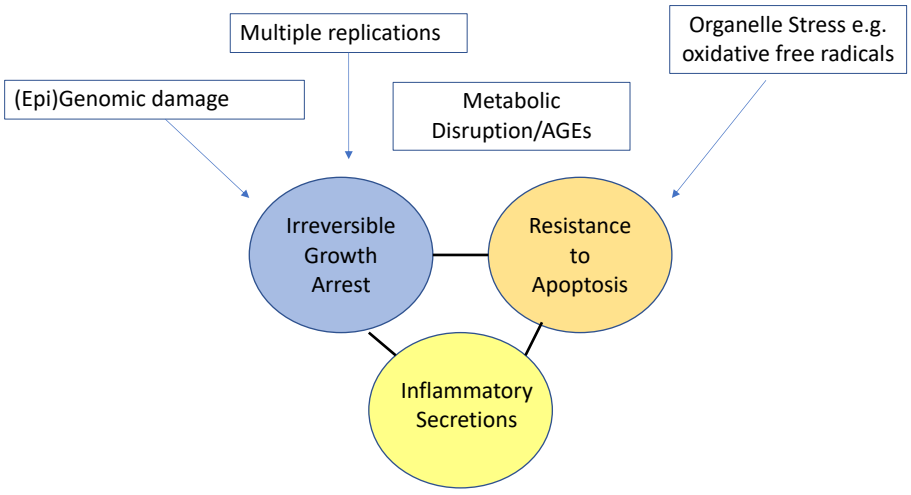
Cellular Senescence: a complex response to stress



Senescence Associated Secretory Phenotype Accelerated Aging

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Senescent cells cause or contribute to:

Alzheimer's@@ and Parkinson's disease*
*Atherosclerosis***
*Cardiovascular dysfunction**#*
*Cancer metastasis and recurrence****
*Chemotherapy (HAART) cardiotoxicity, blood clots, fatigue****
Cognitive decline/loss of neurogenesis
*Cataracts**#*
Diabetes and diabetic complications@
Metabolic syndrome@@
Myeloid→lymphoid skewing #
*Pulmonary fibrosis#**
Osteoarthritis ##
Osteoporosis ###
Sarcopenia/frailty@@@

Wound healing, tissue regeneration@
*Embryogenesis^, parturition^^*

*Chinta et al, Cell Reports, 2018; **Childs et al, Science, 2016; ***Baker et al, Nature, 2016; ****Demaria et al, 2017; #Chang et al, Nature Med, 2016; #*Schafer et al, Nature Comm, 2017; ##Jeon et al, Nature Med, 2017; ###Farr et al, Nature Med, 2017; @ Demaria et al, Dev Cell, 2014; @Krizhanovsky et al, Cell, 2008; @@Bussian et al, Nature, 2018; @@Aguayo-Mazzucato et al, Cell Metab, 2019; @@Palmer et al, Aging Cell, 2019; @@Zhu et al, PLoS One, 2019; ^Munoz-Espin, Cell, 2013; ^Storer, Cell, 2013; ^^Menon, Aging, 2016*

Dr. Judith Campisi Buck Institute

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"The Cause of Everything?"

"Inflammaging"

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Major Metabolic Regulatory Players in the Health span, Aging and Longevity Research Field

- Sirtuins (silent information regulator) family
  Sirtuin Activators e.g. resveratrol, NAD
- AMPK – AMP Kinase
  Metformin
- mTOR – mammalian target of rapamycin
  Fasting, Rapamycin
- Insulin-IgF1 (insulin-derived growth factor)
  Lower Glycemic Foods, less animal protein

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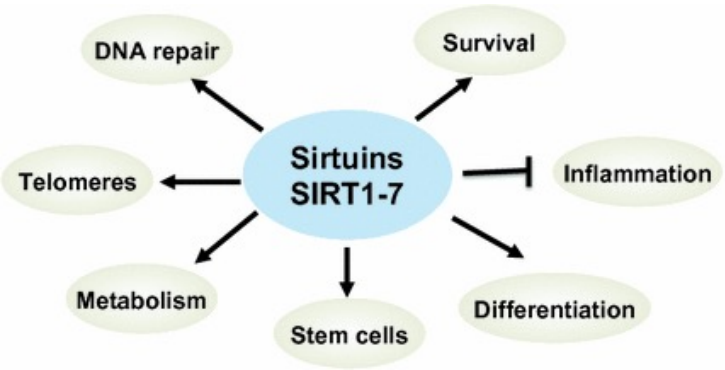
Sirtuins

A class of enzymes that influence aging and longevity through multiple molecular pathways. Sirtuins regulate a variety of metabolic processes, including the release of insulin, response to stress, and modulation of lifespan. They also influence circadian clocks and mitochondrial biogenesis. Sirtuins are activated when NAD levels rise. Plant-based molecules e.g. resveratrol, pterostilbene and quercetin can activate sirtuins, designated as Sirt1 to Sirt7.



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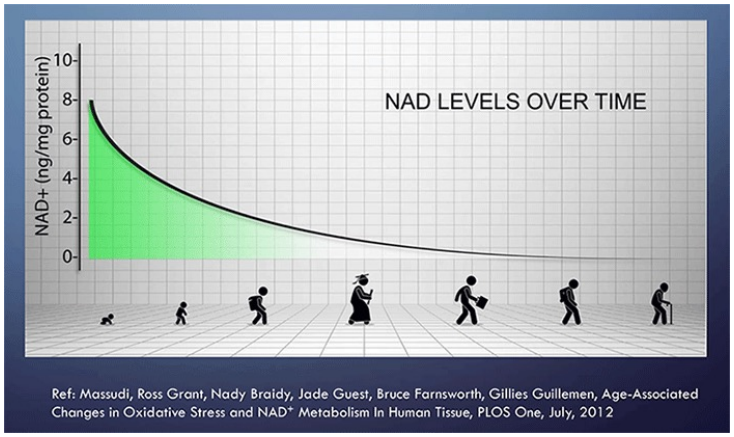
Hallmarks of Aging Associated with Cellular depletion of NAD+

- Altered DNA repair
- Altered epigenetics
- Mitochondrial dysfunction
- Disrupted metabolic-nutrient sensing e.g. Insulin resistance with glucose intolerance
- Cellular senescence
- Decreased autophagy



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NAD Precursors: NMR and NR

- NAD as a precursor for critical metabolic pathways e.g. energy, immune regulation, Sirtuin activation for DNA healing
- NAD levels decline with aging in all tissues studied (*Aging Dis. 2021 Dec; 12(8): 1879-97*)
- All chronic, complex age-related diseases associated with decreased NAD levels (*Biomolecules. 2019 Jan 9(1) 34*)
- Aerobic and resistance exercise raise NAD levels (*Physiol Rep. 2019 Jun 7(12))*
- *NAD levels naturally decline with aging which leads to metabolic and mitochondrial dysfunction associated with aging*
- *Fasting increases NAD levels*
- *Data on efficacy of NAD boosters is predominantly based on animal research. More human clinical trials are needed.*

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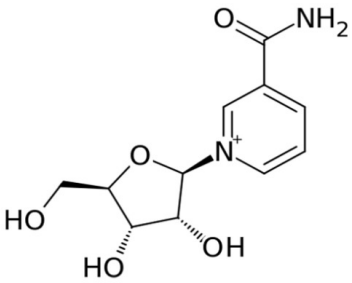
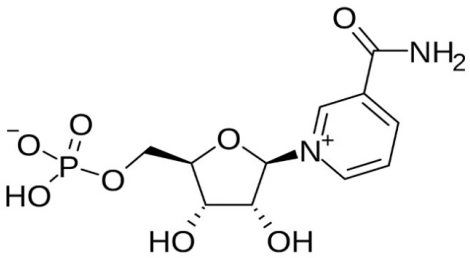
NAD boosters:

Dietary supplements that purportedly increase cellular levels of nicotinamide adenine dinucleotide (NAD+). Examples of potential NAD+ boosters include nicotinamide riboside and nicotinamide mononucleotide.



