Systems Aging

Lecture 7 - Exercise and Longevity

Uri Alon

Recommended book: Peter Attia, Outlive. and its companion podcast: the Drive.

Congratulations - we are beginning the part of the course focused on lifestyle. We will talk about the four pillars of movement, nourishing, rest and connection. Today- movement! Especially exercise.

As we age we want to keep doing the activities that are meaningful to us. To meet this goal, our main tactic is active living and exercise. Exercise also provides superb benefits for our life right now.

When we think of our health goals, we can think of three dimensions - physical, cognitive and emotional. Exercise boosts all three.

Exercise is the most effective intervention we have to slow aging. It reduces the risk for the four horsemen, protects from falls, and improves emotional health. **Not exercising is like taking a depression pill and a diabetes pill.** It works by synergistic combination of improving heart, lungs, mitochondria, the autonomic nervous system, lipids, blood vessel lining and diabetes. Exercise provides 3-5 years of lifespan on average.

Many functions decline linearly with age

Exercise helps with the decline of physiological function. Decline is one of the 'three Ds' of aging - death, disease and decline. Up to now in the course we have dealt with the first two. Death is binary and disease is also binary to some approximation, but decline is continuous. Unlike disease, decline happens in everyone.

There is decline in nerve conduction velocity, kidney filtration rate, basal metabolic rate, cardiac function (Fig 6.1) . Cognitive function also declines (Fig 6.2) - including processing speed and short and long term memory. Only world knowledge - crystalized knowledge- rises with age, as well as some aspects of 'wise' cognition such as emotional control and subjective well-being that we will discuss more in an upcoming lecture.

As we mentioned in lecture 1, the decline of many physiological functions collapses on a straight line when averaged over many people (cross-sectional data). Major physiological measures, when normalized so that 1 is maximal function and zero is the minimal function ever measured, drop linearly with time with the same slope and hit zero at an extrapolated age of 105-110 years. Such a collapse of so many different functions suggests, once again, a common driving factor.

At least that's what a collapse might suggest to physicists. Those trained in biology or medicine might guess differently - maybe it's many entangled biological factors that average out to give such a regularity.

Is there simplicity at the heart of aging or irreducible complexity? We need to test models to find out, as we do below. The more tests that a simple model passes the more confidence we have- especially if it makes surprising predictions that agree with independent data or new experiments.

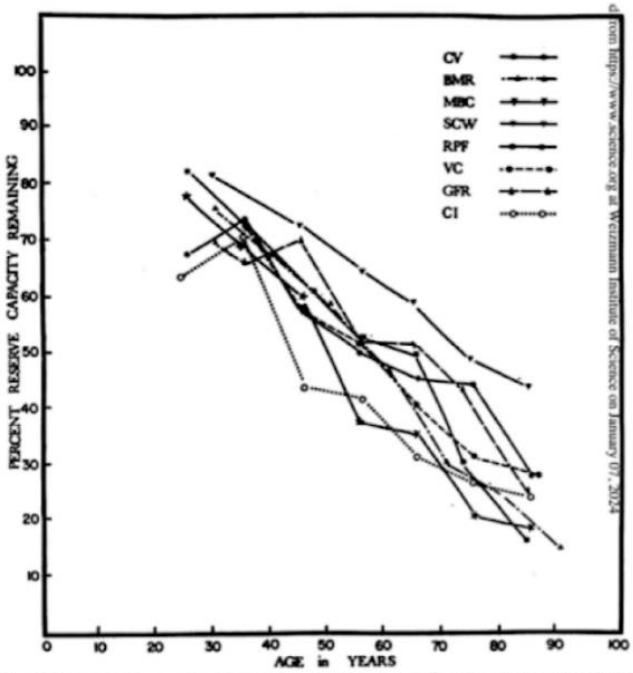


Figure 6.1 Percent of reserve capacity of a number of physiological functions, from cross-sectional data. Reserve capacities are normalized between maximum and basal level. Longitudinal data shows a linear decline and then curves down to an abrupt drop close to death. CV, nerve conduction velocity; BMR, basal metabolic rate; MBC, maximal breathing capacity; SCW, standard cell water; RPF, standard renal plasma flow (Diodrast); VC, vital capacity; GFR, standard glomerular filtration rate (inulin); CI, cargree- diac index.
Reproduced from Strehler & Mildvan (1960).

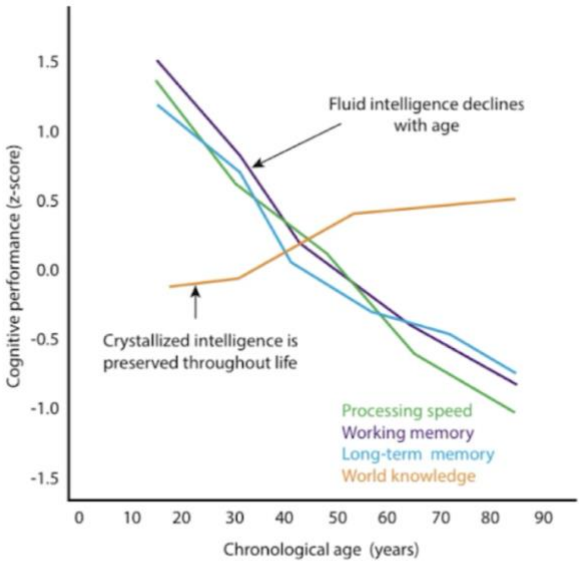


Figure 6.2 Most cognitive functions decline with age. Adapted from Zamroziewicz and Barbey (2018).

One of these linear declines is in VO2max - perhaps the most important physiological function in terms of longevity and physical fitness. VO2max is the maximal rate at which the body can absorb oxygen when we are exercising. It is measured by running or cycling to your maximal ability while wearing a mask that measures the oxygen you breathe in and subtracting the oxygen you breathe out. VO2max is normalized to body weight in units of ml/min/Kg.

VO2max is among the most predictive measures for mortality - going from bottom quartile to top quartile is a five fold decrease in risk of death. More importantly for the present, VO2max limits what you can do- as seen in Fig 6.3.

VO2max drops linearly with age, but depends strongly on fitness.

It is possible to increase VO2max, either by high intensity interval training near VO2max for 4-6 weeks where a 10-15% increase is seen, or by training continually at zone 2 (moderate effort) plus anaerobic training where larger rises of 20-40% have been reported.

https://simplifaster.com/articles/how-trainable-is-vo2-max/.

High oxygen exposure (HBOT, 30 1h sessions at 100% oxygen at 2 atmospheres) increases V02max by about 10% in master athletes [https://pmc.ncbi.nlm.nih.gov/articles/PMC8825926/], as well as their mitochondrial function - apparently increasing quality of mitochondria and their enzymes, enhancing vasculature - the supply pipes for oxygen. For more details on VO2max see appendix 1.

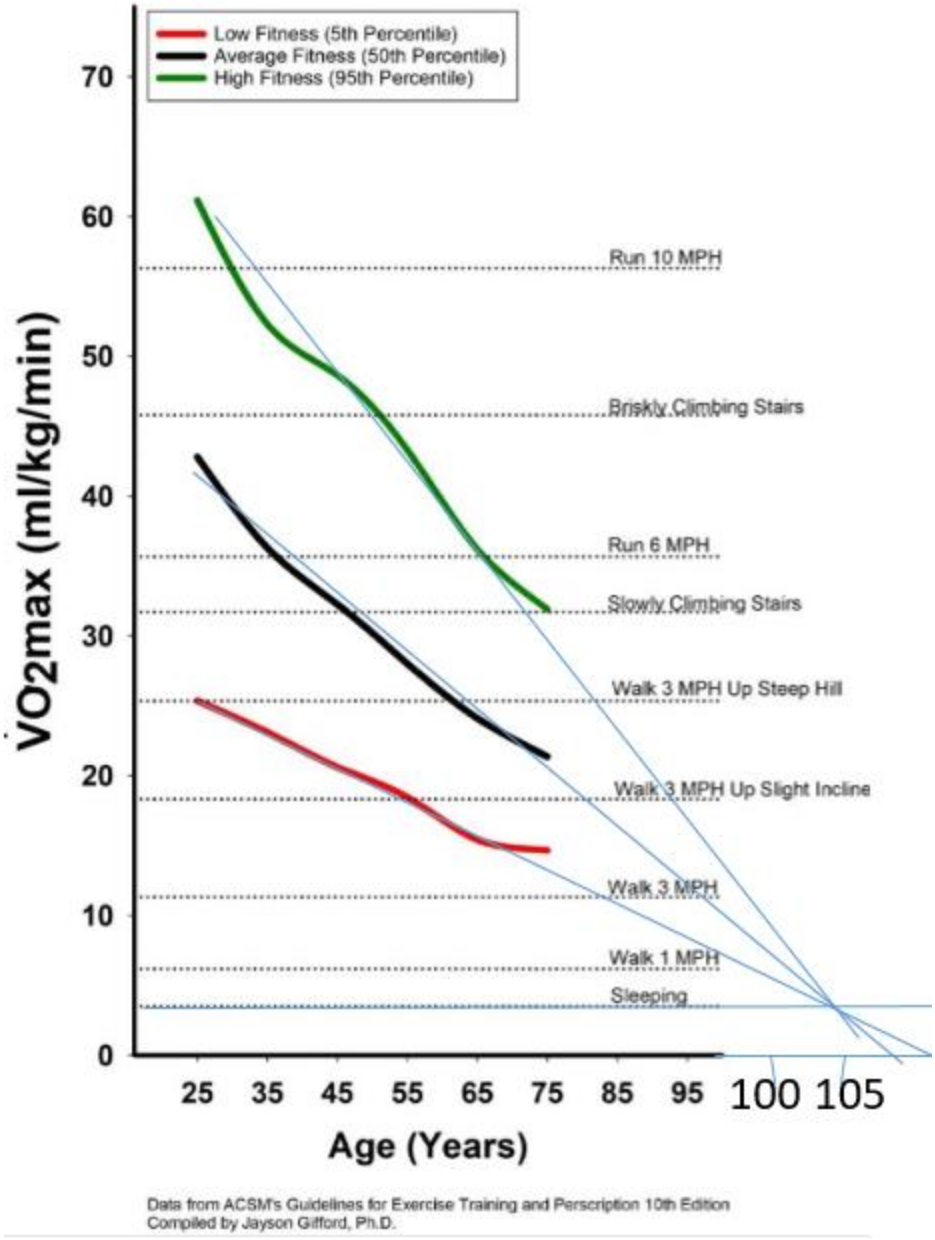


Fig 6.3: Maximal oxygen uptake VO2max determines maximal energy output the body is capable of, and declines linearly with age in cross sectional data, with a maximum that depends on fitness level. Extrapolated curves reach minimal levels around age 105.

Linear decline in the SR model

For a long time the linear decline worried me with respect to the SR model. As we saw, the SR model gives the correct exponential rise for binary outcomes like death and

disease, by means of a first-passage time process. But how can it give a continual steady decline starting from age 20-30 that is linear in time?

The powerful thing about math models is that they are disprovable- if there is a major quantitative prediction that differs from observation, we discard the model. That's why researchers try to challenge their favorite model in all possible ways. The more tests the model passes, the more confident we are that it captures some simplicity inside the undoubted complexity of the real world.

