Longevity FAQ: A beginner's guide to longevity research

Hi! I'm Laura Deming, and I run Longevity Fund. I spend a lot of time thinking about what could increase healthy human lifespan. This is my overview of the field for beginners. Feel free to send me any questions about the below (just include name and affiliation).

Overview:

- Introduction:
  - Basic concepts in aging research
- Explanation:
  - Major areas of aging research
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    - Insulin/IGF
    - Parabiosis
    - Senescence
    - Autophagy
    - Hypothalamus
    - Reproductive System
    - Mitochondria
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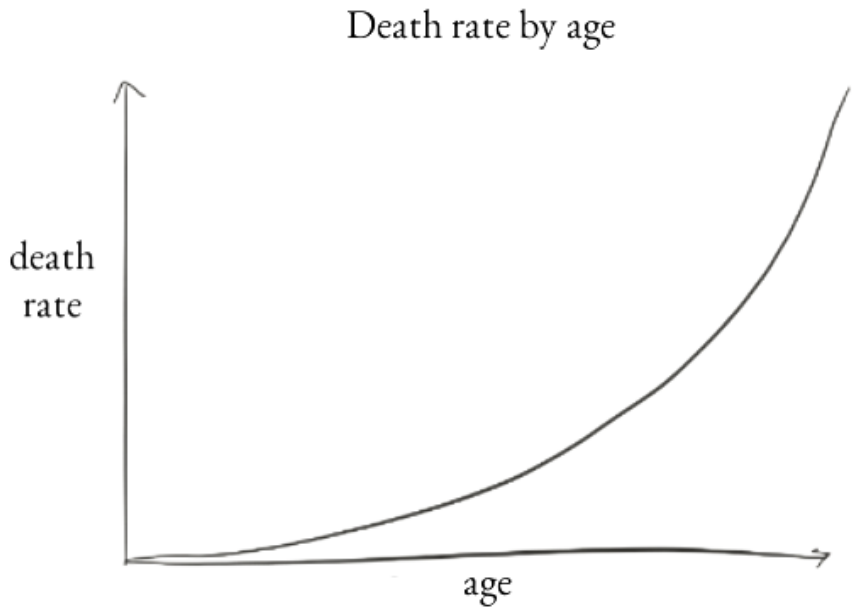
- Data:
  - Comprehensive surveys of longevity

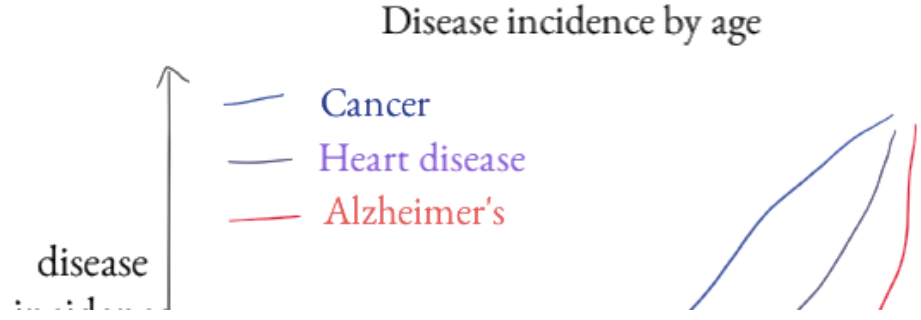
- 95 things that make mice live longer
- 70 drugs in the clinic that might make people live longer

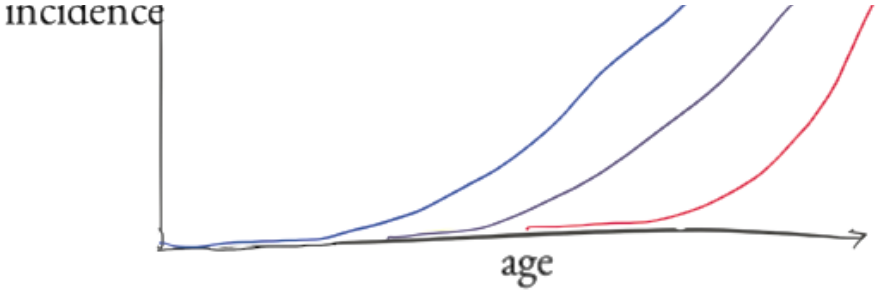
Introduction

As you get older, the chance that you will die goes up.



As you get older, the chance that you will die from certain diseases also goes up.