NR: Nicotinamide Riboside

Wikipedia contributors. "Nicotinamide riboside." *Wikipedia, The Free Encyclopedia*, 20 Nov. 2019. Web. 26 Nov. 2019.



NMN: Nicotinamide Mononucleotide

Wikipedia contributors. "Nicotinamide mononucleotide." *Wikipedia, The Free Encyclopedia*, 14 Nov. 2019. Web. 26 Nov. 2019.

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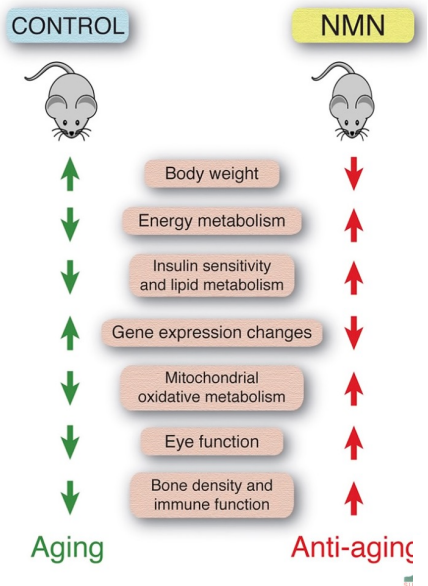
Long-Term Administration of Nicotinamide Mononucleotide Mitigates Age-Associated Physiological Decline in Mice

> Orally administered NMN was quickly utilized to synthesize NAD+ in tissues. Remarkably, NMN effectively mitigates age-associated physiological decline in mice. Without any obvious toxicity or deleterious effects, NMN suppressed age-associated body weight gain, enhanced energy metabolism, promoted physical activity, improved insulin sensitivity and plasma lipid profile, and ameliorated eye function and other pathophysiologies. Consistent with these phenotypes, NMN prevented age-associated gene expression changes in key metabolic organs and enhanced mitochondrial oxidative metabolism and mitonuclear protein imbalance in skeletal muscle. These effects of NMN highlight the preventive and therapeutic potential of NAD+ intermediates as effective anti-aging interventions in humans.

Mills, Kathryn F., et al. "Long-term administration of nicotinamide mononucleotide mitigates age-associated physiological decline in mice." *Cell metabolism* 24.6 (2016): 795-806.



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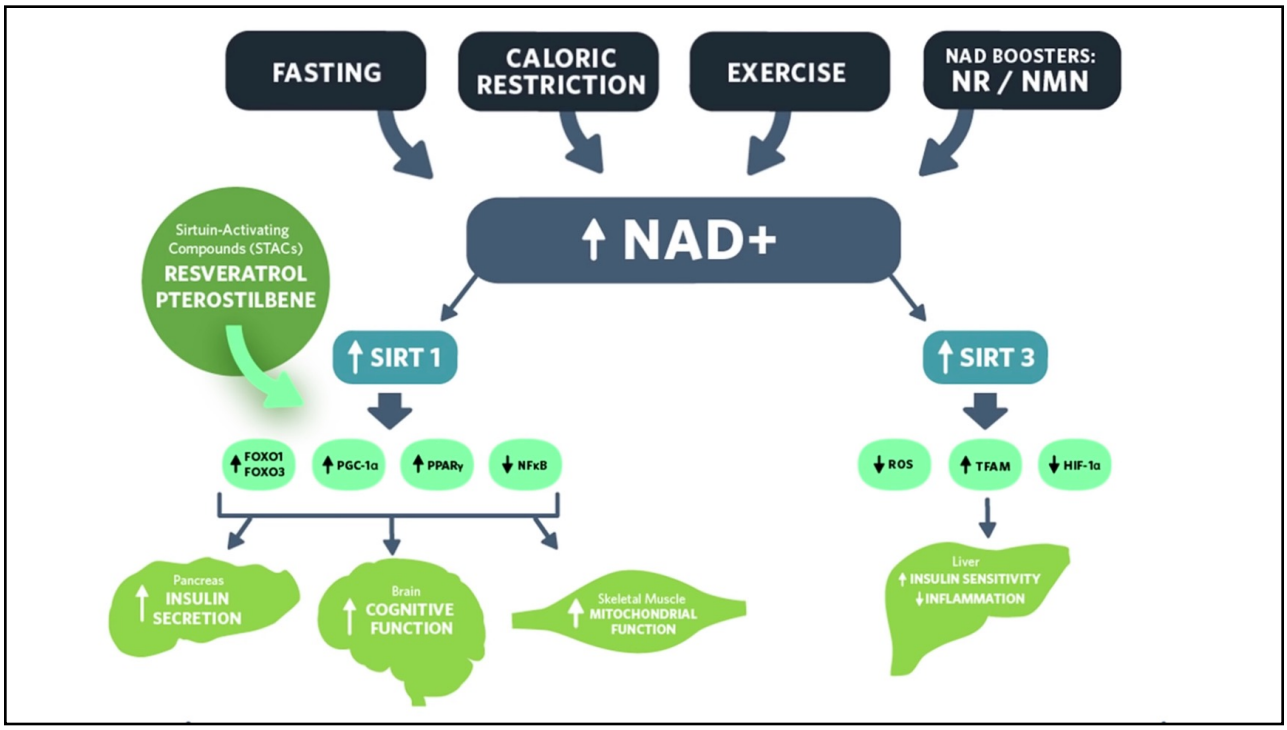

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Poly (ADP-ribose) polymerase, a.k.a. PARP

A family of proteins that *use NAD+ as a substrate* in their role of DNA repair and genomic stability.

As we grow older, the burden of DNA damage grows and it is thought to contribute to aging and cancer.

Increased PARP activity can lead to NAD depletion as DNA repair is a metabolic priority (Bruce Ames PhD, Metabolic Triage Theory)

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mTOR – Mammalian Target of Rapamycin

- mTOR is the major nutrient-sensitive regulator of growth in animals and plays a central role in physiology, metabolism, the aging process, and common diseases.

PNAS PNAS PNAS

Twenty-five years of mTOR: Uncovering the link from nutrients to growth

David M. Sabatini[a,b,c,d,e,1]

[a]Whitehead Institute for Biomedical Research, Cambridge, MA 02142; [b]Howard Hughes Medical Institute, Massachusetts Institute of Technology, Cambridge, MA 02139; [c]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02142; [d]Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02142; and [e]Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, MA 02142

This contribution is part of the special series of Inaugural Articles by members of the National Academy of Sciences elected in 2016.