That's why about a year ago when we discovered that the SR model can in fact provide a linear decline for physiological functions I was finally ready to give this course.
So let's see how we might get a linear decline from the SR model:

$$\frac{dX}{dt} = \eta t \ - \ \beta \frac{X}{X+\kappa} + \sqrt{2\epsilon}\xi$$

Let's assume that X negatively affects function - for example the chronic inflammation caused by damaged and senescent cells X causes organ systems to reduce function. Reduced function of tissues is indeed one of the universal aspects of the inflammatory response(https://doi.org/10.1016/j.mad.2017.04.005,PMID: 30065258).
A plausible way to describe the effect of X and its inflammatory and other consequences on function is to assume that the cells detect the signals by receptors, and so a Michaelis-Menten term makes sense -
Effect ~ $\frac{x}{K_m+x}$,
where K_m is the halfway effect point, namely the amount of damage X needed for 50% of its full effect. Thus normalized function decreases as 1-effect from its maximal value to its minimal value,

$$F \sim 1 - \frac{x}{K_m + x}$$

What is the halfway point K_m? Natural selection would favor designs where the amount of damage X reached at reproductive age would not cause a strong reduction in function, otherwise we would not survive. Thus a plausible choice is to use a halfway point similar to the halfway point of the trucks in the SR model- based on the understanding that trucks also evolved to be effective for removing the damage levels at young ages. Thus we assume $K_m = \kappa$, and obtain
$F(x) = F_{min} + (F_{max} - F_{min})(1 - \frac{X}{X+\kappa})$.
This means that if we normalize function F between zero (minimal function) and one (maximal function) we get

(1) $f \equiv (F - F_{min})/(F_{max} - F_{min}) = 1 - \frac{x}{\kappa+x}$

Using the SR model and averaging over individuals so that noise drops out, we find $\frac{d<x>}{dt} = \eta t - \beta < \frac{x}{x+k} >$. We next take a steady-state approximation since trucks are much

faster than house-building, $\frac{d<x>}{dt}$ =0, and we have $\eta t = \beta < \frac{x}{x+\kappa} >$. Plugging this into our equation for normalized function we find

$f = 1 - \frac{t}{\tau}$

where $\tau = \backslash beta/\backslash eta$ =110 years in humans! That time is the time when production ηt reaches truck maximal capacity β.

It's quite amazing that the SR model gives the correct prediction for the extrapolated age of 110 years at which f hits zero - the value beta/eta=100y is based on parameters measured from completely different data (hazard curves, senescent cell fluctuations) and a model built for a different purpose.

Thus minimal function (f=0) is reached at extremely old ages on average- decades after the median lifespan range of 80s where most people die.This is in agreement with cross sectional observations shown above in Fig 6.1 on VO2 max, kidney filtration, nerve conductance, cardiac index and other functions. For each individual the drop is more stochastic, and accelerates at the very end of life, as observed in longitudinal measurements of physiological functions.

This was an analytical derivation based on a steady state approximation , which is accurate until very old ages but not beyond. At age beyond 90 or so the steady-state approximation is no longer valid - and so we need numerical simulations of the SR to see what happens. The linear decline solution is accurate until 90 or so and then the decline slows down and doesn't quite hit zero (Fig 6.4). This allows for centenarians to preserve modest function.

Physical exercise can help to raise the F_{max} for some functions. Aerobic training (and anaerobic intervals) can raise VO2max - perhaps the most important ability to survive stress.

Similarly, strength can be boosted by strength training. Grip strength is also correlated with risk of all-cause mortality, and is important for carrying things and for gripping the rail and not falling.

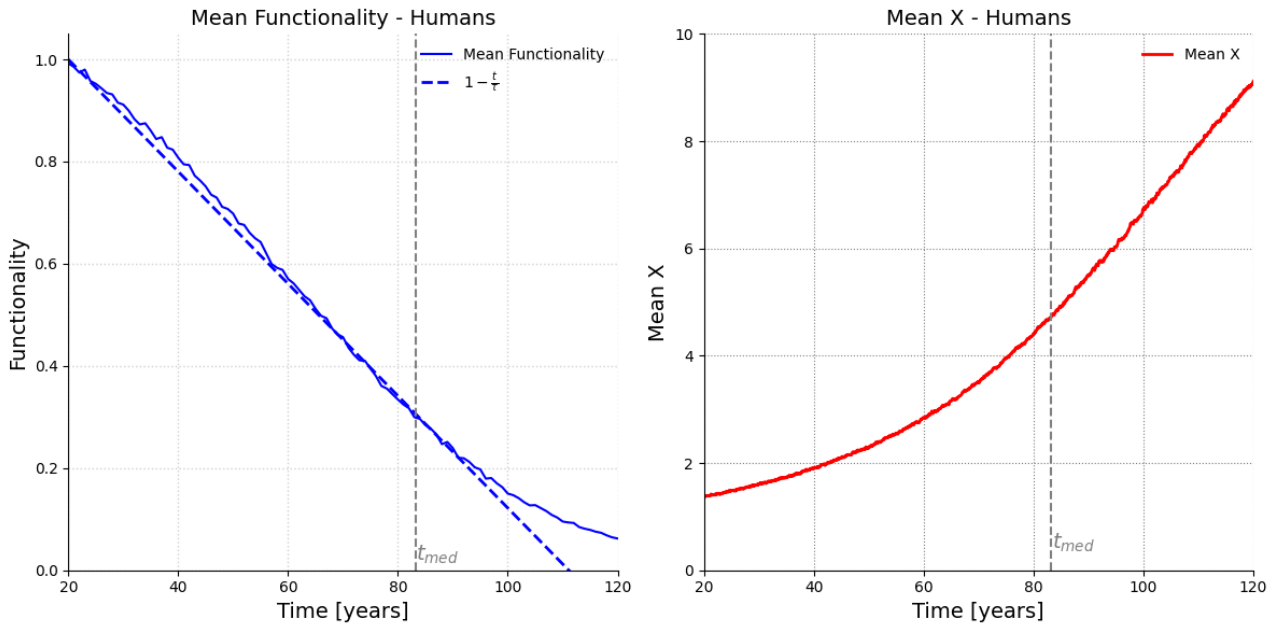


Fig 6.4: Mean decline of physiological function (dashed line is $1-\frac{x}{k+x}$) with age for humans and rise of mean damage x in simulations of the SR model. This is an average over many simulations, in which agents crossing Xc were removed ("died"). After age 100y or so, dynamics is governed by noise 'protecting' individuals from crossing Xc. The analytical formula f=1-t/τ becomes inaccurate at such extreme old ages and underestimates the function.

Muscle functions decline at a delay

Not all physiological functions decline linearly after age 30, especially muscle related functions like hand grip strength. It rises during childhood and adolescence, maximizes at about age 25, stays roughly maximal till age 50, then declines in a slightly convex curve.

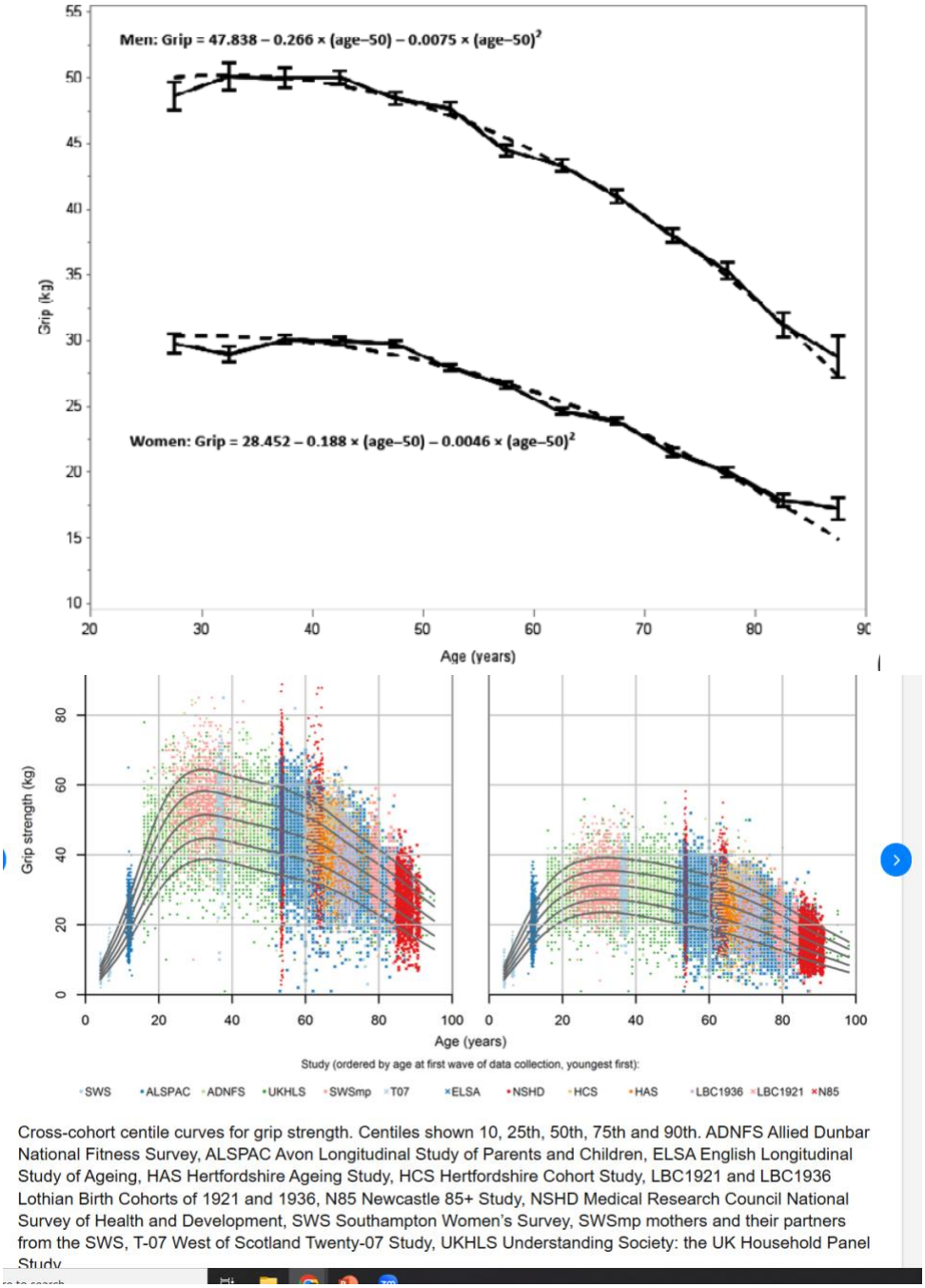


Fig. 6.5: Hand grip strength (kg) by age groups in men and women. a) Plot shows mean and standard error bars for 5-year age groups by sex. Men (mean44.6 kg, SD 10.2); women (mean 26.2 kg, SD 6.5). A fitted regression with a quadratic age term in hashed lines estimates the rate of decline in grip strength. Reproduces from Murabito et al, 2017. B) data from 12 studies reviews in DOI: 10.1371/journal.pone.0113637.

We can obtain such a time dependence in the SR model (the part after age 25) if we assume that a given physiological function is more resilient to the ravages of inflammaging - half reduction is reached at higher levels of damage.
Mathematically, we need to increase the halfway point. To do so we increase the halfway point by a resilience factor a - functional decline goes as $f = 1 - \frac{x}{ak+x}$. The solution is $f = \frac{a(1-t/\tau)}{a(1-t/\tau)+t/\tau}$. For a=1 we recover the linear decline $f = 1 - t/\tau$, and for higher a, the function looks more convex (Fig 6.6). It resembles the observed drop in muscle strength, gait speed and other muscular functions.

This convex decline matches the observation that in their mid seventies people show accelerated decline in sports and strength. Whereas the young are usually limited by heart and lung, after 70 the limiting factor becomes muscle power and frailty. Muscle functions seem to have a nonlinear accelerating decline whereas cardiac function seems to decline linearly.

Many 70 year olds can't get off the floor with one hand of support. Falls and bone fractures become a major killer. That's why it is important as you get into 40s and 50s to add a habit of strength and agility training.

