

**Why should you care about
aging?**

What aging is:

An increasing likelihood of illness and
— breakdown. —

Diseases of Aging

- Cancer
- Heart disease
- Stroke
- Infections
- Brain diseases: Alzheimer's, Parkinson's
- Osteoporosis
- Obesity, diabetes
- Sarcopenia (muscle loss)
- Many others

First reason to stop aging

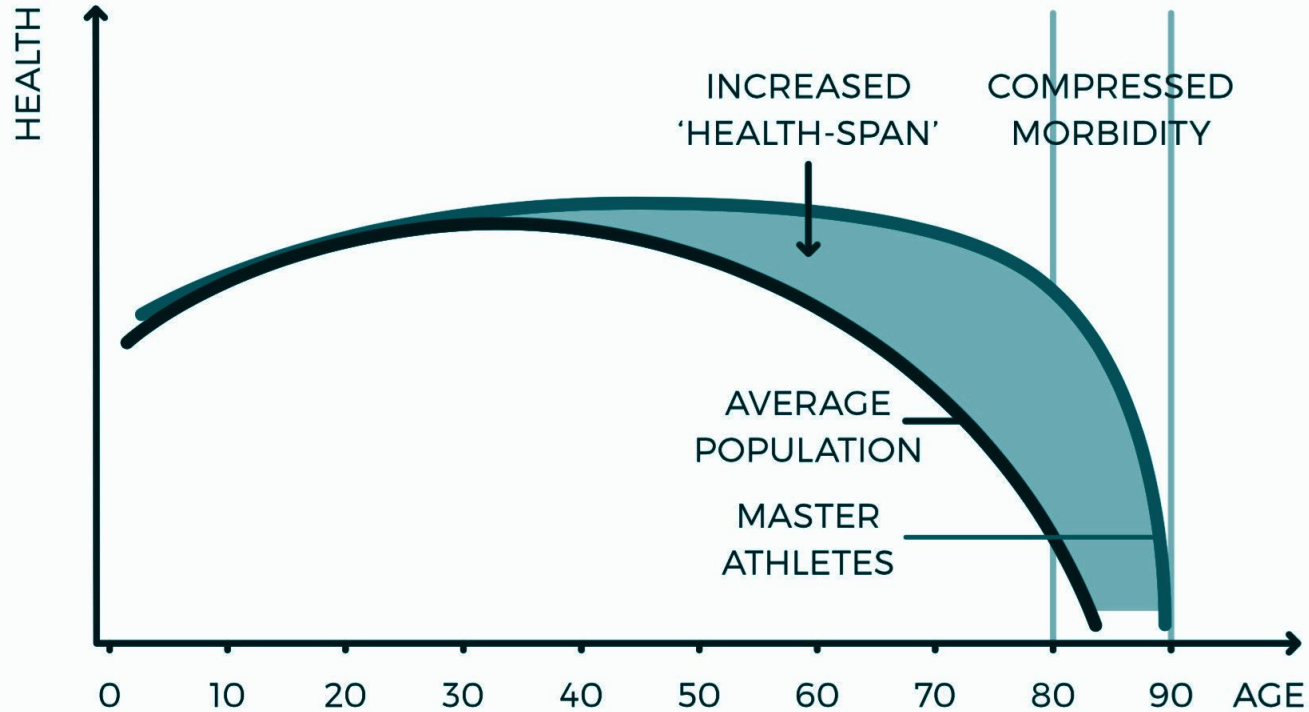
Better health and fewer diseases.

Why wouldn't you? Even if you have no desire to live to be 100 or more, you can have better health and a better life by slowing or reversing aging.

Imagine: no cancer, heart disease, dementia.

No frailty, weakness, or dependence on others.

Healthspan vs Lifespan



Source: World Economic Forum

Healthspan vs Lifespan, II

- Life extension does not mean more years in a nursing home, but is about maximizing years of healthy life.
- Any intervention, for example exercise, that fights aging also extends healthspan, or years of life in which we are healthy.
- Even if some intervention does not extend lifespan, if it extends healthspan, it will be worth it.


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 and [Rafael de Cabo](#)¹

[Author information](#) ► [Copyright and License information](#) ► [Disclaimer](#)

The publisher's final edited version of this article is available at [Nat Commun](#)
See other articles in PMC that [cite](#) the published article.

Abstract

Go to: 

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 LDL and cholesterol levels without a decrease in caloric intake. At a molecular level, metformin increases AMP-activated protein kinase activity and increases antioxidant protection, resulting in reductions in both oxidative damage accumulation and chronic inflammation. Our results indicate that these actions may contribute to the beneficial effects of metformin on healthspan and lifespan. These findings are in agreement with current epidemiological data and raise the possibility of metformin-based interventions to promote healthy aging.