Contributed by David M. Sabatini, September 22, 2017 (sent for review September 14, 2017; reviewed by Lewis C. Cantley and Joseph L. Goldstein)

In my PNAS Inaugural Article, I describe the development of the mTOR field, starting with efforts to understand the mechanism of action of the drug rapamycin, which ~25 y ago led to the discovery of the mTOR protein kinase. I focus on insights that we have contributed and on work that has been particularly influential to me, as well as provide some personal reflections and stories. We now appreciate that, as part of two distinct complexes, mTORC1 and mTORC2, mTOR is the major regulator of growth (mass accumulation) in animals and is the key link between the availability of nutrients in the environment and the control of most anabolic and catabolic processes. Nutrients signal to mTORC1 through the lysosome-associated Rag GTPases and their many regulators and associated cytosolic and lysosomal nutrient sensors. mTOR signaling is deregulated in common diseases, like cancer and epilepsy, and mTORC1 is a well-validated modulator of aging in multiple model organisms. There is significant excitement around using mTORC1 inhibitors to treat cancer and neurological disease and, potentially, to improve healthspan and lifespan.

recollections that highlight work that has been particularly influential to me. I suppose one writes such pieces when one has been around for a while. This appears to be the case, even though I am still surprised when someone refers to me as senior or I am asked by young scientists to talk about my career.

In the fall of 1992, I went to see Sol Snyder about a thesis project. I remember the meeting well, as I would meet with Sol one-on-one very few times during my time in his laboratory. Sol sat in a comfy office chair in the balled-up way that those of us in his laboratory found impossible to mimic, and he was quiet, knowing the power of silence (we assumed it was a trick he learned during his psychiatry training). I was nervous and blurted out that I wanted to talk about potential projects. After a bit, he said, "Well, David, we work on the brain." That seemed like a great start, as I wanted to do neuroscience, but then more silence followed, and, as I was to learn, that meant the conversation was over. I left unsettled because the brain was obviously a big topic, meaning I was project-less. That conversation though was likely the most important scientific interaction of my career, as Sol was giving me the

11818–11825 | PNAS | November 7, 2017 | vol. 114 | no. 45

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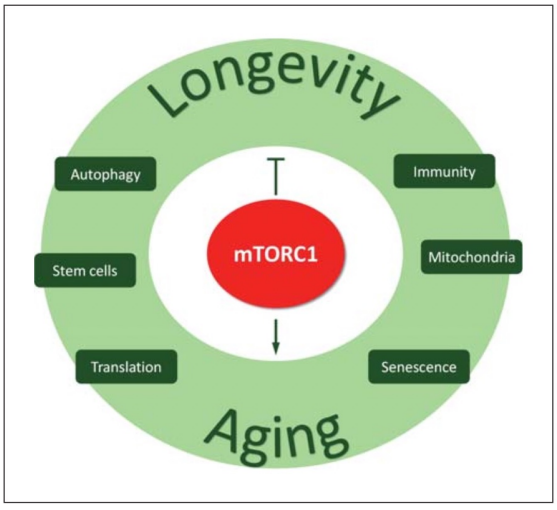

Fig. 2. The role of mTORC1 in longevity and aging. The mechanisms of how mTORC1 regulates longevity and aging.

Gerontology 2018;64:127–134

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nature COMMUNICATIONS

ARTICLE

Received 2 Nov 2012 | Accepted 26 Jun 2013 | Published 30 Jul 2013

DOI: 10.1038/ncomms3192

Metformin improves healthspan and lifespan in mice

Alejandro Martin-Montalvo[1,*], Evi M. Mercken[1,*], Sarah J. Mitchell[1,2,3], Hector H. Palacios[1], Patricia L. Mote[4], Morten Scheibye-Knudsen[5], Ana P. Gomes[6], Theresa M. Ward[1], Robin K. Minor[1], Marie-José Blouin[7], Matthias Schwab[8], Michael Pollak[7], Yongqing Zhang[9], Yinbing Yu[10], Kevin G. Becker[9], Vilhelm A. Bohr[5], Donald K. Ingram[11], David A. Sinclair[6], Norman S. Wolf[12], Stephen R. Spindler[4], Michel Bernier[1] & Rafael de Cabo[1]

Metformin is a drug commonly prescribed to treat patients with type 2 diabetes. Here we show that long-term treatment with metformin (0.1% w/w in diet) starting at middle age extends healthspan and lifespan in male mice, while a higher dose (1% w/w) was toxic. Treatment with metformin mimics some of the benefits of calorie restriction, such as improved physical performance, increased insulin sensitivity, and reduced low-density

Screenshot

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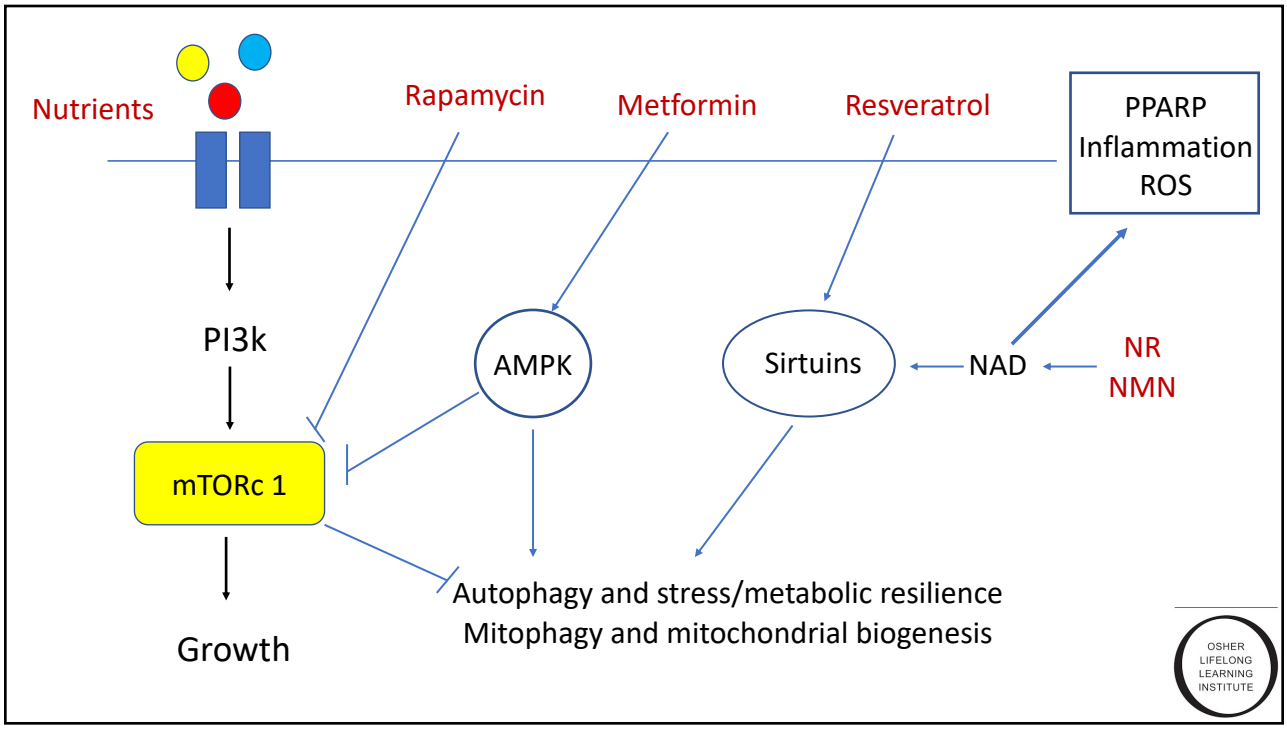