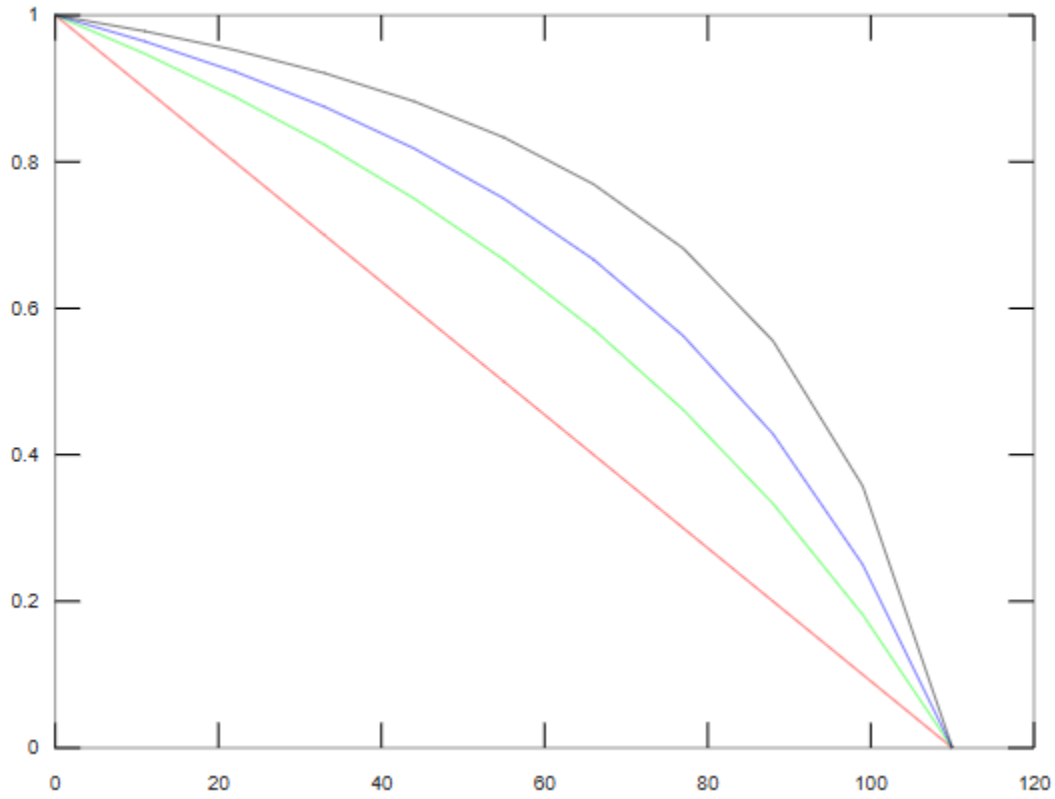


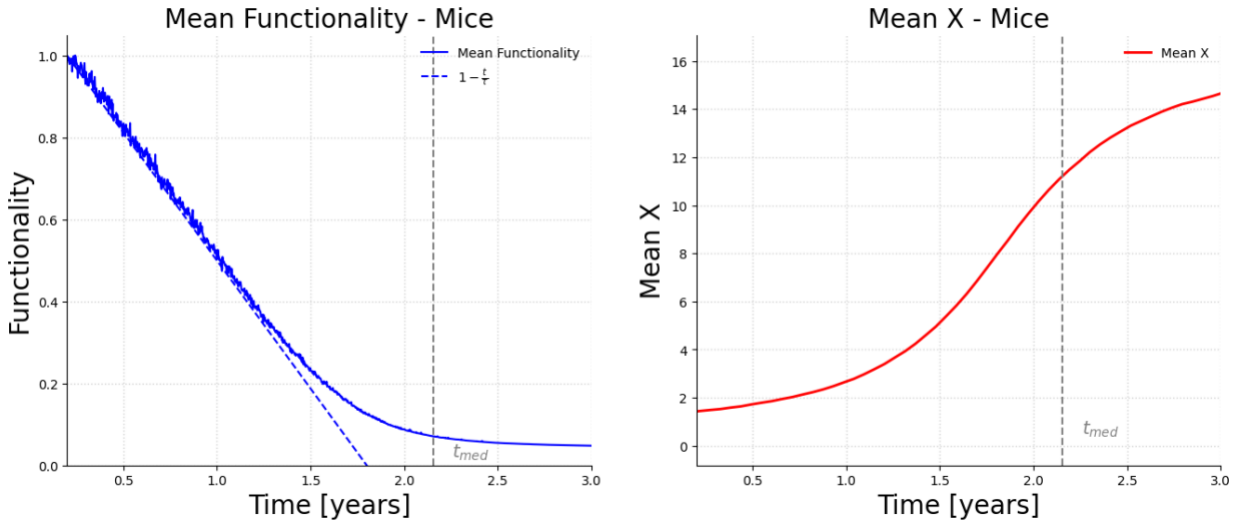
Fig. 6.6: Cross-sectional function versus age in the SR model for functions whose decline goes as $1-\frac{x}{ak+x}$ With a=1 (red), and a=2, 3 and 5 in green, blue and black. The higher a, the higher the halfway point damage for functional decline, and the longer high function is preserved with age.

The SR model correctly predicts that mice decline faster in mice years

Is this a fluke, or can the model predict decline in other organisms as well? The SR model predicts a surprising difference in the rate of decline of mice and men.

It turns out that in mice the 'zero crossing age' is $\beta/\eta = 1.8$ years, which is shorter than their median lifespan of 2.5 years - unlike humans where β/η=110y is longer than the median lifespan.

Thus, the SR model predicts that mouse decline is at first linear and reaches close to F_{min} at around the age of 2 years. After this age, simulations show that function decays slowly - it stays above zero but is low. According to this, old mice in the wild have very poor chances. In other words, the sr model predicts that function should plummet much earlier in mice than in humans in terms of fraction of lifespan (Fig. 6.7).



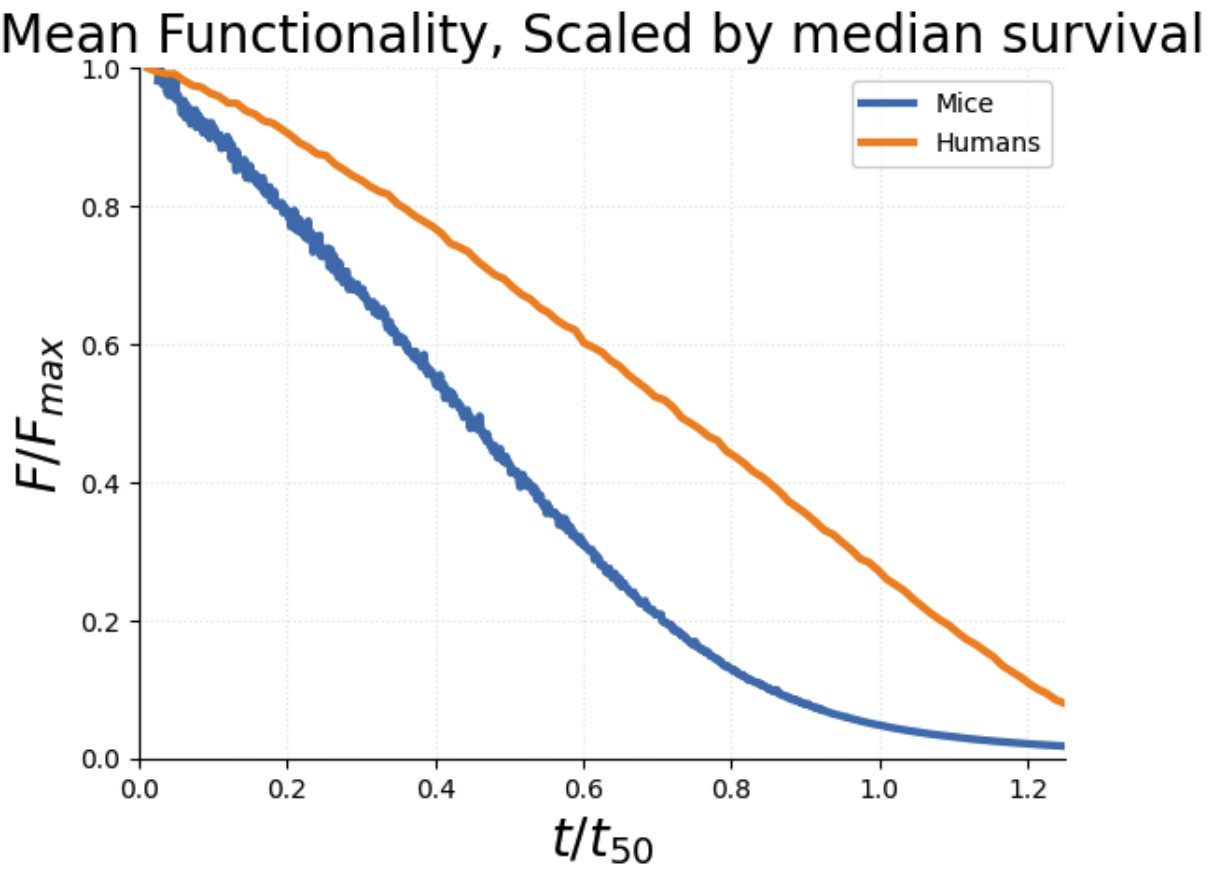


Fig 6.7: Functionality for humans and mice scaled by their respective median lifespans, from SR model simulations in which dead individuals were removed. Mice burn out faster than humans.

This prediction agrees with mice data on physical and cognitive function (Fig 6.8). Mice burn out faster in “mouse years”. They survive beyond two years in the lab thanks to the protected conditions of sterile housing in which they are studied, away from cats and owls. I count this mouse prediction as another unanticipated success of the SR model, predicting something that is way outside its original purpose.

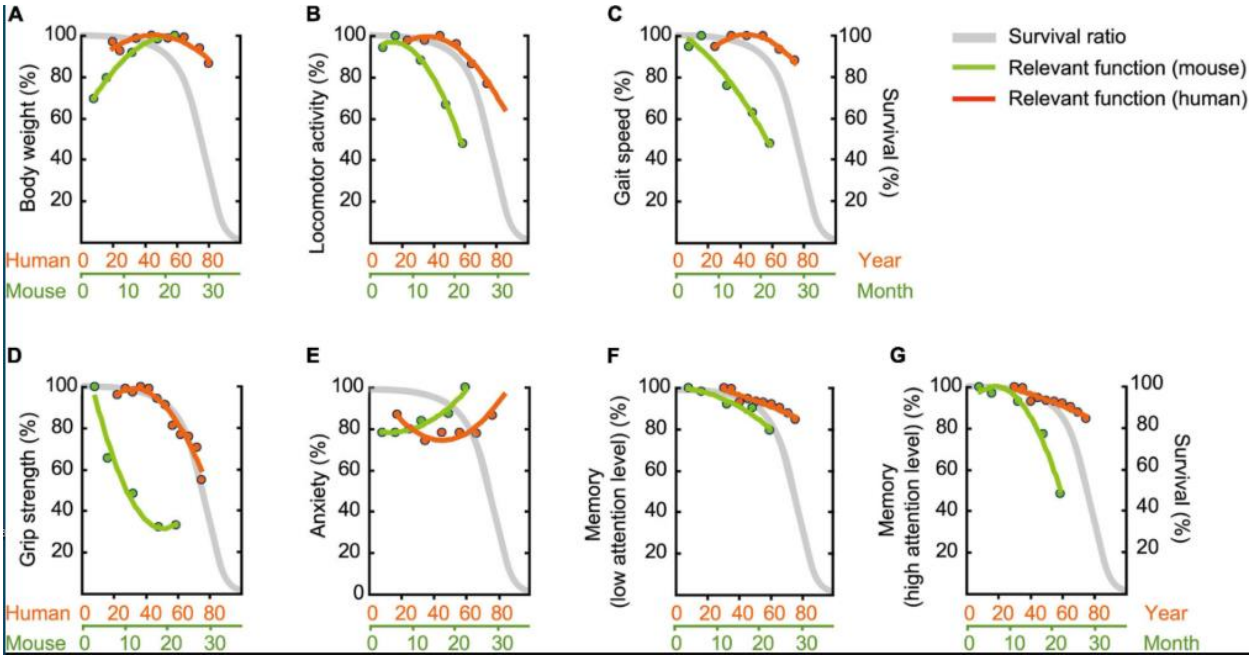


Fig 6.8: Mice mean functional decline with age is faster than human decline relative to the median lifespan of each species. Reproduced from Yanai 2021 https://doi.org/10.3389/fnagi.2021.697621

Exercise increases median lifespan but not maximal lifespan

High amounts of exercise provides about 5 years of extra life compared to the median of the general population (and about a decade compared to the lowest fitness quartile).
We discuss below how much exercise is enough, but for now let's take olympic athletes as a (high) benchmark. Their survival curve is shifted towards older ages (Fig 6.9). Their maximal lifespan however does not differ from the general population- they don't live to 140.
This is a *steepening* of the survival curve.
Steep curves that increase median but not maximal lifespan are found in the SR model when the death threshold Xc is increased. Biologically we may interpret this as increased robustness: exercise increases physiological functions needed to survive such as VO2max. In extreme crises (such as a bad respiratory infection), one needs all the energy one can muster in order to pull through. If you don't have the needed VO2max you will not make it. A given level of damage X has less of a chance to kill you if you have higher Xc, gained by a life of exercise.