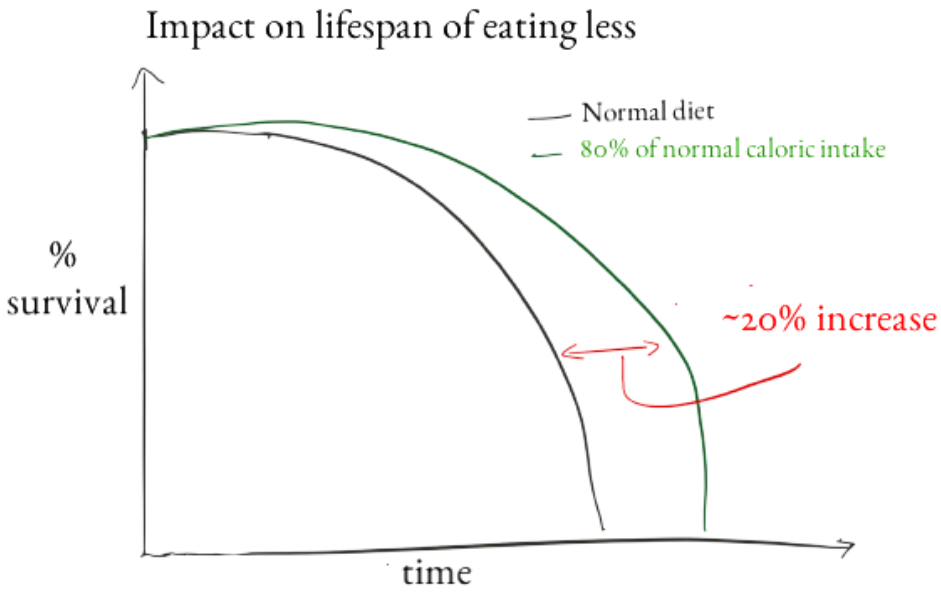


Why does this happen?

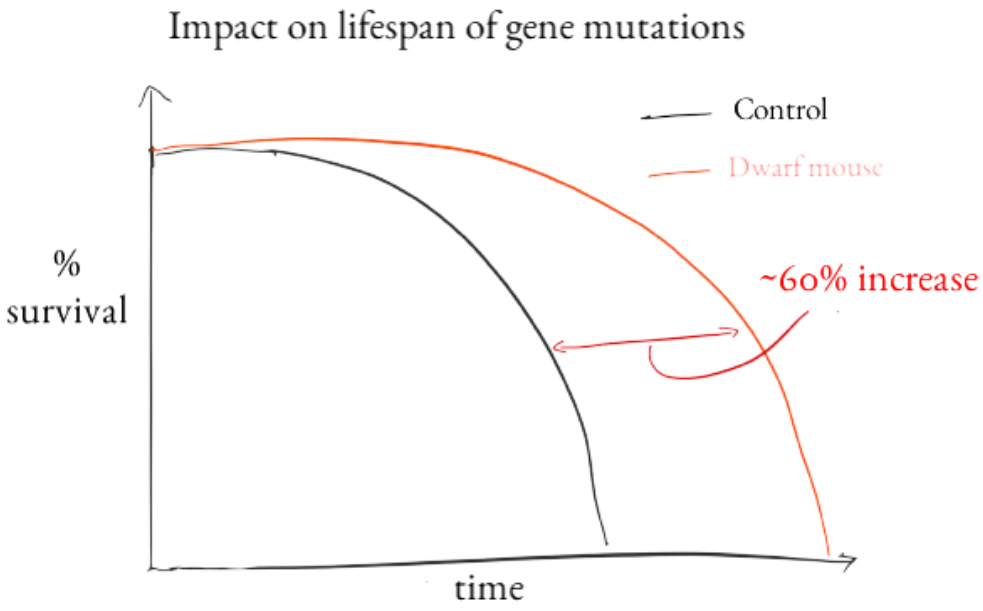
A simple explanation would be that, like an old car, you accumulate damage in a random fashion.

However, there are many simple things that we can do to make animals live longer. Why? We don't really know.

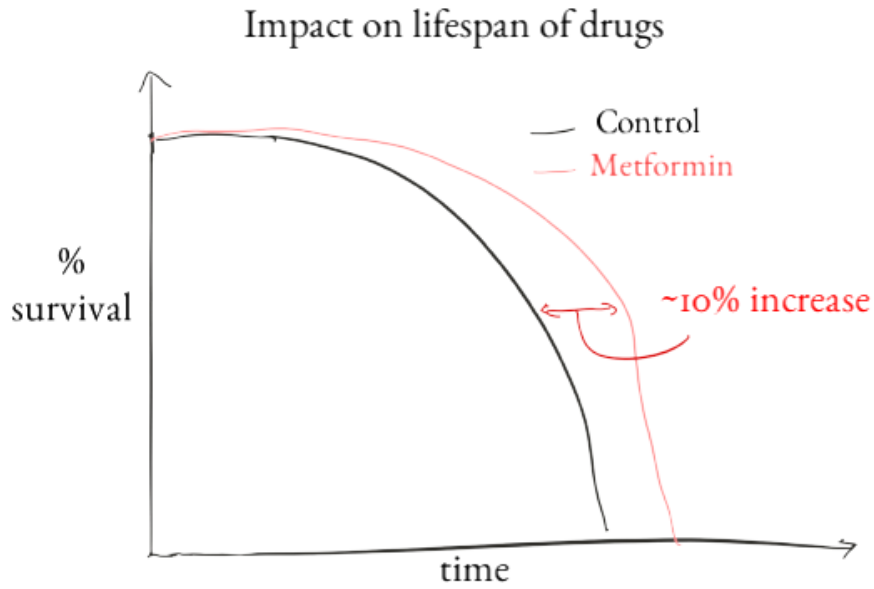
Eating less makes mice live longer.



Some genes, when mutated, make mice live longer,



A few drugs, approved for human use, also make mice live longer.



There are others - we will cover them below.

So what is the study of aging?