What's the difference between a machine and a person?

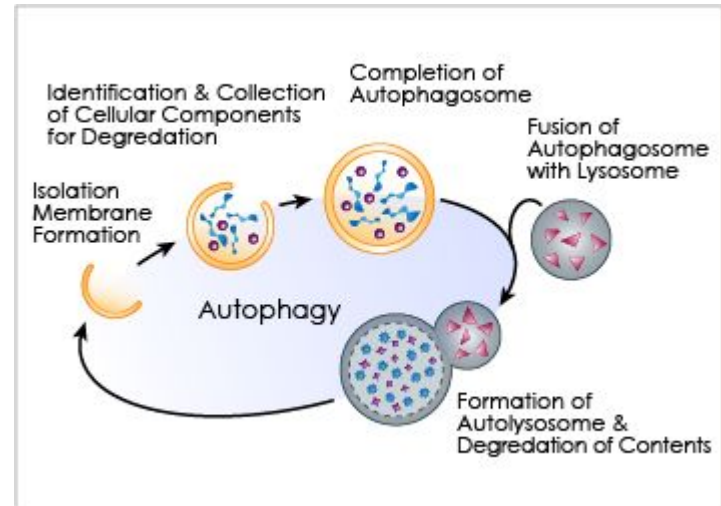
A machine can't repair itself.



Living things can repair themselves

Autophagy: Cellular self-repair and junk recycling.

The ability to regulate autophagy declines with age.



We can repair ourselves

But you must allow yourself to do so!

The couch potato lifestyle ages you faster.

The opposite of the couch potato lifestyle rejuvenates you.

The Garbage Catastrophe of Aging

- Decline in ability to clear cells of junk molecules that are passed their expiration date means an accumulation of poorly functioning components as we age.
- Everything then doesn't work as well because the components need replacement or repair.
- Leads to disease as the body can't function properly.
- Leads to the garbage catastrophe of aging.

How to Slow or Reverse Aging

- Increase the body's capacity of self-repair.
- Every anti-aging, life-extension process causes better self-repair.
- Youth = better maintenance and repair of the body.
- Aging = loss of that ability.

J Clin Invest. 2015 Jan 2; 125(1): 85–93.

Published online 2015 Jan 2. doi: [10.1172/JCI73946](https://doi.org/10.1172/JCI73946)

PMCID: PMC4382258

PMID: [25654554](https://pubmed.ncbi.nlm.nih.gov/25654554/)

Essential role for autophagy in life span extension

[Frank Madeo](#),^{1,2} [Andreas Zimmermann](#),¹ [Maria Chiara Maiuri](#),^{3,4} and [Guido Kroemer](#)^{3,4,5,6}

[Author information](#) ► [Copyright and License information](#) ► [Disclaimer](#)

This article has been [cited by](#) other articles in PMC.

Abstract

Go to:

Life and health span can be prolonged by calorie limitation or by pharmacologic agents that mimic the effects of caloric restriction. Both starvation and the genetic inactivation of nutrient signaling converge on the induction of autophagy, a cytoplasmic recycling process that counteracts the age-associated accumulation of damaged organelles and proteins as it improves the metabolic fitness of cells. Here we review experimental findings indicating that inhibition of the major nutrient and growth-related signaling pathways as well as the upregulation of anti-aging pathways mediate life span extension via the induction of autophagy. Furthermore, we discuss mounting evidence suggesting that autophagy is not only necessary but, at least in some cases, also sufficient for increasing longevity.