A similar thing occurs when comparing survival of men and women from the general population -women have higher median lifespan and steeper survival curves than men, in a way consistent with higher Xc. Women seem more robust.

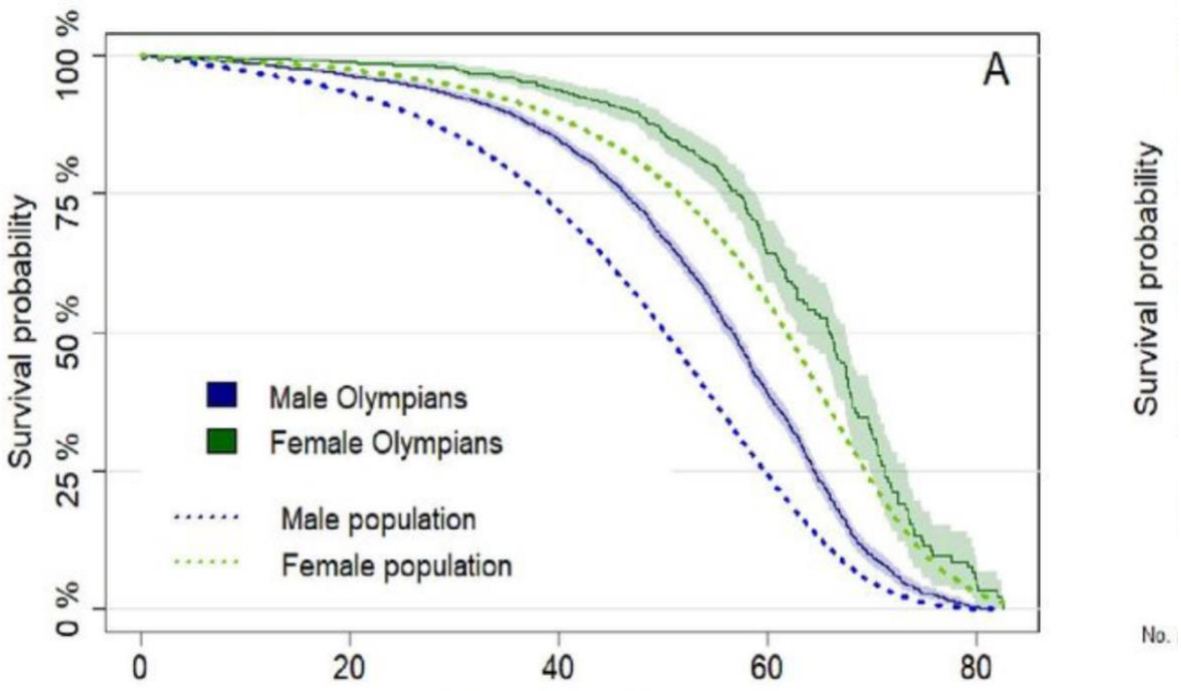


Fig 6.9 Longer median lifespan and steeper survival of US Olympians as a function of time after Olympic participation versus controls sampled from the general population with the same birth year and sex as the olympians. From https://doi.org/10.1136/bjsports-2019-101696

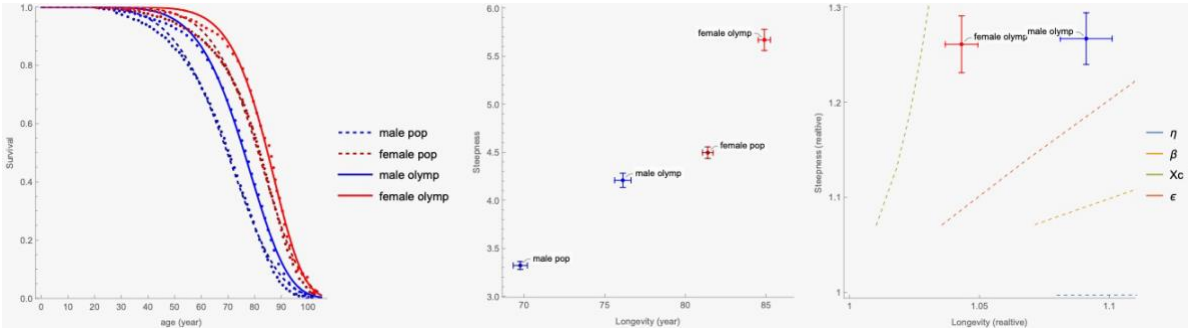


Fig 6.10 Olympic athlete survival curves are steeper than the general population.

Similar survival curve steepening effects are seen in exercising mice - which were provided with a running wheel -versus non exercising mice.

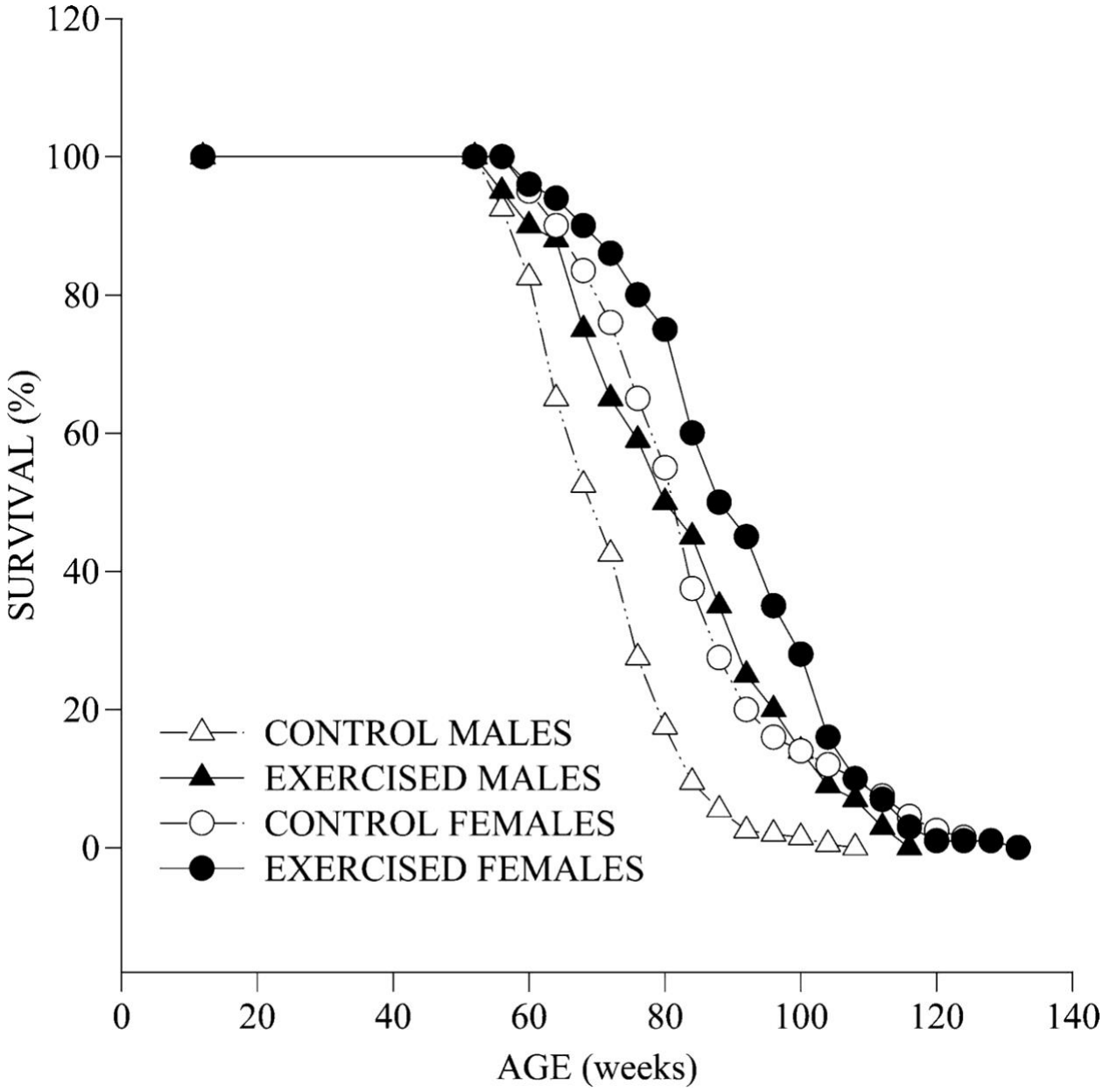


Fig 6.11 Mice survival curves https://doi.org/10.1152/ajpregu.00208.2003

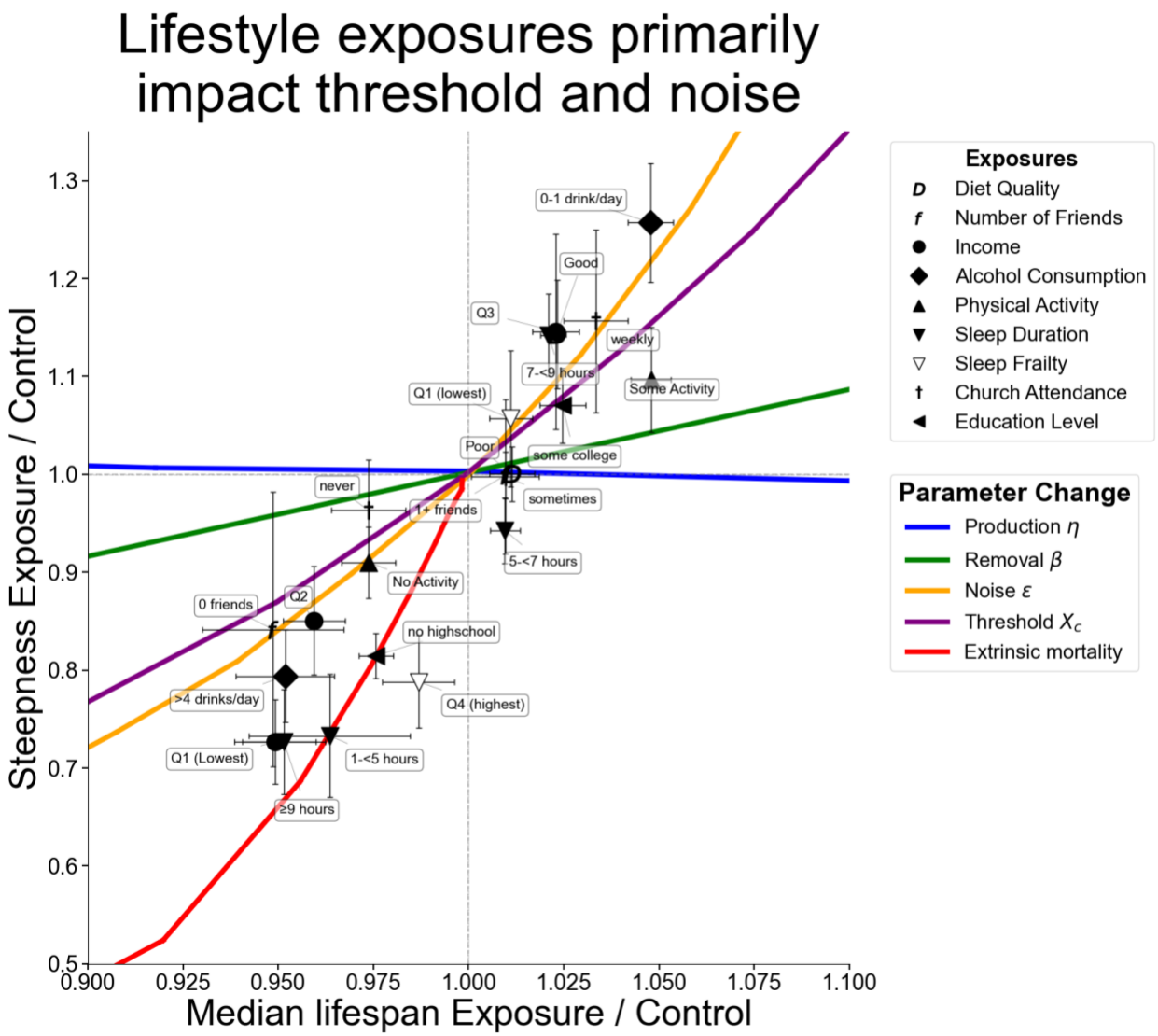


Fig 6.xx Lifestyle cohorts from a large US cross-sectional dataset NHANES have survival curves that suggest effects on Xc or noise epsilon. Some deleterious exposures seem to raise extrinsic mortality. Source: Shenhar et al submitted.