I sum it up as the following: trying to figure out what kinds of damage accumulate with age, how to reverse that accumulation, and the search for

switches that we could flip in human biology to increase lifespan.

Research areas in longevity

Caloric Restriction

at a glance: eating less, in a variety of ways, can make you live longer - but is your body just using number of calories as a signal?

In the 1930s, investigators wanted to do an experiment to see if stunted growth rates during the Great Depression might impact lifespan. They tested this in rats by feeding them less food than they would normally eat. To their surprise, this actually made the rats live longer! This was a seminal discovery. For the first time, we changed the environment of an animal to make it live longer than it normally would.

Since then, investigators have tried to uncover how this works. The effect depends on what genes you have, what you are eating and how much less you eat. If you take many genetically distinct mouse strains and put them on the same diet (cutting calories by ~40%), sometimes fewer than 1/5 of the mouse strains live longer. Diet composition also plays a role. Just decreasing protein or a specific amino acid, while keeping total calorie intake the same, can result in a lifespan extension in mice. Feeding mice a ketogenic diet also seems to help. Decreasing food intake by too much will result in starvation, so finding a diet that works can depend on the situation.

While long-term human studies are sparse, investigators have run two caloric restriction experiments in monkeys, one of which showed promising results for an increase in survival. To avoid the difficulty of continuous dieting, fasting ~8+ hours a day, or 5 days/month, or on a variety of different cycles might also be helpful. This is called intermittent fasting. Medically, intermittent fasting may aid recovery during chemotherapy. Some longevity-related pathways involve sensing amino acid levels, so it is possible that a specific biological process, not total calorie intake, controls the increase in lifespan.

Insulin/IGF

at glance: genetic pathways related to growth and insulin signaling are linked to aging

In papers published in 1983-1993, investigators introduced the concept that a gene could control lifespan. I got my start in science when one of the founders of this field, Cynthia Kenyon, agreed to let me work in her lab as a 12 year old kid. I'll always be grateful for her kindness and mentorship. Previously we'd known that caloric restriction could make animals live longer, but Kenyon and other scientists including Michael Klass, David Friedman and Tom Johnson found mutant genes that could make worms live longer. The gene that Kenyon found encoded a protein that is similar to insulin-like growth factor and insulin receptors in humans. In mice, mutating members of both of those pathways can increase lifespan. One of the longest-lived mouse mutants we have today is a dwarf mouse. In one study, people with similar dwarf mutations seemed to suffer less age-related disease than their non-mutated relatives.

I'm fascinated by the fact that many drugs which have been developed for diabetes, without any thought for their use elsewhere, turn out later to be relevant to aging. Good examples of this are metformin and FGF-21.

Metformin is a small molecule used to treat Type 2 Diabetes, and FGF-21 is a protein in your blood that can increase lifespan in mice. We are still figuring out how the insulin/IGF pathway works, in particular what kinds of molecules might be driving the lifespan effect that we observe.

Parabiosis

at a glance: young blood makes old mice healthier, but why?

Dracula wanted to drink young blood, but what does that have to do with aging? A paper published in the 70's showed that linking old and young female mice so that they share a bloodstream increased lifespan. Decades later, in 2005, scientists at Stanford showed that this procedure might help old muscle stem cells repair wounds. Then, in 2011, a succession of papers came out showing that this procedure and others like it (such as injecting young blood into old mice) made mice better at remembering things, and improved heart and muscle function with age. These discoveries increased excitement and interest in the field, and lead to a wave of startups.

Investigators in the field have proposed many possible causes for this phenomenon. Proteins, small vesicles, or cells in the young mouse cleaning the blood of the old mouse might all be part of the effect. Many companies are trying to figure out whether there is a special protein or molecule involved. The big questions to resolve will be whether we can isolate a few key factors that are responsible for the parabiosis effect, and how many of the longevity-related phenotypes will translate to improve human health.

Senescence

at a glance: a fraction of your cells get older than the others, so we'd like to eliminate them

As you get old, so do your cells. But some of your cells get old in a way that is much worse than the others. You may have heard of a thing called telomerase. If you remember correctly, it's the thing that keeps the end of your DNA long enough that your cells can still divide. When one of your cells runs out of telomerase, it can't make many more copies of itself. If the cell sticks around, refuses to die even when it stops working, and starts secreting signals to the immune system, we call that a 'senescent cell'.

What happens when you get rid of these cells? Some animals that age faster than normal have a lot of these 'senescent cells' and are good experimental models in which to ask that question. In 2011, a group from the Mayo Clinic cleared out many of the senescent cells in one of those animal models, and found that the resulting mice were healthier in old age (among other things, they did not get cataracts and bent spines, which typically emerge in old age). In 2016, the same investigators found that getting rid of senescent cells in normal mice made them live a longer healthy lifespan. Knocking out senescent cells is tricky, because they don't have many unique identifiers. Companies are working to either find things empirically that kill senescent cells, or figure out specific mechanisms by which to try to destroy them.