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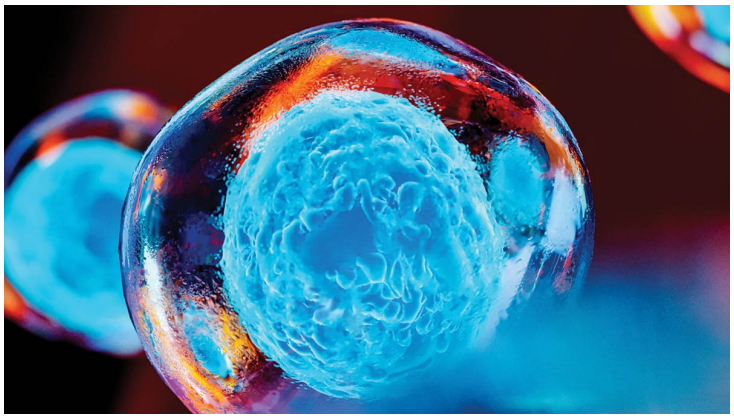
Stem cells and regenerative medicine

- Embryonic: pluripotent, can form almost any cell type in the human body
- Tissue specific: can form only limited types of cells
- Induced pluripotent: engineered by scientists to behave like embryonic stem cells



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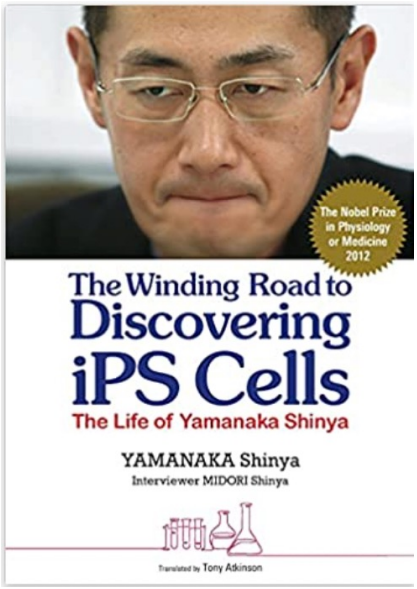

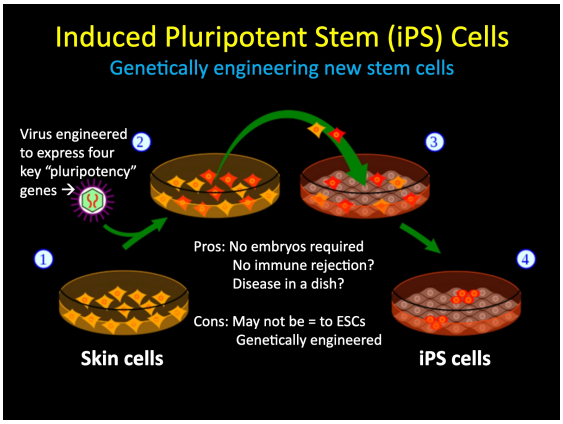

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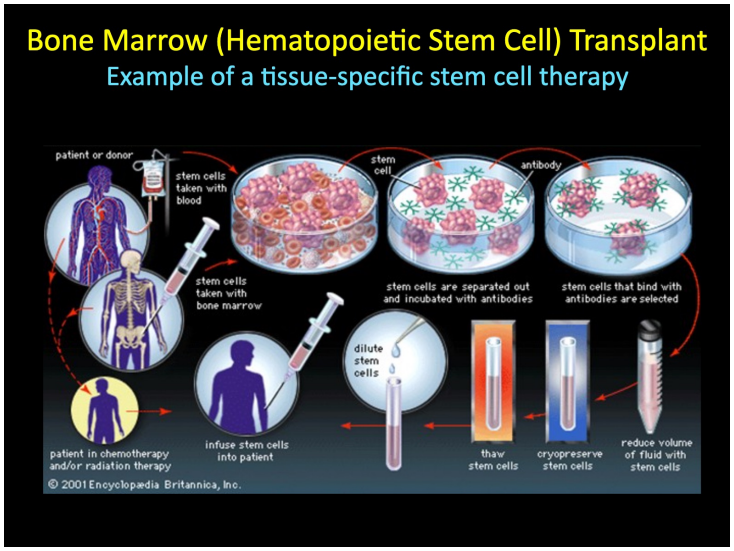
Diseases that stem cells have the potential to treat

- Blood diseases
- Heart diseases
- Parkinson's
- Alzheimer's
- ALS
- Multiple sclerosis
- Macular degenerations
- Cancer
- HIV/AIDS
- Spinal cord injury
- Stroke



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Telomere Attrition

- Too much telomere erosion causes cells to malfunction and die.

- Telomeric DNA partially shortens during the decades of human lifetimes

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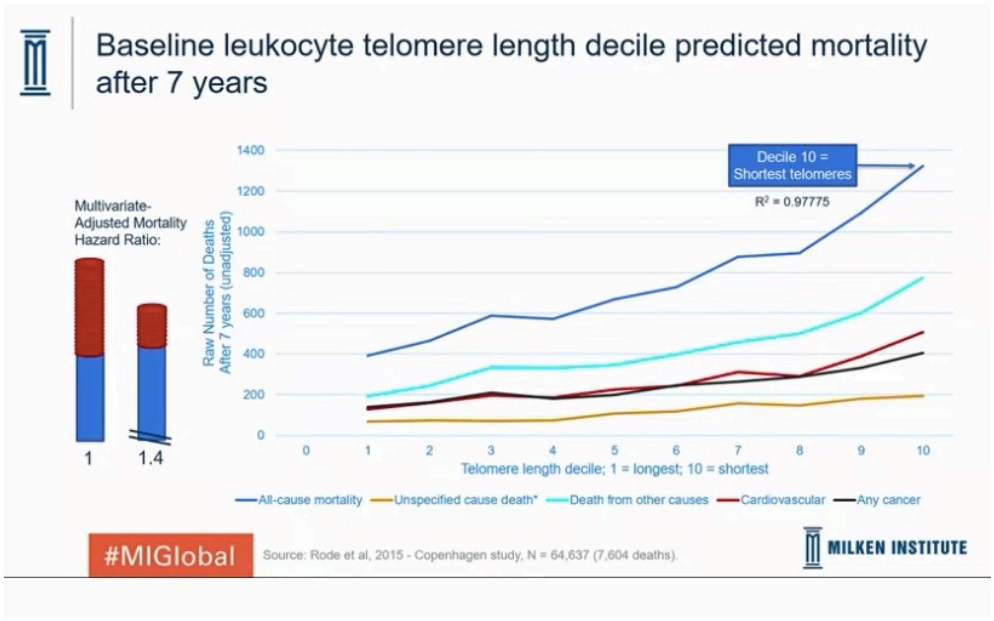

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Received: 11 May 2019 | Revised: 16 July 2019 | Accepted: 4 August 2019
DOI: 10.1111/acel.13028

ORIGINAL ARTICLE

Aging Cell WILEY

Reversal of epigenetic aging and immunosenescent trends in humans

Gregory M. Fahy[1] | Robert T. Brooke[1] | James P. Watson[2] | Zinaida Good[3] | Shreyas S. Vasanawala[4] | Holden Maecker[5] | Michael D. Leipold[5] | David T. S. Lin[6] | Michael S. Kobor[6] | Steve Horvath[7]

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[6]Department of Medical Genetics, BC Children's Hospital Research Institute, Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, BC, Canada
[7]Human Genetics, David Geffen School of Medicine, University of California, Los

Abstract

Epigenetic "clocks" can now surpass chronological age in accuracy for estimating biological age. Here, we use four such age estimators to show that epigenetic aging can be reversed in humans. Using a protocol intended to regenerate the thymus, we observed protective immunological changes, improved risk indices for many age-related diseases, and a mean epigenetic age approximately 1.5 years less than baseline after 1 year of treatment (−2.5-year change compared to no treatment at the end of the study). The rate of epigenetic aging reversal relative to chronological age accelerated from −1.6 year/year from 0–9 month to −6.5 year/year from 9–12 month. The GrimAge predictor of human morbidity and mortality showed a 2-year decrease in epigenetic vs. chronological age that persisted six months after discontinuing treatment. This is to our knowledge the first report of an increase, based on an epigenetic age estimator, in predicted human lifespan by means of a currently accessible aging intervention.