The four dimensions of effective exercise

You can set your training goal so that by age 100 or in your last decade you can do the activities you want to- such as picking up a grandchild, carrying grocery bags and climbing stairs. This is preparing for the 'centenarian decathlon' of Peter Attia. You can thus see how much you need to increase your VO2max, muscle strength and so on starting from now. It is key to get into a habit that is sustainable because you like it enough to persist.

At the same time, not everyone may need exercise to have a long active life- quoting Churchill- ""I get my exercise serving as pallbearer to my many friends who exercised all

their lives,". In historical truth he was active in many ways till his death at 90 (https://winstonchurchill.hillsdale.edu/churchill-autumn-years/).

Exercise is the best scientifically validated lifestyle intervention for reduction of disease risk (metabolic, CVD, Alzheimer), stress reduction.

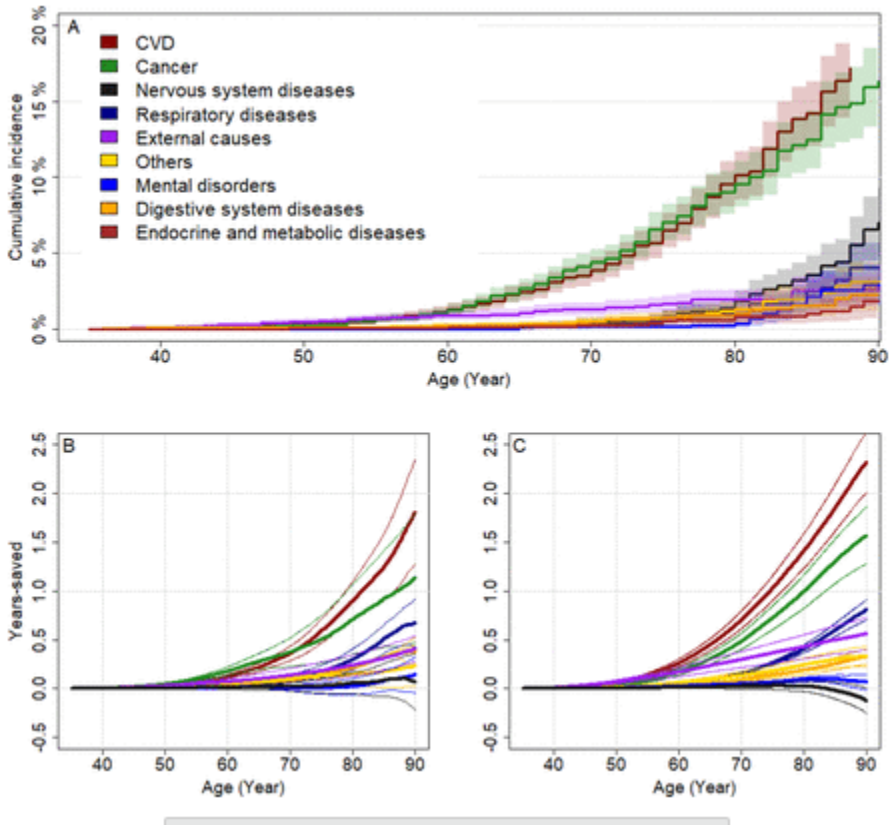


Fig 6.12 US olympians have reduced incidence of cancer, cardiovascular disease and most other classes of diseases. From https://doi.org/10.1136/bjsports-2019-101696

What kind of exercise is important?

Exercise is founded on four essentials: aerobic, anaerobic, strength, and stability. All of these are important for current health and future ability to carry out the activities of daily living.

Aerobic Zone 2 training: Aerobic exercise, particularly Zone 2 training, plays a crucial role in our health. Zone 2 activities like moderate swimming, running, and cycling engage our mitochondria to burn fat and build cardiovascular capacity. During Zone 2 exercise, you should be able to hold a conversation, though not comfortably - this is a practical way to gauge if you're in the right zone.

Zone 2 training is typically reached when exercising at 70-85% of your maximum heart rate.

While the traditional formula for calculating maximum heart rate is 220 minus your age, a more accurate calculation is 210 minus ¾ of your age. The lowest max heart rate recorded is about 130, and the extrapolated population mean reaches it at - you guessed it- 110!

Interestingly, even regular endurance training doesn't significantly affect this equation - exercise doesn't move the needle on max heart rate; but it does for VO2max.

The benefits of Zone 2 training extend beyond cardiovascular health. It enhances cognitive function by increasing brain blood flow and boosting brain-freindly growth factors. Research reviews suggest it can reduce the risk of dementia and Alzheimer's by approximately 20%.

At the cellular level, Zone 2 exercise promotes mitochondrial health through two key processes: biogenesis, which creates fresh new mitochondria, and mitophagy, which recycles defective ones. This maintenance of cellular energy production is vital for overall health and longevity.

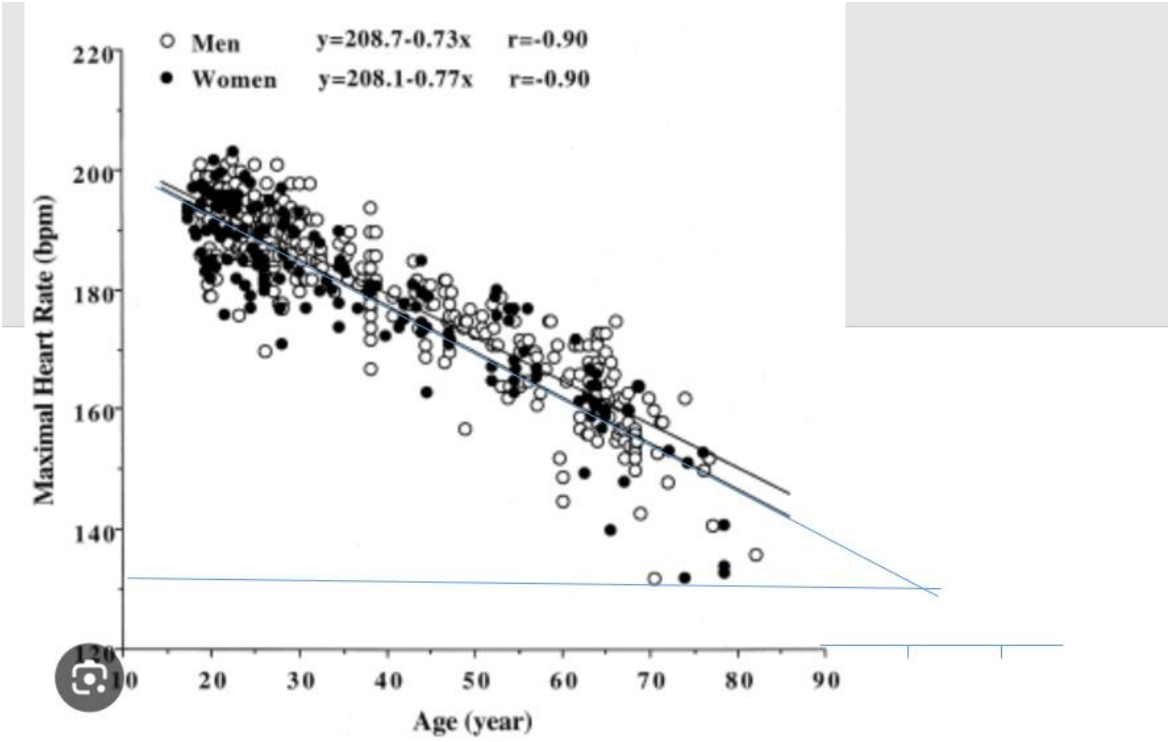


Fig 6.13 Maximal heart rate declines linearly with age. Endurance athletes do not have much higher maximal heart rates. [https://www.jacc.org/doi/10.1016/S0735-1097%2800%2901054-8].

Anaerobic training, particularly focused on building VO2 max, involves high-intensity interval training. A typical protocol consists of alternating four-minute high-pace intervals with four-minute moderate-pace recovery periods. during the recovery periods ensure that your heart rate drops below 100. This pattern should be repeated 4-6 times, typically once per week.

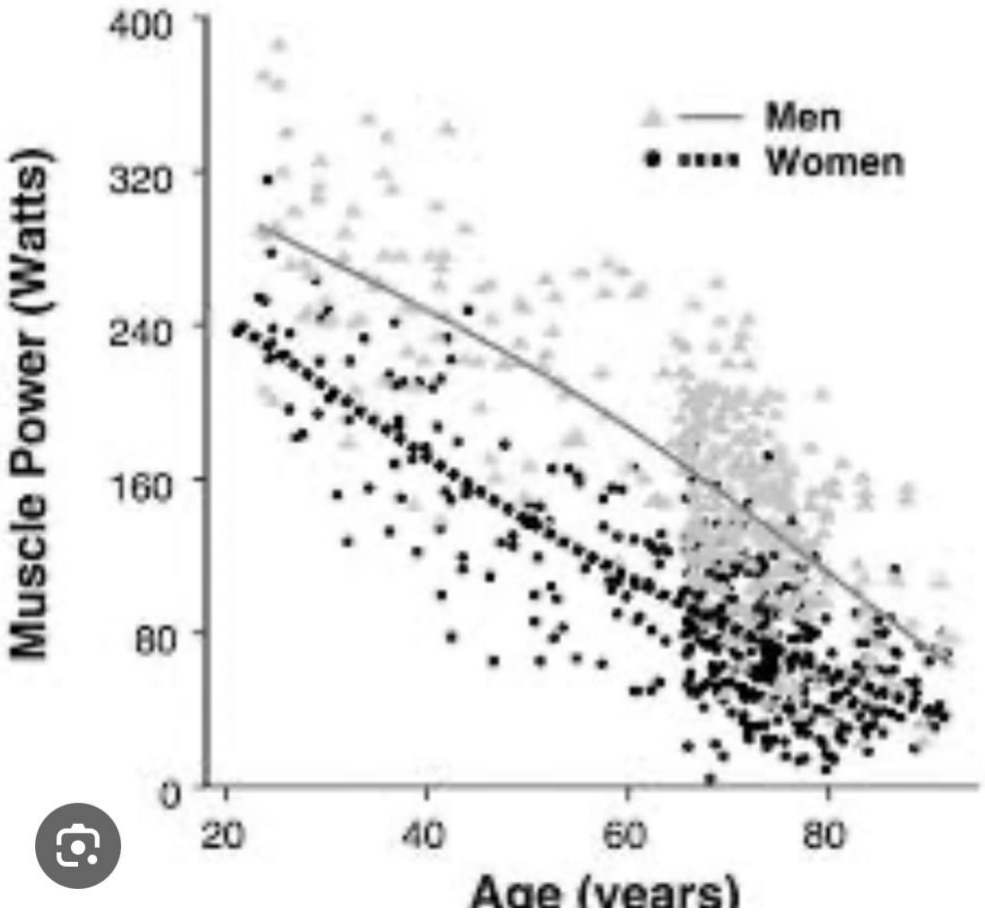
A combination of aerobic and anaerobic training may mirror our evolutionary history as hunter-gatherers, where hunting required both sustained moderate effort for tracking (zone 2) and explosive power (Vo2max) for the kill.