Autophagy

at a glance: the garbage disposal unit of the cell worsens with age, improving it might increase healthy lifespan

Your body makes a lot of junk, on the molecular level, and cells need to clean this up. Just increasing the expression of one protein that helps to clean up this junk was enough to make mice live ~17% longer. Cells recycle old proteins and other molecules into a big vesicle, called a lysosome. It contains many proteins, and their job is to chop up old cell parts that it engulfs. Genes for proteins that do work in the lysosome are mutated in diseases such as Parkinson's. So improving this process has immediate relevance to neurodegenerative disease. As the lysosome gets older, more junk builds up in it that it cannot degrade. Finding ways to make more lysosomes, or help lysosomes degrade junk, may be interesting therapeutic avenues to pursue.

Hypothalamus

at a glance: a surprising number of things can increase lifespan when only changed in the brain tissue

Changing something just in the brain can be enough to make a mouse live longer. If the hypothalamus thinks it is too warm, for example, it can decrease the core body temperature of a mouse, resulting in a slightly longer lifespan. Changing the level of a variety of genes in a brain-specific way can also make a mouse live longer.We know that the hypothalamus makes something called growth hormone releasing hormone (GHRH), which is in charge of, well, releasing growth hormone. Growth hormone appears to be closely tied to lifespan, so the hypothalamus could be an important control point. One interesting question is how much you can affect the lifespan of a whole organism by just making changes to the brain.

Reproductive System

at a glance: removing the ability to reproduce can increase lifespan

10 years ago, one of the first projects I worked on was trying to understand a weird fact about reproduction in worms. If you take little worms and get rid of their gonads (I know, it's weird), they live ~60% longer than normal. But this only works if you get rid of the stuff inside (sperm/eggs - these worms are hermaphrodites, which means they carry around both). If you get rid of the whole thing, lifespan goes back to normal.

This isn't restricted to worms. From court records of Korean eunuchs, the eunuchs tend to live longer than their contemporaries by 14-19 years. Some people have tried to do things such as transplant young ovaries into old mice, to see if that helps (it might add a bit to lifespan). There are also many reports showing that when you make things live longer, fertility goes down. There might be a tradeoff (fertility takes away resources that could be used for something else), or a signal coming from the reproductive system that tries to hold up aging if it is damaged.

Mitochondria

at a glance: mitochondrial mutations impact lifespan in counterintuitive ways

You may have heard mitochondria referred to as the 'powerhouses' of the cell. It's funny, they do literally run like a dam generating hydroelectric power! - They pump protons (positively charged particles) one way, then use them as they slide back to run a kind of motor that makes a small energetic molecule used by many entities in the cell. One concept that comes up when people talk about mitochondria is 'oxidative stress' - the idea that if molecules are very reactive (say they have oxygen, acquire some extra electrons, and now want to

discharge them onto other molecules), they are likely to interfere with a lot of other molecules in the cell that should be left to their own devices.

Weirdly, the story has turned on its head over time. It's true that it is bad to pump an animal full of reactive oxygen species, and that you can make a mouse live longer by increasing the level of proteins that are supposed to clean up mitochondria. But you can also mutate things that should be helping the mitochondria, and end up increasing lifespan! It's counterintuitive, and one hypothesis is that a little bit of stress is good because it forces your cells to put up their defenses and ramp up production of molecules that neuter the reactive oxygen species. But we don't really know.

Sirtuins

at a glance: sirtuins can change DNA and increase lifespan

Sirtuins add tags to the structural protein balls that DNA wraps around. It sounds odd, but think of yarn wrapping around a cardboard tube. When they add tags to the DNA yarn ball, it changes how the DNA is folded and expressed. So one of their actions is to control what genes do.

Sirtuins were first discovered to increase lifespan in yeast, and seem to also do so in worms, flies and mice. They depend on NAD to do their job, so when you see people talking about NR or other precursors of NAD, you can think about them as also helping the sirtuins do their job. You can extend lifespan a little bit in mice by giving them NR in old age.

[That's all for this part for now - I'm planning to add to the above, as time allows. There's lots more to talk about!]

Data on longevity

To give some context for the field, I thought it would be fun to do a more comprehensive survey. Below are virtually all the things we've seen that might improve mouse lifespan, listed in order of citations/year.

I think some of the papers on the bottom of the list are actually pretty cool and might have been given a short shrift

(Methodology - I took all papers that had a demonstrated mouse lifespan effect, extracted the key lifespan figure, and in cases where the text didn't list actual median or other lifespan used a virtual pixel ruler to count the pixels to the median point. Allow for some standard deviation of error accordingly!).

95 things that make mice live longer

Ordered by citations/year

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
Senescent cell removal	135%	2016	Does not affect rotarod performance, object discrimination. Slight delay in wound closure.	1

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
Rapamycin	110%	2009	Late-life rapamyicn treatment extends lifespan (pooled females from multiple-site NIA study)	2
NR	105%	2016	Claim an increase in running distance	3
Catalase	117%	2005	Mitochondrially-targeted catalase expression extended mouse lifespan compared to control	4
Sirt6 overexpression	115%	2012	Sirt6-overexpression increases male mouse lifespan	5
Metformin	106%	2013	In males, small but significant lifespan extension after metformin application	6
DN-IκBα	110%	2013	Dominant negative to downregulate IKK-beta activity, delivered to hypothalamus of middle-aged mice	7
Klotho	120%	2005	Overexpression under human elongation factor 1α promoter increases lifespan, slight fertility loss	8