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Maybe We Can!

September 8, 2019:
We published the first strong evidence that ***aging can be reversed in humans.***

Aging Cell Open Access ANATOMICAL SOCIETY

ORIGINAL ARTICLE | Open Access

Reversal of epigenetic aging and immunosenescent trends in humans

"This is to our knowledge the first report of an increase . . . in predicted human lifespan by means of a ***currently accessible*** aging intervention."

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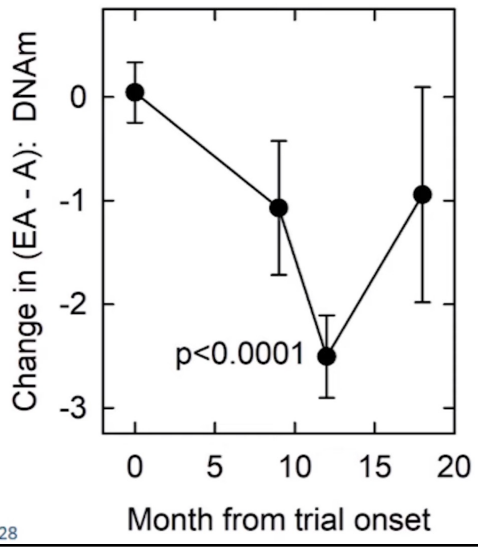
So We Tested *Generalized* Aging: Epigenetic Aging Was Reversed!

The Horvath epigenetic aging "clock":

Reveals biological age more accurately than your birthday can.



Aging Cell 08 September 2019 | https://doi.org/10.1111/acel.13028

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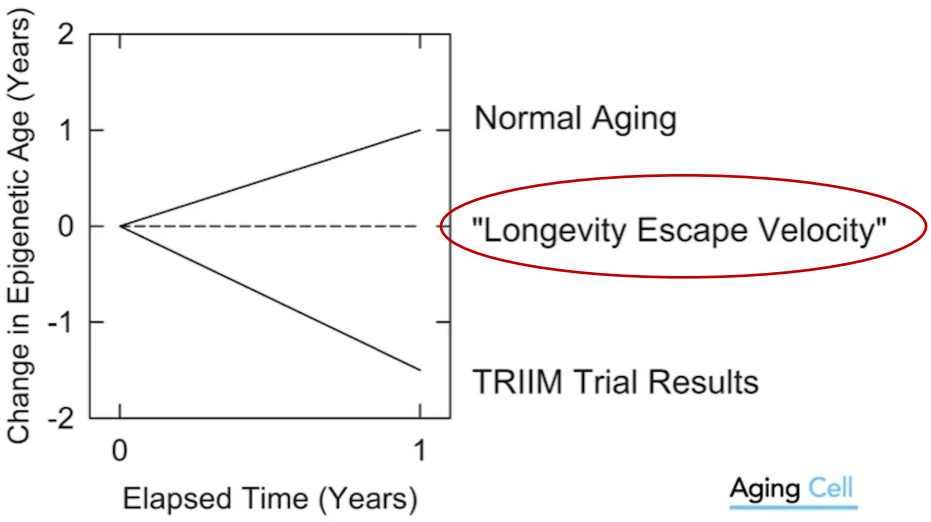
Implications

Aging Progression Patterns



Aging Cell

08 September 2019 | https://doi.org/10.1111/acel.13028

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Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

bioRxiv posts many COVID19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.

New Results

Follow this preprint

Reversal of ageing- and injury-induced vision loss by Tet-dependent epigenetic reprogramming

Yuancheng Lu, Anitha Krishnan, Benedikt Brommer, Xiao Tian, Margarita Meer, Daniel L. Vera, Chen Wang, Qiurui Zeng, Doudou Yu, Michael S. Bonkowski, Jae-Hyun Yang, Emma M. Hoffmann, Songlin Zhou, Ekaterina Korobkina, Noah Davidsohn, Michael B. Schultz, Karolina Chwalek, Luis A. Rajman, George M. Church, Konrad Hochedlinger, Vadim N. Gladyshev, Steve Horvath, Meredith S. Gregory-Ksander, Bruce R. Ksander, Zhigang He, David A. Sinclair