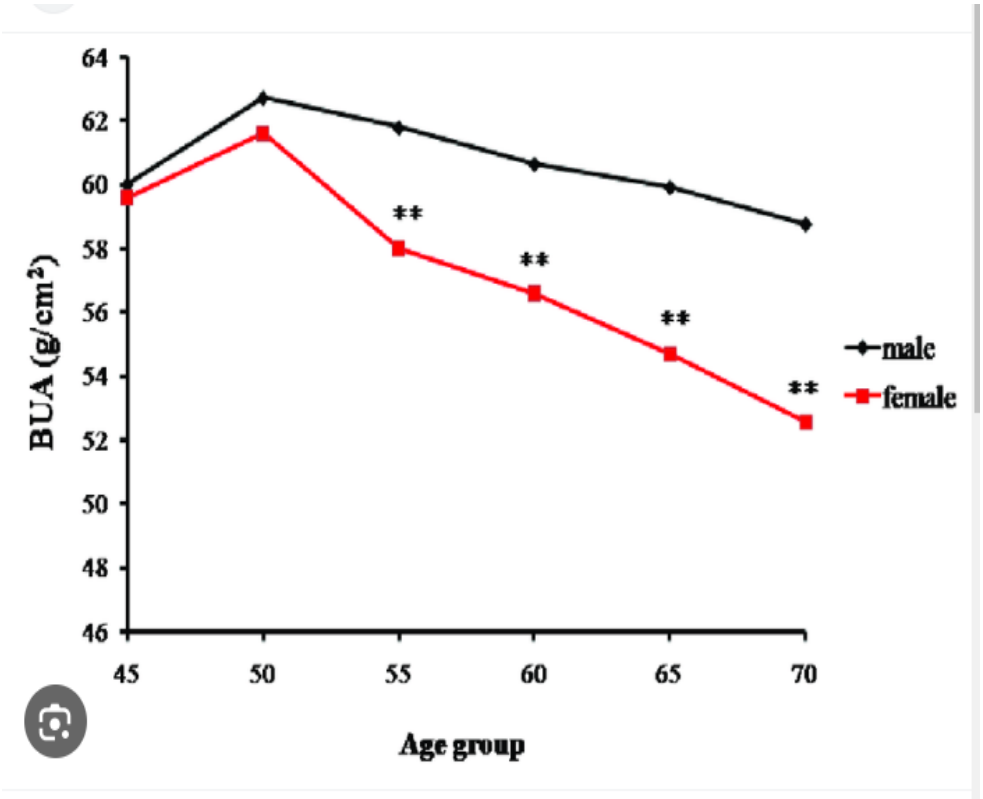
Strength training is another crucial component, whether through exercises that use your bodyweight like push ups (one good protocol is the 7-minute workout) or gym-based resistance training with weights and machines. Building and maintaining muscle mass helps maintain a healthy metabolic rate since muscle helps dispose of blood glucose and burns calories even at rest.

Age brings a particular challenge: we lose fast-twitch muscle fibers more rapidly than other types, and these can only be maintained through consistent resistance training. Muscle power - force times velocity - drops steeply with age (Fig 6.13ac) The impact of muscle loss can be dramatic - for instance, just 10 days of bed rest can result in a loss of 2 kg of muscle mass. This becomes especially concerning in frail individuals, who often struggle to rebuild lost muscle.

Equally important is bone health, as bone mineral density naturally decreases with age (Fig 6.13b). This decline can be slowed through resistance training, and for menopausal women, hormone replacement therapy.

The combination of muscle loss and bone loss creates a dangerous scenario, increasing the risk of fractures. Hip fractures are particularly serious - for those aged 65 and over, they carry a frightening 30% mortality rate in the following year. Having good strength can help you grab the rail and prevent a hard fall. This underscores the importance of maintaining both muscle strength and bone density through regular exercise.


400
320
240
160
80
0
Muscle Power (Watts)
20
40
60
80
Age (years)
Men
Women


64
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BUA (g/cm²)
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Age group
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male
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Fig 6.14

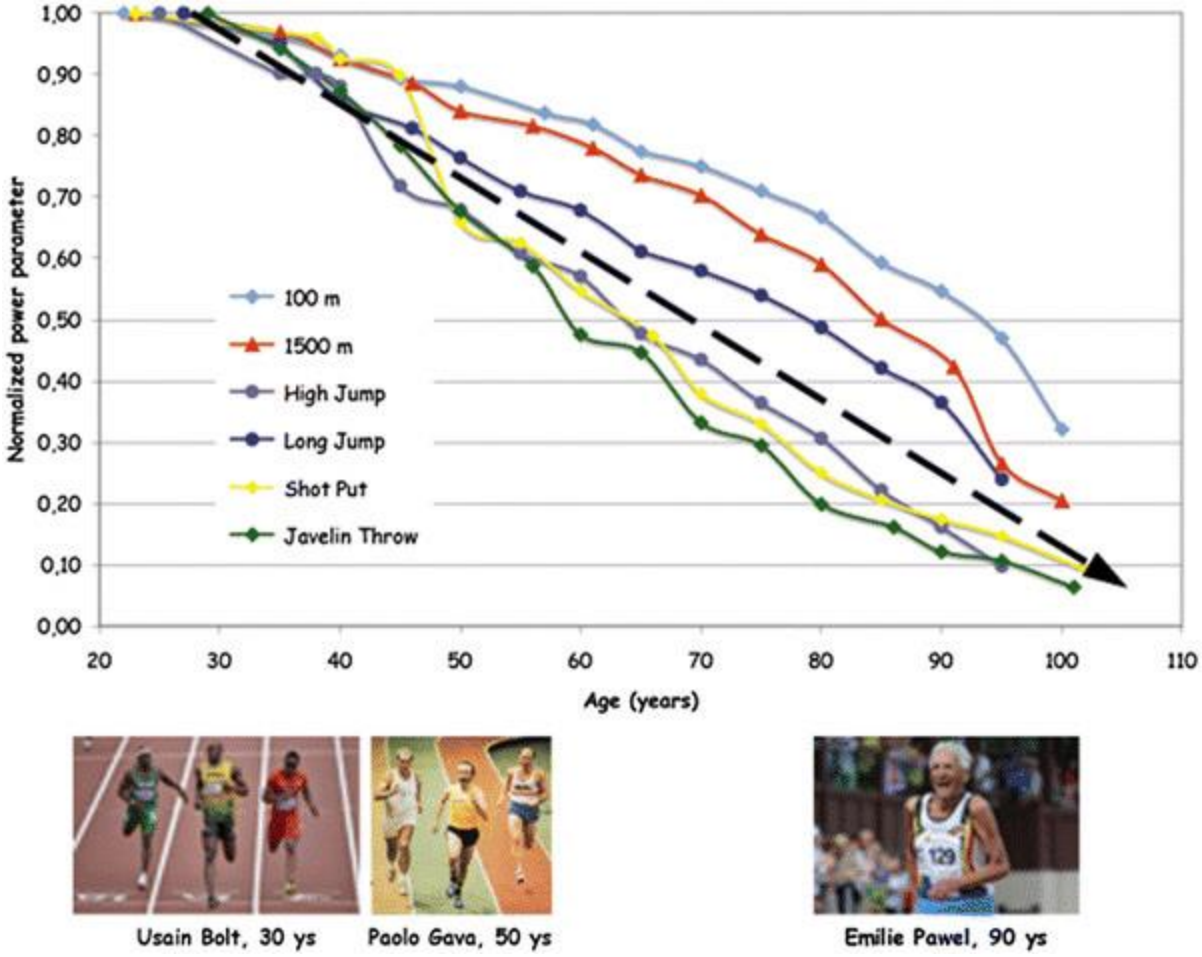


Fig 6.15 Muscle power, bone mineral density and world records drop linearly with age. a) Muscle power, b) bone mineral density declines especially in women after menopause (ages 50-55) [DOI:10.3390/ijms18071358]. c) Age-related decline of skeletal muscle power derived from world records of running, jumping and throwing events of Masters of different age classes. Whatever the extent of training, even in the extreme cases of Master world record-holding men, muscle power almost linearly decreases with age pointing to around 110 years of human survival. Source for a,c: DOI: 10.1007/s40520-016-0619-1

The fourth essentialq, stability practice, encompasses practices like yoga and pilates that play a crucial role in injury prevention. Stability is about how efficiently your body can transfer force during movement - when stability is poor, energy gets wasted through inefficient movement patterns or, worse, gets channeled into joints in ways that can cause injury. Through stability exercises, combined with work on flexibility and balance, you create a resilient body that's less prone to injury. This aspect of fitness is often overlooked

but is important for long-term health and getting the most benefit from other forms of exercise.

How much exercise is enough? Diminishing returns

The current recommendation is a minimum of 150 min per week of moderate or 75 min per week of vigorous exercise, supplemented with strength and stability training.
There is benefit to exceeding this dose , but with diminishing returns. A full dose gains about 3 years of life to the average exerciser, a double dose adds another year, a triple dose adds another ⅓ of a year and so on.

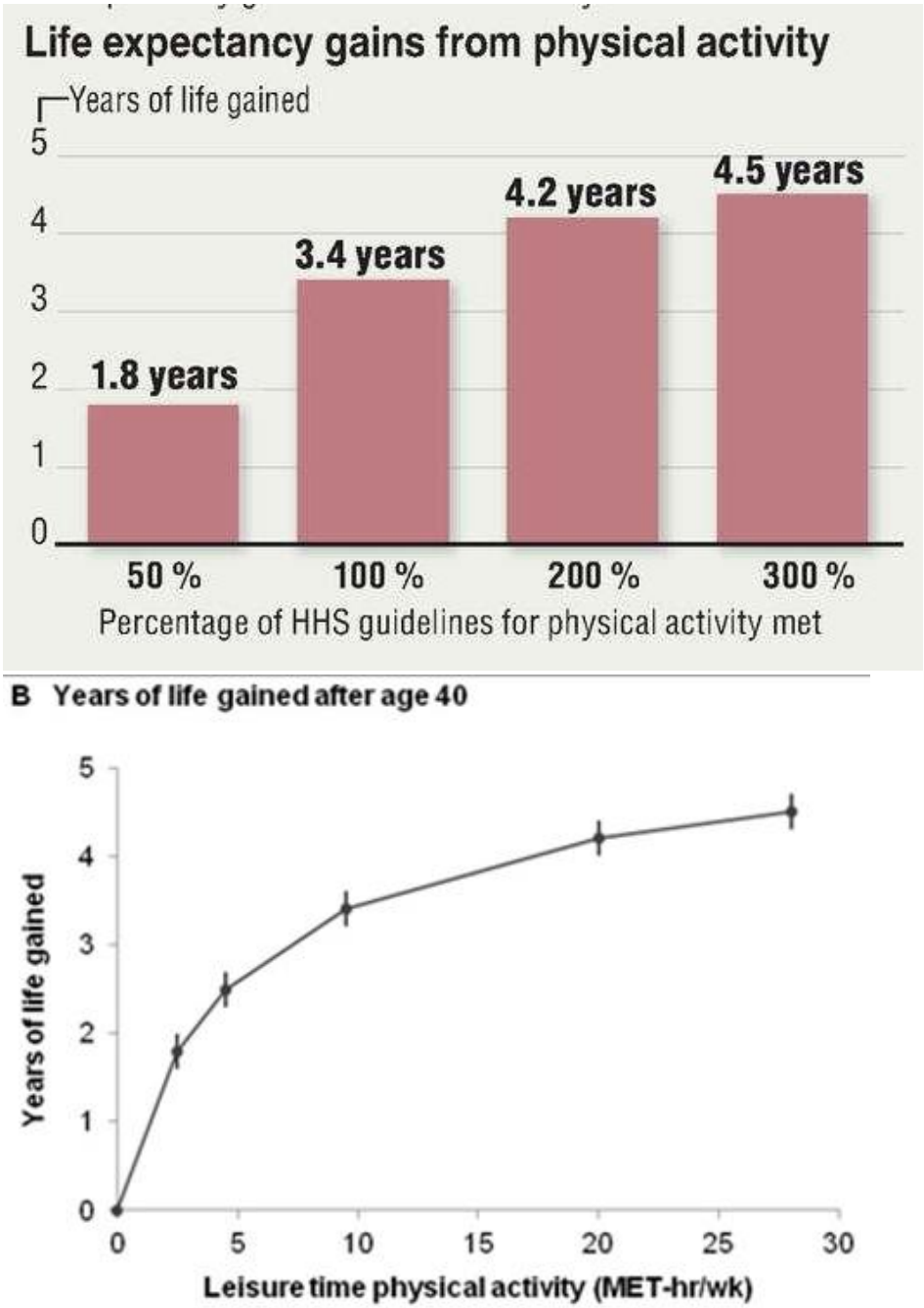


Fig 6.16 Diminishing returns of exercises - years of life gained at age 40 by walking briskly for various amounts of time per week. The x-axis is in units of MET-hr/week, where a MET is the rate at which you burn energy when sitting quietly. One MET is roughly equivalent to one kcal/kg/hour. Moderate-intensity activities fall in the range of 3-5.9 METs. Vigorous-intensity activities are 6 METs or greater. Source doi: 10.1371/journal.pmed.1001335.