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
S6K1	118%	2009	KO of S6K1 extends lifspan compared to wildtype mice	9
p66	128%	1999	Mutation of a p66shc, member of proto-oncogene locus SHC, extends lifespan. May be just due to cancer effect.	10
Lowering protein:carbohydrate ratio	128%	2014	Varied protein, carbohydrate, and total energy levels.	11
Fat-specific insulin receptor knockout mice	111%	2003	Fat-specific insulin receptor knockout mice show a significant increase in lifespan	12
C57BL/6 mice with NZB/OlaHsd mitochondrial mutations	120%	2016	Same nuclear, different mitochondrial DNA.	13
Fasting mimicking diet	112%	2015	FMD followed by 10 days of normal, then repeat	14
Rapamycin	127%	2014	Rapamycin from 9 months of age, weight decreased ~30% at highest dose	15
Brain-specific Sirt1 expression	116%	2013	Brain-specific Sirt1 expression in female mice increases lifespan over wildtype	16

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
SRT1720	104%	2014	Start diet at 28 weeks of age, very small increase on lifespan	17
Spermidine	111%	2016	Polyamine, administered in drinking water	18
Atg5 overexpression	117%	2013	Transgenic mice ubiquitously expressing Atg5 (crucial for autophagasome confirmation) live longer.	19
Telomerase	124%	2012	Paper showing telomerase therapy increasing life	20
Insulin receptor substrate null	132%	2008	Insulin receptor substrate 1 null mouse lifespan extension in females	21
Snell Dwarf Mice	142%	2001	Snell dwarf mouse paper showing life extension	22
Ames Dwarf Mice	168%	1996	Original Ames dwarf mouse paper showing life extension	23
s-Arf/p53	113%	2007	An extra copy of p53 and upstream regulator Arf/p16Ink4a increases lifespan	24
Slow growth during lactation	106%	2004	Male mice suckled by dams fed a low-protein diet lived longer than their control cohort	25

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
Methionine restriction	111%	2005	Methionine restriction increases mouse lifespan, here median lifespan increase in mice that survived at least 1 yr.	26
Rapamycin (3 months)	114%	2016	Lifespan given from time of treatment which was 23-24 mo, used 24 mo to get percentage so this is an estimate	27
GHR-BP	138%	2000	Mice deficient in growth hormone receptor / binding protein live longer (female mean, not median, lifespan shown here)	28
mTOR	116%	2013	mTOR depletion extends lifespan	29
PTEN overexpression	112%	2012	Overexpression of PTEN, a tumor suppressor which counteracts PI3K, extends mouse lifespan	30
Myc (+/-)	121%	2015	Claim no correlation between weight and lifespan	31

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
FGF-21	139%	2012	Hepatic-specific expression of FGF-21 (which suppresses growth hormone and reduces the production of IGF) increases lifespan, female lifespan shown here	32
BubR1 overexpression	114%	2012	Kinase which localizes to kinetochore, overexpression increases lifespan	33
AC5 KO	132%	2007	AC5 knockount mice lived longer than control, potentially linked to effects on cAMP production and beta-adrenergic receptor signaling.	34
17-alpha-estradiol	112%	2013	17-alpha-estradiol extended lifespan in males, but not females (as expected)	35
Acarbose	122%	2013	Acarbose extended male more than female lifespan	36
TRPV1 -/-	114%	2014	Resting exchange ratio similar at 16 mo to 3 mo	37
SRT2104	106%	2014	Start diet at 28 weeks of age, very small increase if there	38

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
Hcrt-UCP2	128%	2006	UCP2 under hypocretin promoter lowers core body temp, increases lifespan	39
G6PD overexpression	114%	2016	Reduces NADP+	40
IGF-1 Receptor Brain KO (+/-)	109%	2008	Brain-specific IGF-1 Receptor +/- mice live longer than WT	41
SURF-1 KO	121%	2007	Mutations in SURF1, a cytochrome c oxidase assembly factor, extend lifespan. Mitochondrial.	42
Litter enlargemnet (CR)	118%	2009	50% enlargement of litter in first 20 days, to induce caloric restriction	43
mclk-1 heterozygous	115%	2005	A heterozygous knockout of mclk1 (important in mitochondrial respiration) results in mouse lifespan extension compared to wildtype	44
Nordihydroguairaitic acid	112%	2008	NDGA and aspirin extend lifespan by a little bit. Small molecule.	45
Aspirin	108%	2008	NDGA and aspirin extend lifespan by a little bit. Small molecule.	46

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
SOD mimetic carboxyfullerene	115%	2008	Carboxyfullerene, described as an SOD mimetic, increased the lifespan of treated mice compared to wildtype control	47
Removal of visceral fat tissue	108%	2008	Removal of visceral fat tissue increases lifespan over control	48
Low glycotoxin diet	112%	2007	Low glycotoxin (low levels of AGE's) shown to extend lifespan	49
Per2 (-/-)	118%	2016	Lifespan study incomplete	50
Neonatal metformin	120%	2015	Animals recieved on 3, 5, 7th day after birth - bad for females, good for males.	51
GHRH KO	146%	2013	GHRH (Growth-Hormone Releasing Hormone) disruption extends lifespan, presumably through the insulin/IGF pathway axis	52
Sod-2 overexpresion	104%	2007	Overexpression of SOD-2 targeted to the mitochondrion increases mouse lifespan relative to wildtype	53