doi: https://doi.org/10.1101/710210

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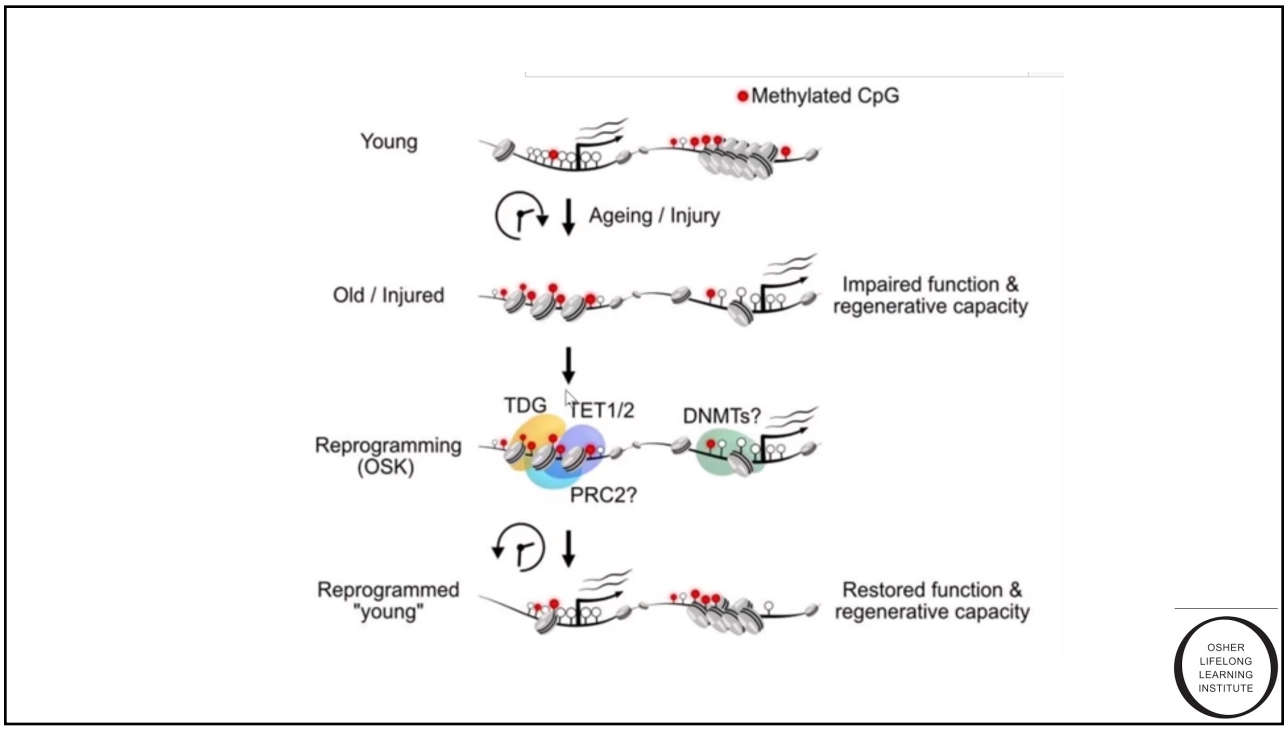
Methylated CpG
Young
Ageing / Injury
Old / Injured
Impaired function & regenerative capacity
TDG
TET1/2
DNMTs?
Reprogramming (OSK)
PRC2?
Reprogrammed "young"
Restored function & regenerative capacity
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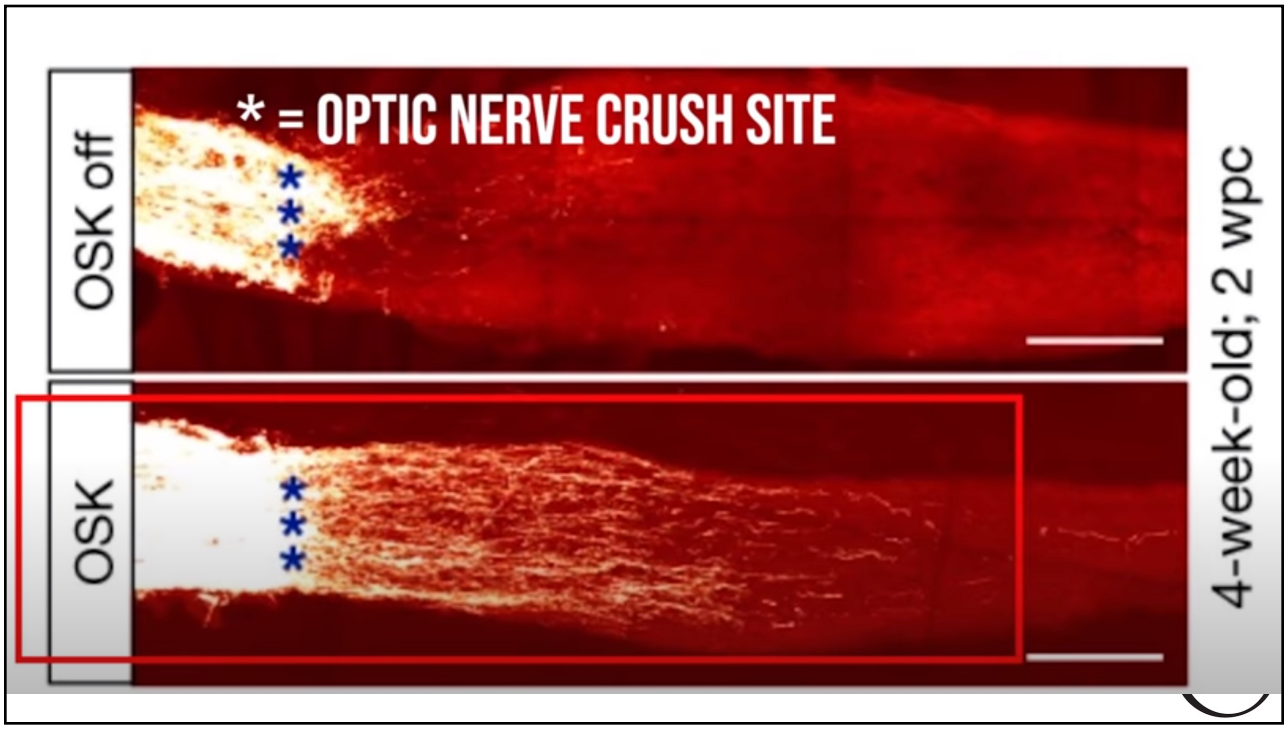
* = OPTIC NERVE CRUSH SITE
OSK off
OSK
4-week-old; 2 wpc

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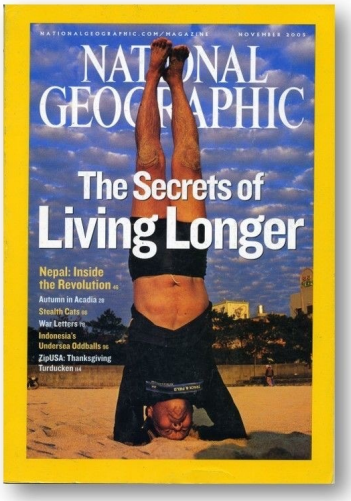
How can I translate this science into my day-to-day routine in 2022?

57



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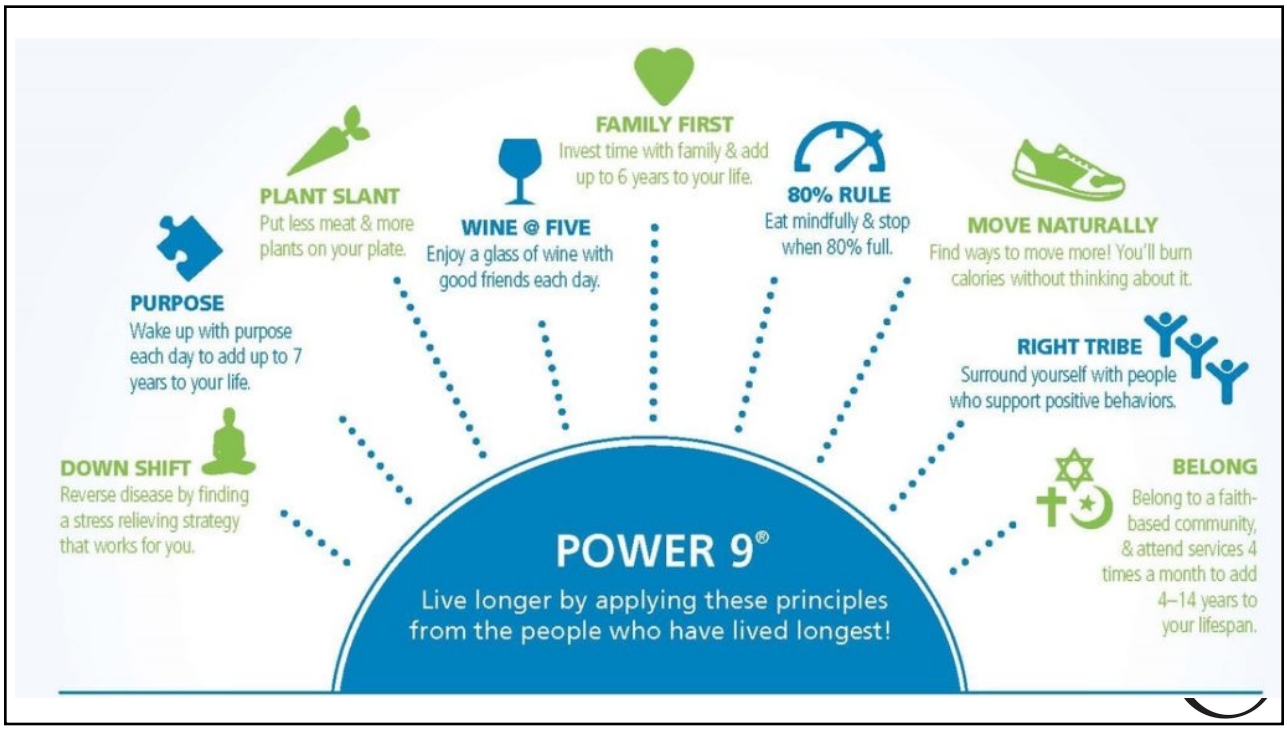

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Regarding Food

Test and track **BG response** *(WTE-7 Day Carb Test)*

Be aware of **immunogenic foods**

Eat with the **seasons**

Get **as much variety as possible** without getting in trouble - hyperpalatability

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REVIEW

AGING

Antiaging diets: Separating fact from fiction

Mitchell B. Lee[1], Cristal M. Hill[2], Alessandro Bitto[1], Matt Kaeberlein[1]*

Caloric restriction has been known for nearly a century to extend life span and delay age-associated pathology in laboratory animals. More recently, alternative "antiaging" diet modalities have been described that provide new mechanistic insights and potential clinical applications. These include intermittent fasting, fasting-mimicking diets, ketogenic diets, time-restricted feeding, protein restriction, and dietary restriction of specific amino acids. Despite mainstream popularization of some of these diets, many questions remain about their efficacy outside of a laboratory setting. Studies of these interventions support at least partially overlapping mechanisms of action and provide insights into what appear to be highly conserved mechanisms of biological aging.