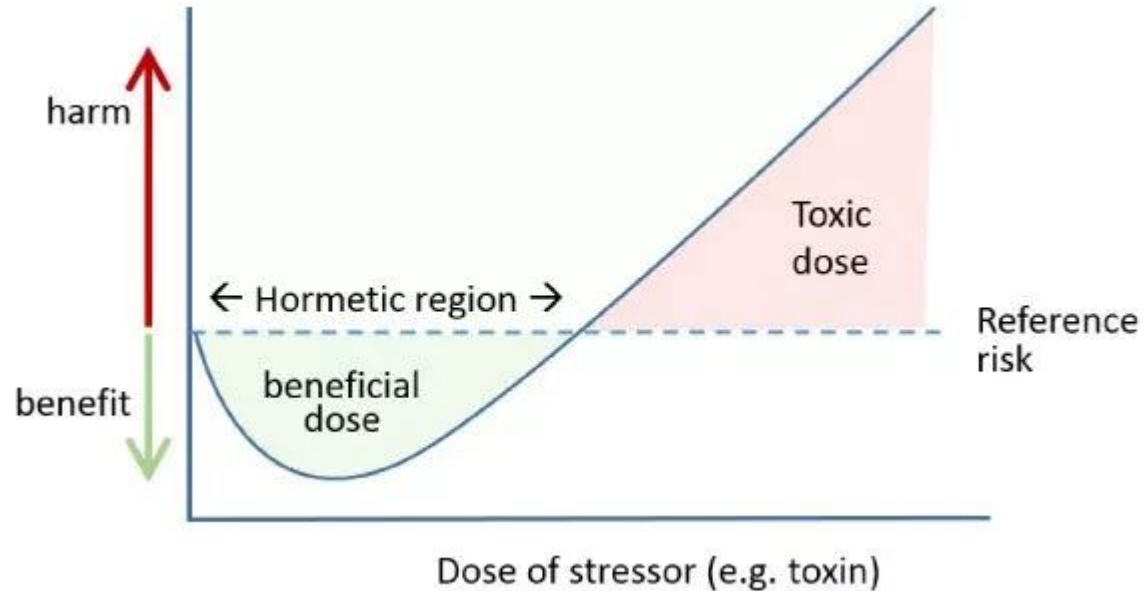
Hormesis

“What doesn’t kill me makes me stronger.”

Something of an exaggeration, but not much.

The J Curve of Hormesis

J-curve: low doses of toxins or stressors are beneficial.



How long can you live?

Jeanne Calment lived to 122, and she didn't even try.

However, she

- Had only coffee for breakfast (fasting)
- Prayed every morning (religious)
- Favorite meal was beef (protein and low-carb)
- Drank red wine
- Consumed chocolate and olive oil.

No doubt she had a genetic advantage.



Inflammation

Inflammation is the body's defensive reaction to pathogens and injury.

While absolutely necessary, chronic, low-level inflammation increases with age, and is harmful.

Why does inflammation increase? Bacterial load, poor diet, and lack of exercise are all involved.

Inflammation is characteristic of aging.

Oxidative stress

Our bodies are finely tuned to keep oxygen and its byproducts under control.

Free radical theory of aging.

We have our own internal antioxidants to quench free radicals, notably glutathione.

Glutathione declines with age, and oxidative stress increases, causing damage.

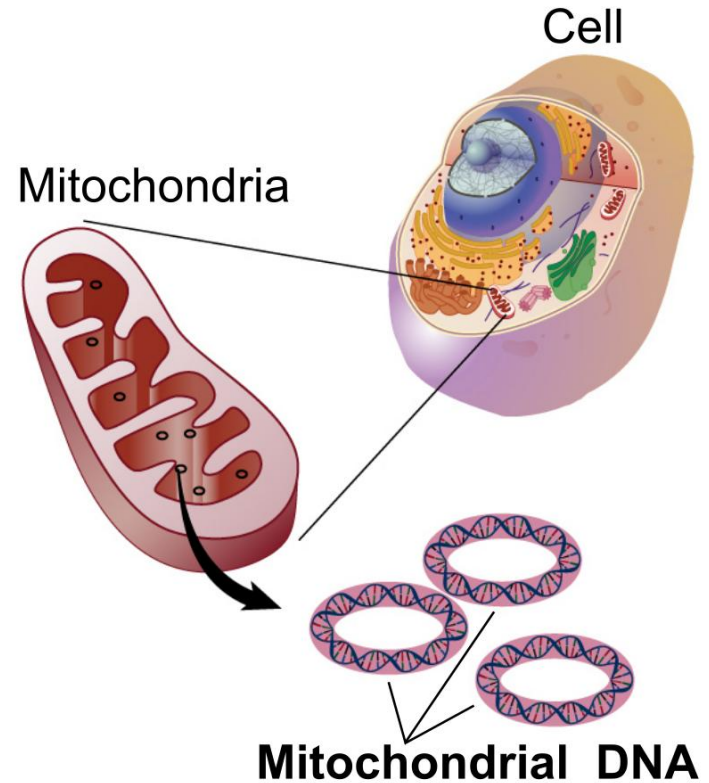
To fight aging, we must stop oxidative stress.

Mitochondria

Mitochondria are the powerhouses of the cell.

Their function diminishes with age.

Keeping mitochondria finely tuned is critical.



Senescent cells

Hayflick limit is the number of times cells can divide. After this limit, they become senescent.

Senescent cells crank out toxic, inflammatory chemicals (cytokines) that poison the internal atmosphere of the body.

We know how to get rid of senescent cells right now, and better methods are on the horizon.

Escape velocity

Technology is advancing at an exponential rate. In the not distant future, powerful life extension technologies will allow us to return to a youthful state.

Live long enough and you'll have access to these technologies.

Summary

Science has made huge strides in understanding how aging changes our biology.

We know a number of interventions that slow or reverse aging, both in lab animals and in humans.

The task before us is to implement those interventions to have longer healthspan and lifespan, and to await the arrival of the cavalry of anti-aging technology.

What those interventions are will be the subject of the rest of this course.