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
Metallothionein cardiac-specific expression	114%	2006	Cardiac-specific expression of antioxidant metallothionein extended the lifespan of wildtype mice compared to WT FVB control.	54
IGF1R(+/-)	121%	2013	Tyrosine kinase receptor activated by IGF1/2	55
Ink4a/Arf/Ink4b	116%	2009	Encodes 2 CDKs (p16 and p15), and Arf (upstream of p53)	56
Adult-onset Ghr (-/-)	100%	2016	Male mice have >2x higher insulin than female mice	57
Ovary Transplantation	117%	2003	Original paper showing that transplantation of young ovaries into old animals could result in lifespan increase	58
UCP-1 transgenic	111%	2007	Transgenic mice with skeletal muscle-specific UCP1 had increased longevity. Small increase if there.	59

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
PAPP	131%	2010	Knockout of PAPP-A (which enhances IGF-1 activity by degrading the inhibitory IGF-binding protein) increases lifespan over wildtype, female lifespan shown here	60
CR diet with lard	132%	2015	40% decrease starting at 4 months	61
loss of function of Riib (PKA subunit)	114%	2009	Knockout of RIIbeta, a subunit of PKA, increased lifespan in mice compared to wildtype	62
Myostatin (+/-)	109%	2015	Knockout induces double-muscle mice	63
Akt1 +/-	113%	2013	Haploinsufficiency of Akt1 increases mouse lifespan relative to wildtype. Insulin/IGF-1 pathway.	64
miR-17	117%	2014	Not clear if there is a main function for miR-17	65
NDGA	111%	2015	Makes up ~12.5% of the dry weight of leaves	66
FAT10ko	119%	2014	Ubiquitin-like protein which can signal for protein to go to proteasome.	67

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
Intranasal Hsp70	116%	2015	Seemed to extend lifespan when started at 17 months	68
RasGRF1(-/-)	120%	2011	Ras-guanine nucleotide exchange factor (Ras-GRF1) -/- mice displayed increased lifespan compared to wildtype.	69
Lmna-Lcs (Lamin C alone)	113%	2014	Body weight and tumor incidence increase in mice expressing only Lamin-C	70
Cisd2 overexpression	119%	2011	Cisd2 transgenic mice (expressing more of it) lived longer than wildtype. Cisd2 is a transmembrane protein expressed on the mitochondrial outer membrane and associated with a human longevity locus.	71
metoprolol	110%	2013	Administration of the beta-adrenerginc receptor blocker metoprolol to mice increased lifespan compared to wildtype	72

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
nebivolol	106%	2013	Administration of the beta-adrenerginc receptor blocker nebivolol to mice increased lifespan compared to wildtype	73
uPA (in ocular lens/CNS nerve cells)	118%	1997	uPA expression under alpha-crystallin promoter increases lifespan, small/eat less	74
MIF-1 KO	116%	2010	MIF-1 knockout mutant (T-cell derived cytokine) extends lifespan	75
mGsta4-null	113%	2009	Enzyme protects against lipid peroxidation, weird that less of its activity might increase lifespan	76
Muscle-specific GHRKO	109%	2015	Knockout under muscle creatinine kinase promoter	77
CAM-α(1A)AR mice	110%	2011	Mice with a constitutively active mutant form of the alpha1-adrenergic receptor (CAM-alpha1aAR) lived longer than wildtype control	78
Cardiac-specific catalase overexpression	113%	2007	Overexpression of catalase specifically in the heart in mice	79
Icariin	108%	2015	Flavonoid	80

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
miR-29 brain-specific KO	112%	2016	miR-29 highly expresed in brain during development	81
Bi-maternal mice	128%	2010	Mice prepared to be bi-maternal were found longer-lived than their normal cohort	82
RNase-L(-/-)	127%	2007	Knockout of RNase-L, which accelerates cell senescence when expressed, increases lifespan in mice compared to wildtype	83
hMTH1-Tg	116%	2013	Express high levels of hMTH1 hydrolase, thought to degrade 8-oxodGTP and 8-oxoGTP. Oxidative stress.	84
DGAT-1 -/-	126%	2012	Knockout of DGAT1, which catalyzes triglyceride synthesis, extends mouse lifespan relative to wildtype	85
IGFBP-2 overexpression	105%	2016	Proteins bind IGF1/2, degraded during pregnancy, delay in sexual maturity	86

Intervention	Median lifespan increase (treated/control)	Year Published	Notes	Reference
PAPP-A on high-fat diet	105%	2015	Males chosen so no adverse developmental effect on fat depots	87
clk-1(-/-) with clk-1 transgene	128%	2014	clk-1 functions in ubiquinone synthesis, but levels weren't very affected.	88
AgRP -/-	110%	2006	Neuropeptide that is appetite stimulator, overexpression leads to hyperphagia and obesity.	89
Bone marrow transplantation	106%	2013	Bone marrow transplantation from young to old mice was claimed to extend lifespan	90
Young blood injections	94%	2014	Resulted in decreased lifespan	91
Nas(-/-) mice	125%	2011	Hyposulfatemic NaS1 null mice (Nas1 -/-) had an increased lifespan compared to wildtype control.	92
Cyclophilin D (+/-)	119%	2017	Decrease in maximum lifespan	93
PAPP-A in adults	120%	2017	Tamoxifen-induced knockdown	94
Mtbp (+/-)	120%	2016	Rotarod, open field, blood glucose, insulin, IGF-1 were the same.	95

SOURCE: **See References for Table 1**

For fun, I then took the list and matched the entries to drugs in the clinic. Part of the below might be outdated (companies sometimes take a long time to update on trial progress), but it's an interesting representation of the number of things in play that have a non-zero chance of having some impact on lifespan (would guess it to be pretty small in almost all cases though). Methodology is similar - just used clinicaltrials.gov to try to hunt down relevant trials and molecules, or googling generally.