Lee et al., Science 374, eabe7365 (2021) 19 November 2021

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nature COMMUNICATIONS

ARTICLE

Received 12 Oct 2013 | Accepted 5 Mar 2014 | Published 1 Apr 2014

DOI: 10.1038/ncomms4557 OPEN

Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys

Ricki J. Colman[1], T. Mark Beasley[2,3], Joseph W. Kemnitz[4], Sterling C. Johnson[5,6], Richard Weindruch[5,6] & Rozalyn M. Anderson[5,6]

Caloric restriction (CR) without malnutrition increases longevity and delays the onset of age-associated disorders in short-lived species, from unicellular organisms to laboratory mice and rats. The value of CR as a tool to understand human ageing relies on translatability of CR's effects in primates. Here we show that CR significantly improves age-related and all-cause survival in monkeys on a long-term ~30% restricted diet since young adulthood.

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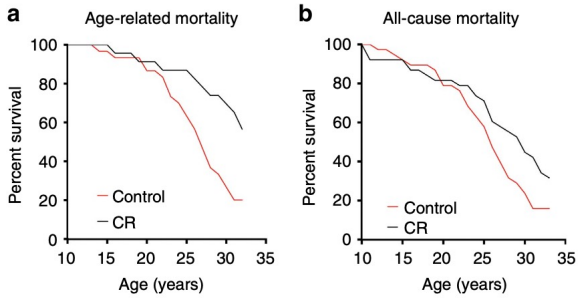

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IMAGE: KELLIE HOLOSKI/SCIENCE

At the buffet of antiaging diets, which is the best plate? Diets clockwise from top left: CR, time-restricted feeding, protein restriction, and ketogenic.

Lee *et al.*, *Science* **374**, 953 (2021) 19 November 2021

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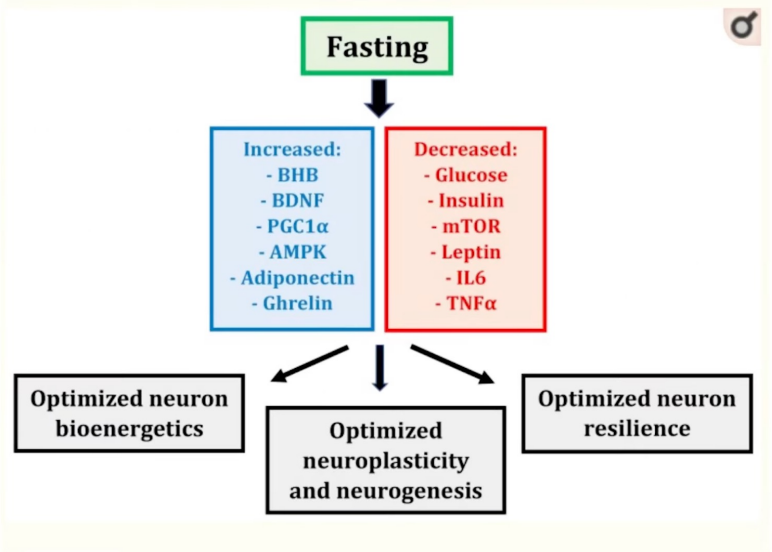

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Cell Metabolism
Article

Cell PRESS

Low Protein Intake Is Associated with a Major Reduction in IGF-1, Cancer, and Overall Mortality in the 65 and Younger but Not Older Population

Morgan E. Levine,[1,11] Jorge A. Suarez,[1,2,11] Sebastian Brandhorst,[1,2] Priya Balasubramanian,[1,2] Chia-Wei Cheng,[1,2] Federica Madia,[1,3] Luigi Fontana,[4,5,6] Mario G. Mirisola,[1,2,7] Jaime Guevara-Aguirre,[8] Junxiang Wan,[1,2]

A good daily target for protein intake for those 60+ years of age is 1 – 1.2 grams/kg body weight per day. This should be comprised of protein sources from plant and if desireable, animal sources that are pasture raised and fed. Someone weighing 70 kg would target 70 – 85 grams/day.

[10]Buck Institute for Research on Aging, Novato, CA 94945, USA
[11]These authors contributed equally to this work
*Correspondence: vlongo@usc.edu
http://dx.doi.org/10.1016/j.cmet.2014.02.006

Cell Metabolism *19*, 407–417, March 4, 2014 a2014 Elsevier Inc.

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JAMA Network | Open

Original Investigation | Cardiology

Association of Cardiorespiratory Fitness With Long-term Mortality Among Adults Undergoing Exercise Treadmill Testing

Kyle Mandsager, MD; Serge Harb, MD; Paul Cremer, MD; Dermot Phelan, MD, PhD; Steven E. Nissen, MD; Wael Jaber, MD

Abstract

CONCLUSIONSANDRELEVANCE Cardiorespiratory fitness is inversely associated with long-term mortality with no observed upper limit of benefit. Extremely high aerobic fitness was associated with the greatest survival and was associated with benefit in older patients and those with hypertension.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study enrolled patients at a tertiary care academic medical center from January 1, 1991, to December 31, 2014, with a median follow-up of 8.4 years. Data analysis was performed from April 19 to July 17, 2018. Consecutive adult patients referred for symptom-limited exercise treadmill testing were stratified by age- and sex-matched cardiorespiratory fitness into performance groups: low (<25th percentile), below

Key Points

cardiorespiratory fitness was inversely associated with all-cause mortality without an observed upper limit of benefit. Extreme cardiorespiratory fitness (≥2 SDs above the mean for age

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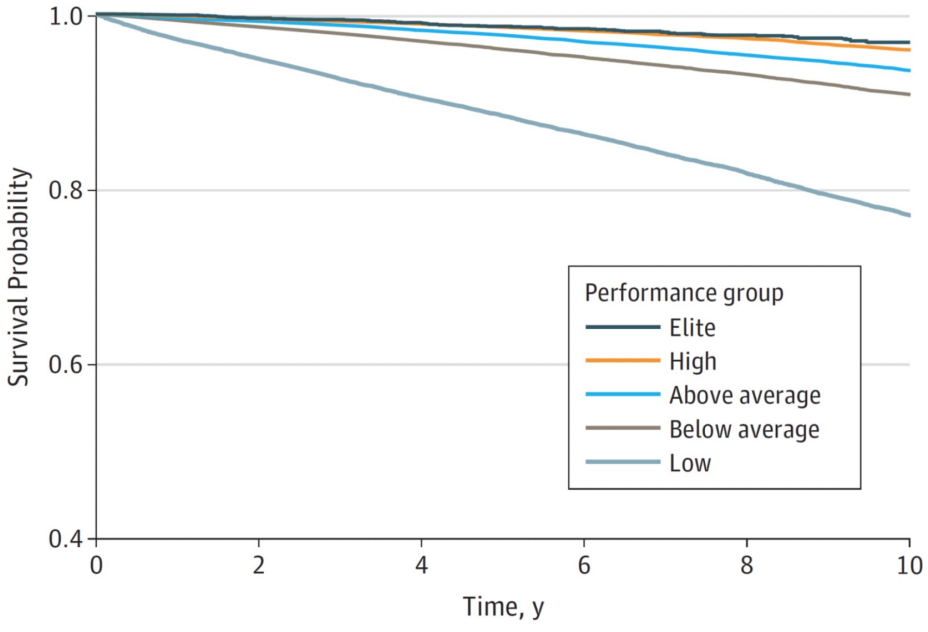