The benefits start with even tiny improvements- a 2025 lancet study found that a 5 min/day increase in activity can make a difference - it prevented 6·0% (95% CI 4·3–7·4) of all deaths in prospective studies with wearable activity readouts. A similar increase in MVPA in all participants except the most active might prevent 10·0% (6·3–13·4) of all deaths. Reducing sedentary time by 30 min/day might prevent 3·0% (2·0–4·1) of all deaths in the high-risk approach and 7·3% (4·8–9·6) in the population-based approach (DOI: 10.1016/S0140-6736(25)02219-6).

In this table you can find your vo2max ranking. it may be a good idea to go up at least one level which is a large gain in health (except high to elite which is only a tiny benefit).

Figure 12. VO_2 Max by Age, Sex, Fitness

Age	Performance Group by VO_2 max (ml/kg/min)				
	Low	Below Average	Above Average	High	Elite
Women					
18-19	< 35	35-39	40-45	40-52	≥ 53
20-29	< 28	28-35	36-40	41-50	≥ 51
30-39	< 27	27-33	34-38	39-48	≥ 49
40-49	< 26	26-31	32-36	37-46	≥ 47
50-59	< 25	25-28	29-35	36-45	≥ 46
60-69	< 21	21-24	25-29	30-38	≥ 40
70-79	< 18	18-21	22-24	25-35	≥ 36
≥ 80	< 15	15-19	20-22	23-29	≥ 30
Men					
18-19	< 38	38-45	46-49	50-57	≥ 58
20-29	< 36	36-42	43-48	49-55	≥ 56
30-39	< 35	35-39	40-45	46-52	≥ 53
40-49	< 34	34-38	39-43	44-51	≥ 52
50-59	< 29	29-35	36-40	41-49	≥ 50
60-69	< 25	25-29	30-35	36-45	≥ 46
70-79	< 21	21-24	25-29	30-40	≥ 41
≥ 80	< 18	18-22	23-25	26-35	≥ 36

Group comparisons for VO_2 max are Low (bottom 25%), Below Average (26th to 50th percentile), Above Average (51st to 75th percentile), High (75th to 97.6th percentile), and Elite (top 2.3%).

Fig 6.17, VO2max quartile per age, reproduced from Mandsager et al 2018.

Not exercising is a major risk factor for mortality

Research shows a striking difference in life expectancy between fitness levels: those in the top quartile of fitness typically live about a decade longer than those in the bottom quartile. Despite this benefit, approximately 75% of Americans don't meet recommended exercise guidelines.

Going from just being low to being below average is a 50% reduction in mortality over a decade (‘hazard ratio’ of 0.5). If you go from low to above average, it’s about a 60% or 70% reduction in mortality. Then it just continues monotonically to increase. The mildest improvement is going from high to elite—That doesn’t buy you a lot. It is still statistically significant.. If you compare someone of low fitness to elite, it is a five fold difference in mortality over a decade.

These reductions in hazard are very large if you compare them to what we commonly think of as being problematic for mortality… For example, smoking, coronary artery disease, Type 2 diabetes, hypertension, and end-stage renal disease. As you can see in Fig 6.17, smoking has a 41% increase in mortality over the decade, Coronary artery disease, 29%. Diabetes, 40%, High blood pressure, 21% and end-stage renal disease, about 180% increase in mortality. So not exercising is a huge risk factor, bigger than all of these. If you look at the biggest driver of mortality, which would be end-stage renal disease in this cohort, it’s the same as going from low cardiorespiratory fitness to above average cardiorespiratory fitness -going from the bottom 25th percentile to being in the 50th to 75th percentile *which is a totally achievable feat*. (From Peter Attia, the Drive notes).

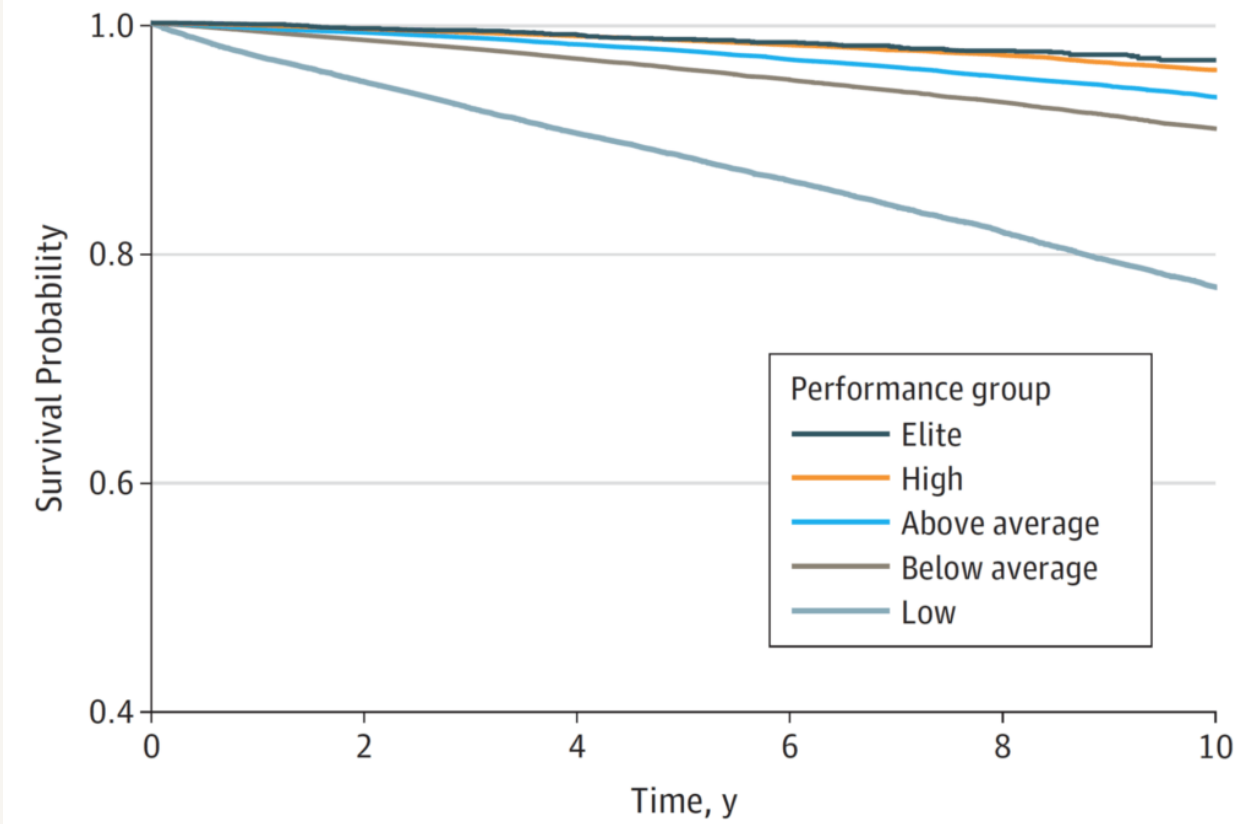


Fig 6.18. At 50, survival over ten years is dismal when not exercising. (Mandsager et al., 2018). 122,000 people that were 53 years old on average were ranked by a VO2 max test by quartiles, with 'elite' defined as the top 5% . By far the biggest gap in survival is between the people in the bottom 25%. which are categorized as low fitness, and everyone above them.

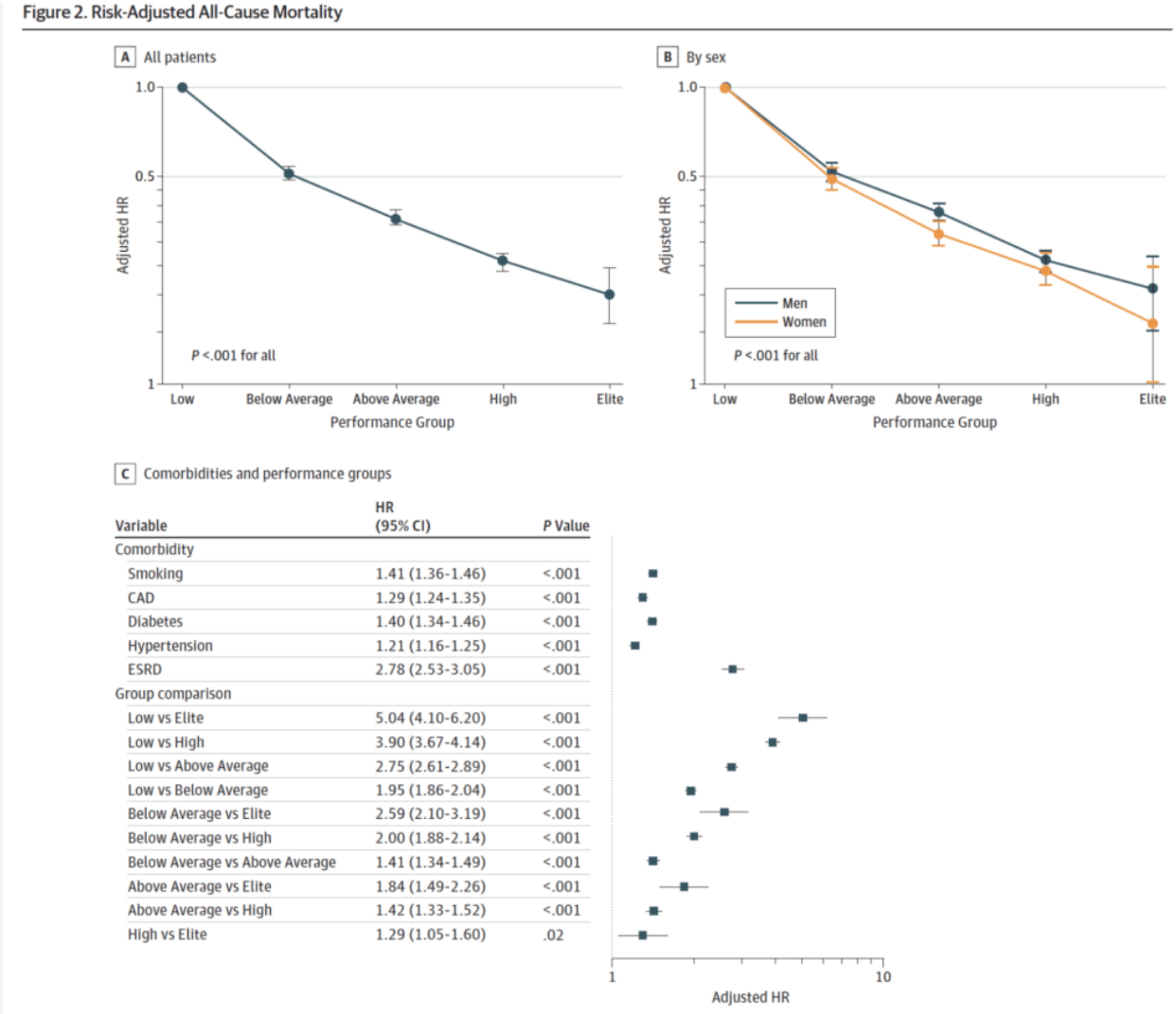


Fig 6.19 . Smoking and chronic diseases are less risky than not exercising. Risk-adjusted all-cause mortality for serious risk factors such as smoking, and for the fitness quartiles of Fig 6.16. (Mandsager et al., 2018). HR- hazard ratio, CI - confidence interval.