70 drugs in the clinic that might make people live longer

Ordered by mechanism of action

Longevity class	Drug	Phase	Developed For	Develc
Insulin/IGF				
Growth Hormone Receptor Antagonist				
	Pegvisomant (Somavert)	Approved (March 2003)	Acromegaly (normalizing IGF-1 levels)	Pfizer
Akt1 antagonist				
	Archexin (Akt1 antisense)	Phase 2	Pancreatic/Renal Cancer	Rexahr Pharm
PAPP-A				
	PAPP-A antibodies published	Preclinical	-	
Insulin Receptor Antagonist				

Longevity class	Drug	Phase	Developed For	Develc
	S961 and S661	Preclinical / Not Developed	-	
IGF-1 Receptor antagonists				
	AMG-479 (Ganitumab)	Phase 2	Pancreatic cancer	Amgen
	AVE1642	Phase 2 (terminated)	Liver and breast cancer	Sanofi-Immun
	Cixutumumab	Phase 2	Cancer	Lilly/In
	Linsitinib	Phase 2	Ovarian Cancer	OSI Pharm / Astel
	AXL-1717	Phase 2	Cancer	Axelar
	Figitumumab	Phase 3 (terminated)	NSCLC	Pfizer
	PL-225b	Phase 1 (suspended)	Cancer	Pirama Enterp / Merc
	BIIB022	Phase 1 (discontinued)	Cancer	Biogen
	RG1507	Phase 2 (discontinued)	Cancer	Genma Roche)
	Dalotuzumab	Phase 2	Cancer	Merck
	NT219	Preclinical	-	TryNov
GHRH Antagonist				
	JV-1-36	Preclinical	-	
	JMR-132, MZ-5-156, MIA-601, MIA-479	Preclinical	-	
Somatostatin analogues				
	Octreotide	Approved	Acromegaly and certain cancers	Novart
	Pasireotide	Approved	Cushing's disease	Novart
	Sandostatin	Approved	Acromegaly and certain cancers	Novart

Longevity class	Drug	Phase	Developed For	Develc
Caloric Restriction				
Methionine-free diet				
	Methionine-restriction diet	Phase 2	Metabolic Syndrome	
Caloric Restriction Regimens				
	Caloric restriction	-	Age-related diseases	
TOR				
mTORC1 Inhibitors				
	Sirolimus	Approved	Organ transplantation	Pfizer
	Temisirolimus	Approved	Advanced renal cell carcinoma	Pfizer
	Everolimus	Approved	Advanced renal cell carcinoma, SEGA associated with TS	Novart
	Ridaforolimus	NDA Rejected	Metastatic soft tissue or bone sarcoma	Merck ARIAD
S6K1 Inhibitors				
	PF-4708671	Preclinical	-	
Sirtuins				
Sirt1 Agonists				
	SRT2104	Phase 2	Diabetes, psoriasis	GSK/Si
	SRT2739	Phase 1	Endotoxin-induced inflammation	GSK/Si

Longevity class	Drug	Phase	Developed For	Develc
Available Therapeutics Shown to Extend Mouse Lifespan with No Oustanding Mechanistic Hypotheses				
	NDGA	Phase 2	Prostate cancer	
	Aspirin (generic)	Approved	Vascular indications, reascularization procedures, and rheumatological disease indications	
	Metformin (generic)	Approved	Type II diabetes	
	17-alpha-estradiol (generic)	Marketed	Hair Loss	
	Acarbose	Approved	Type II diabetes	
Telomeres				
	TA-65	Marketed supplement	-	Sierra S
NFkB Inhibitors				
IKK-beta inhibitors				
	Compound A	Preclinical	-	
	Compound 1	Preclinical	-	
NFkB Inhibitors				
	CAT-1004	Phase 1/2	DMD	Cataba
	19 known drugs found to inhibit NFkB signaling	Preclinical work	-	
FGF-21 Analogues				
	LY2405319	Phase 1	Type II Diabetes	Lilly

Longevity class	Drug	Phase	Developed For	Develc
	BMS-986036	Phase 2	Type II Diabetes, NASH	BMS
Ovary transplantation				
	Ovarian cortex transplantation	n/a	Improving later-life fertility	
Surgical removal of visceral fat tissue				
	Surgical removal of visceral fat tissue	Phase 2/3	Insulin resistance, obesity, metabolic syndrome	
Mitochondrial manipulation				
NAD+ Precursors	NAD+ Precursors			
	Nicotinamide	Marketed supplement	-	
	Nicotinamide Riboside (NIAGEN)	Marketed supplement	-	Chrom
	Nicotinamide Riboside/pterostilbene	Marketed supplement	Acute kidney injury	Elysiur
Lysosome Function Improvement				
Lysosome Modulators				
	AT3375	Preclinical	Parkinson's	Amicus Therap
	PBT2	Phase 2	Alzheimer's and Huntington's	Prana Biotecl
	Lysosomal Therapeutics	Preclinical	-	
AC5 Inhibition				