Figure 1. Patient survival by performance group. (Mandsager et al., 2018)

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Sauna Therapy

- Evidence for health promotion and disease prevention strong
- 30” minutes 3-4x/week
- Steam or infrared
- Stimulates our bodies defense mechanisms

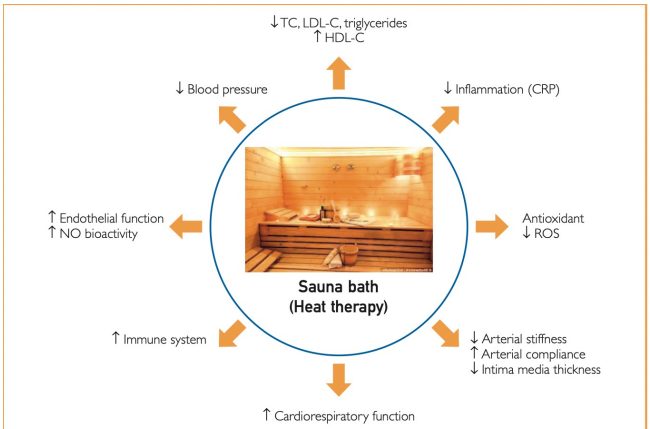

FIGURE 2. Pleiotropic effects (proposed mechanistic pathways) of Finnish sauna baths. CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NO = nitric oxide; ROS = reactive oxygen species; TC = total cholesterol.

Mayo Clin Proc. ■ August 2018;93(8):1111-1121 ■ https://doi.org/10.1016/j.mayocp.2018.04.008

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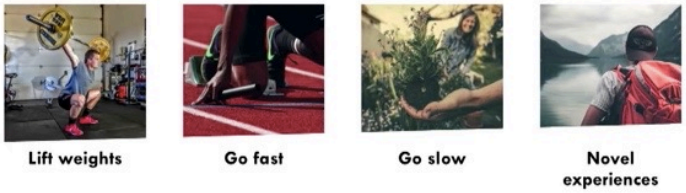
Reclaiming and maintaining our metabolic flexibility (ie. mitochondrial health)



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PNAS PNAS

Optimism is associated with exceptional longevity in 2 epidemiologic cohorts of men and women

Lewina O. Lee[a,b,1], Peter James[c], Emily S. Zevon[d], Eric S. Kim[d,e], Claudia Trudel-Fitzgerald[d,e], Avron Spiro III[b,f,g], Francine Grodstein[h,i,2], and Laura D. Kubzansky[d,e,2]

[a]National Center for Posttraumatic Stress Disorder, Veterans Affairs Boston Healthcare System, Boston, MA 02130; [b]Department of Psychiatry, Boston University School of Medicine, Boston, MA 02118; [c]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA 02215; [d]Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, MA 02115; [e]Lee Kum Sheung Center for Health and Happiness, Harvard T.H. Chan School of Public Health, Boston, MA 02115; [f]Massachusetts Veterans Epidemiology Research and Information Center, Veterans Affairs Boston Healthcare System, Boston, MA 02130; [g]Department of Epidemiology, Boston University School of Public Health, Boston, MA 02118; [h]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA 02115; and [i]Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA 02115

Edited by Bruce S. McEwen, The Rockefeller University, New York, NY, and approved July 30, 2019 (received for review January 18, 2019)

Most research on exceptional longevity has investigated biomedical factors associated with survival, but recent work suggests nonbiological factors are also important. Thus, we tested whether higher optimism was associated with longer life span and greater likelihood of exceptional longevity. Data are from 2 cohorts, women from the Nurses' Health Study (NHS) and men from the Veterans Affairs Normative Aging Study (NAS), with follow-up of 10 y (2004 to 2014) and 30 y (1986 to 2016), respectively. Optimism was assessed using the Life Orientation Test–Revised in NHS and the Revised Optimism–Pessimism Scale from the Minnesota Multiphasic Personality Inventory-2 in NAS. Exceptional longevity was defined as survival to age 85 or older. Primary analyses used accelerated failure time models to assess differences in life span associated with optimism; models adjusted for demographic confounders and health conditions, and subsequently considered the

assets that promote health across the life course, particularly in aging, could contribute to optimal functioning and improved health. Among psychosocial factors that appear to be potential health assets (e.g., social integration; ref. 14), optimism has some of the strongest and most consistent associations with a wide range of health outcomes, including reduced risk of cardiovascular events, lung function decline, and premature mortality (4–10), and associations that are independent of other psychosocial factors such as depression, anxiety, or anger (12). Investigators have speculated that optimism may facilitate healthier biobehavioral processes, and ultimately longevity, because optimism directly contributes to how goals are translated into behaviors (15). Optimism is ~25% heritable but is also shaped by social structural factors and can be learned, as demonstrated in experi-

PSYCHOLOGICAL AND COGNITIVE SCIENCES

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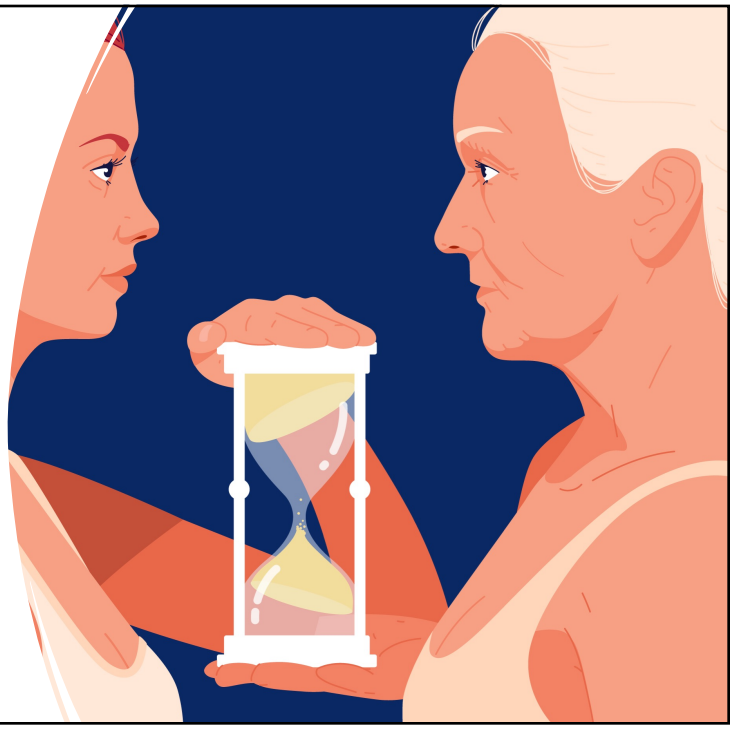
Horizons of Longevity Innovation

- Computational Biology
- Wearable devices
- Health software and apps with AI-based diagnostics
- Gene therapies and editing
- Stem cell technologies
- Nanotechnology with health augmentation
- Age regression "cocktails"
- "Quantum-access" therapies
- Consciousness expansion therapies



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