Longevity class	Drug	Phase	Developed For	Develc
	SQ22,536 [9-(tetra-hydro-2-furanyl)-9H-purin-6-amine],vidarabine (9-β-D-arabinosyladenine) and NKY80	Preclinical	-	
DGAT1 Inhibition				
	PF-04620110	Phase 1	Type II Diabetes	Pfizer
PKA Inhibitor				
	H89, KT5720, PKI analogues	Preclinical	-	
Low glycotoxin diet				
Low-AGE diet				
	Low-AGE diet	Phase 2	Metabolic Syndrome	
AGE-Breakers				
	Alagebrium	Phase 2 (terminated)	Chronic Heart Failure	Synvist Therap
	Benfotiamine	Phase 4	Diabetic Nephropathy	
MIF-1 Inhibition				
	MIF-1 Program	Preclinical	-	Carolu Therap
	ISO-1	Preclinical	-	
alpha1-adrenergic receptor agonist				
	Midodrinre	Approved	Orthostatic Hypotension	Shire
Plasminogen activators				
Urokinase				

Longevity class	Drug	Phase	Developed For	Develc
	Kinlytic	Approved (in the process of returning to market)	Pulmonary embolism, removing blood clots from intraveous catheters	Microb
PAI-1 inhibitors				
	TM5614	Phase 2	CP-CML	Renasc
p53				
p53 gene therapy				
	p53 gene therapy	Approved (China)	HNSCC	SiBion GeneTe
p53 agonists				
	APR-246	Phase 2	Ovarian cancer	Aprea Therap
MDM2 antagonist				
	idasanutlin	Phase 3	AML	Roche
AgRP Inhibition				
	TTP435	Phase 2 (discontinued)	Obesity	vTv Therap
TRPV1 inhibition				
	ALD403 (anti-CGRP mAb)	Phase 3	Chronic migraine	Alder
	LY2951742 (anti-CGRP mAb)	Phase 3	Chronic migraine	Lilly
	AMG334 (anti-CGRP receptor mAb)	Phase 3	Chronic migraine	Amgen
	TEV48125 (anti-CGRP mAb)	Phase 3	Chronic migraine	Teva
Myostatin inhibition				

Longevity class	Drug	Phase	Developed For	Develc
	PF-06252616 (anti-myostatin mAb)	Phase 2	DMD	Pfizer
	BMS-986089 (anti-myostatin mAb)	Phase 3	DMD	BMS
Cyclophilin D inhibition				
	CC-1233	Preclinical	Acute pancreatitis, neurodegeneration	Cypral

SOURCE: **See References for Table 2**

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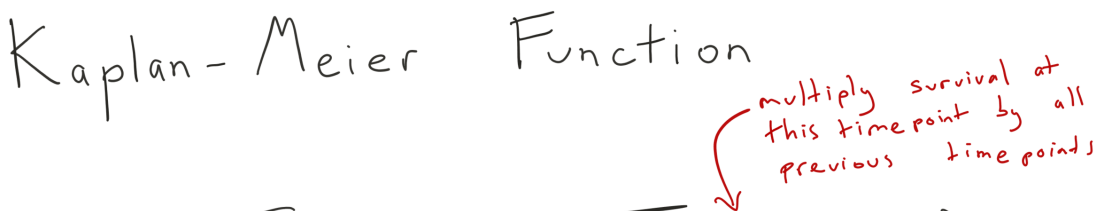
Appendix: What is a Kaplan-Meier curve?

Those curves you saw up top (illustrating metformin or eating less increasing lifespan) were generated by the following equation. It's ubiquitous in aging biology, and allows you to draw lifespan curves when, for example, some of the population could be censored.

d_i is the *number of events* at time i
n_i is the *total individuals at risk* at time i.



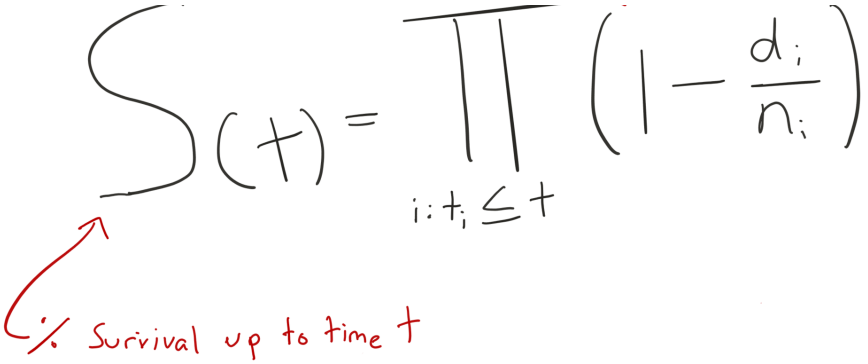


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TABLE 1: 95 THINGS THAT MAKE MICE LIVE LONGER

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