Converting Hazard ratios into years of life gained or lost

As you see in the table in Fig 6.17, medical research often reports hazard ratios (HR) to express mortality risk. Halving your mortality risk (HR = 0.5) corresponds to approximately 8 years of additional life expectancy. This relationship stems from the Gompertz law of mortality, in which human mortality risk doubles approximately every 8 years.Thus, if you double mortality risk (by smoking for example), it's as if you are 8 years older in terms of mortality hazard compared to nonsmokers (see solved exercise 5.1)

Exercise boosts mood

many studies that find a good correlation between exercise and improved mood/decreased depression. But do we exercise because we feel good or do we feel good because we exercise? If we study an exercise intervention, what is the control experiment to show that the mood improvement is not placebo?

Recent techniques help address such confounding questions. These new techniques include activity monitoring devices and a clever use of genetic data called **Mendelian randomization.** They indicate that causality points from exercise to improved mood- about a 25% reduced risk of depression for every std of movement as recorded by wearable devices. Choi et al JAMA psychiatry (2019).

Some biological mechanisms have been suggested for mood improvement via exercise, reviewed here [https://pmc.ncbi.nlm.nih.gov/articles/PMC8602192/]. These include anti-inflammatory effects in the brain, enhanced neuroplasticity, and hormones such as endorphins endocannabinoids - natural painkillers and euphorics associated with 'runners high'[https://pmc.ncbi.nlm.nih.gov/articles/PMC10159215/].

To exercise we need scheduling and allies

In summary- take out your phone calendar and schedule an hour this week for exercise of your choice. The person sitting next to you will be your **exercise ally**- they will put on their calendar your phone number and schedule when to call you twice - before to remind you, and after to ask you how it was. Scheduling and social commitment makes it more likely that you will actually do it. Enjoy!

To exercise our breathing muscles, Let's take a nice deep sigh of relief.

Song for this lecture /Amy Weinhaus

He tried to make me go to Yoga, I said 'no,no,no'
Yes I've been lax 'bout my VO2max, which is low low low
I ain't got the time, and my professor just can't rhyme
He's tried to make me go to yoga, I won't go, go, go.

E. Am
No more Beta-oxidation,
F Ab
mitochondria lost their vibration

E. Am
Fatty acids not burning no more,
F. Ab
if you want to make a change … you gotta open the door
G
But I think i'll just stay at home
F
I got my friends to talk to on the phone

He tried to make me go to Yoga, I said ‘no,no,no’
Yes I've been lax ‘bout my VO2max, which is low low low
I ain't got the time, and my professor just can't rhyme
He’s tried to make me go to yoga, I won’t go, go, go.

Solved exercise

5.1 Every 10% mortality risk is about one year of life: Lets see this mathematically (feel free to skip the next two paragraphs). The Gompertz hazard function describes mortality risk over time as $h = A e^{at}$, where A is the initial mortality rate and a is the rate of mortality increase with age. When we apply an intervention that changes our hazard ratio to HR, this effectively multiplies our hazard function by HR, which is mathematically equivalent to changing A to $A' = A \times HR$. The survival function S(t) is: $S(t) = \exp(-\int h\, dt) \sim \exp(-A/a\, e^{at})$. From the survival function we can find the median lifespan t_{50}, where $S(t_{50}) = ½$: $t_{50} = (1/a) \ln(\ln(2)a/A)$.

When we modify the hazard by changing A to A', the gain in median lifespan is (1/a) ln(A/A'). Since we know from the Gompertz doubling time that ln(2)/a = 8 years, we can rewrite the gain in median lifespan as 8 years x ln(A/A')/ln(2). When risk is halved (A/A' = 2), this equation yields an 8-year gain. For smaller changes, the relationship becomes approximately linear - as a rule of thumb, every 10% reduction in hazard ratio corresponds to about 1 year of additional life expectancy.

5.2 Read about Mendelian randomization. What are the conditions needed for it to work? How can you use it to check if lowering LDL cholesterol raises risk of cancer? See if such studies exist- what do they find?

5.3 How does function decline in a ballistic aging organism?
let's assume, as in the main text, that damage x reduces function in a saturating way
f=1-x/(k+x)=k/(k+x)
In a ballistic Ager, damage goes on average as x=½ eta t^2. Thus
f=1/(1+(1/2k) eta t^2)~t^(-2).
Thus function drops quadratically with age at very old ages.

5.4 Functional decline and the variation between people in eta and beta

Look at the decline in max heart rate in fog 6.x. Does this relate to the statment form our lecture in genetics of aging that house rate eta and truck rate beta need to vary little between people
5.4 Why does inflammation affect kidney GFR in a saturating way?

1. Initial Stage: GFR Declines Proportionally (Near-Linear Phase)

- In **mild to moderate chronic inflammation**, GFR declines **roughly in proportion** to inflammatory marker levels (e.g., **CRP, IL-6, TNF-α**).
- This is due to **progressive endothelial dysfunction, oxidative stress, and mild renal vasoconstriction**, which **gradually reduce renal perfusion**.

2. Advanced Stage: GFR Reaches a Plateau (Saturation Phase)

- As inflammation worsens, multiple **protective and compensatory mechanisms** (e.g., hyperfiltration in remaining nephrons, increased RAAS activation) attempt to maintain function.
- However, when inflammation becomes severe, additional damage does not proportionally decrease GFR further because:
    - Many nephrons are already **dysfunctional**.
    - **Fibrosis and structural damage** become limiting factors, meaning that more inflammation **cannot accelerate the loss of nephrons indefinitely**.
    - The kidney **can only lose so many nephrons** before reaching a near-complete loss of function.

3. Biological Evidence for Saturation

- Studies show that **mild inflammation (e.g., obesity, metabolic syndrome)** causes a gradual **decline in GFR**.
- However, in **severe inflammatory conditions (e.g., sepsis, late-stage autoimmune disease)**, the damage reaches a **threshold where additional**

inflammation no longer significantly changes GFR because the kidney is already failing.

Mathematical Representation

A **Michaelis-Menten-like saturation curve** fits well:

GFR decline=CI/(K+I)

- I = inflammation strength,
- C = maximal effect on GFR,
- K = inflammation level at which half-maximal effect occurs.

Key Takeaway:

- **At low inflammation levels, GFR declines proportionally (linear effect).**
- **At high inflammation levels, GFR decline plateaus due to nephron loss saturation (saturating function).**

appendix 0 how to build an exercise habit
I recommend the books “atomic habits” and “miracle morning”
Form a cue- a time and place, stacked on top of another habit.
When the time to exercise each day comes
You will feel angry
Make it easy- have a bag with all the swimming gear.
Make it rewarding- have a friend ally to report to
Stack a pleasant habit- sipping soda and watching sunset

Reminder: uri add senescence as a biomarker for health - advanced after 2024

Appendix 1
Physiological changes in exercise

When we exercise our muscles need energy. This energy comes from ATP -a molecule with high energy phosphate bonds that can be utilized by enzymes that break these bonds. ATP is broken in this way by motor enzymes that contract the muscle fibers to produce force.
When we move, muscles need ATP. They have a short term supply that lasts for a few seconds- stored atp and creatine phosphate. After that, they must produce atp from burning the sugar glucose.
There is at first not enough oxygen to burn the glucose completely to co2, so the cells ferment glucose to get 2 atps per sugar molecule and emit “smoke” like a fire without enough oxygen- the smoke is lactate. This makes the muscles less effective and causes burning sensation.
The lactate in the blood makes the blood acidic and signals the body to get more oxygen. The acidity is sensed by special neurons in the arteries that signal the brain stem to increase breathing rate. Oxygen in the lung dilates the lung capillaries in and causes the lung to efficiently absorb oxygen and release co2- the lung breathes fully and has less dead space.

The brain also causes activation of the sympathetic nervous system (fight or flight response) that secretes adrenaline which makes the heart beat faster. Adrenaline also contracts blood vessels in inner organs- digesting a meal is less important now that we need to move, part of the fight or flight response.
The lactate in the moving muscles makes the local arteries expand. This blood is thus redirected to where it is needed- the exercising muscles.
Now the muscles have ample oxygen and sugar can be burned completely down to co2 by the tca cycle in the mitochondria gaining 32 atps per glucose molecule.
After more exercise blood glucose begins to drop. This causes beta cells in the pancreas to release the hormone glucagon. Glucagon instructs the liver to make glucose out of stored glycogen. It also instructs fat cells to release fatty acids. Fatty acids can be turned to ATP by mitochondria in the muscles (about 130 atp per fatty acid). We burn fat.
At this stage the fun hormones are released like cortisol, beta endorphins and endocannabinoids - natural pain killers and euphoric.

The maximum rate of oxygen consumption (VO2max) in exercising humans is primarily limited by the cardiorespiratory system's ability to deliver oxygen to working muscles, not by the muscles' ability to use oxygen. This conclusion is supported by three key lines of evidence:

1. VO2max responds directly to changes in oxygen delivery: Whether through blood doping (increasing oxygen-carrying capacity), hypoxia (reducing available oxygen), or beta-blockade (affecting heart function), when we modify oxygen delivery, VO2max changes predictably.
2. Training improvements in VO2max come mainly from enhanced cardiac output: The increase in VO2max through training is primarily due to the heart's ability to pump more blood (cardiac output) rather than from improved oxygen extraction by muscles (arterial-venous O2 difference).
3. Small muscle groups show exceptional oxygen consumption capacity: When a small muscle mass is given abundant blood flow (overperfusion), it demonstrates remarkably high oxygen consumption abilities, suggesting that muscles themselves have more capacity than they typically use.

While oxygen delivery is the primary limiting factor for VO2max, metabolic adaptations in skeletal muscle remain crucial for improving submaximal endurance performance. Endurance training increases mitochondrial enzyme activity, which enhances performance in two ways: better fat oxidation and reduced lactic acid buildup at any given oxygen consumption level.
VO2max serves as a fundamental ceiling for endurance performance - athletes cannot sustain effort above 100% of their VO2max for extended periods. However, two other factors also significantly influence endurance performance: running economy (efficiency

of movement) and fractional utilization of VO2max (percentage of maximum that can be sustained). The speed at lactate threshold (LT) effectively combines all three of these variables, making it the most reliable physiological predictor of distance running performance. כ מי ל דגש תתל

For example to complete a 2:15 marathon, a V̇O2 of about 60 mL·kg⁻1·min⁻1 must be maintained throughout the run. Consequently, even if a marathon could be run at 100% V̇O2max, the runner would need a V̇O2max of 60 mL·kg⁻1·min⁻1 for the above performance. However, since the marathon is typically run at about 80–85% of V̇O2max, the V̇O2max values needed for that performance would be 70.5–75 mL·kg⁻1·min⁻1.

Appendix 2

Choi et al abstract about exercise and depression
This study used Mendelian Randomization and genetic data (SNPs) from genome-wide association studies (GWAS) to explore if physical activity protects against depression. SNPs linked to higher accelerometer-measured activity were associated with lower depression risk, suggesting a protective effect. However, SNPs linked to depression did not predict activity levels. This method strengthens the causal link between being more active and preventing depression.

Paper abstract: GWAS summary data were available for a combined sample size of 611 583 adult participants. Mendelian randomization evidence suggested a protective relationship between accelerometer-based activity and MDD (odds ratio [OR], 0.74 for MDD per 1-SD increase in mean acceleration; 95% CI, 0.59-0.92; P = .006). In contrast, there was no statistically significant relationship between MDD and accelerometer-based activity (β = -0.08 in mean acceleration per MDD vs control status; 95% CI, -0.47 to 0.32; P = .70). Furthermore, there was no significant relationship between self-reported activity and MDD (OR, 1.28 for MDD per 1-SD increase in metabolic-equivalent minutes of reported moderate-to-vigorous activity; 95% CI, 0.57-3.37; P = .48), or between MDD and self-reported activity (β = 0.02 per MDD in standardized metabolic-equivalent minutes of reported moderate-to-vigorous activity per MDD vs control status; 95% CI, -0.008 to 0.05; P = .15). [https://pubmed.ncbi.nlm.nih.gov/30673066/]

This isn't the first study to show that exercise may benefit mood. But until now it's largely been something of a chicken-and-egg discussion — which came first?"We hear a lot that exercise and mood are connected. What we don't know for sure is whether being physically active can improve emotional well-being, or if we simply move less when we

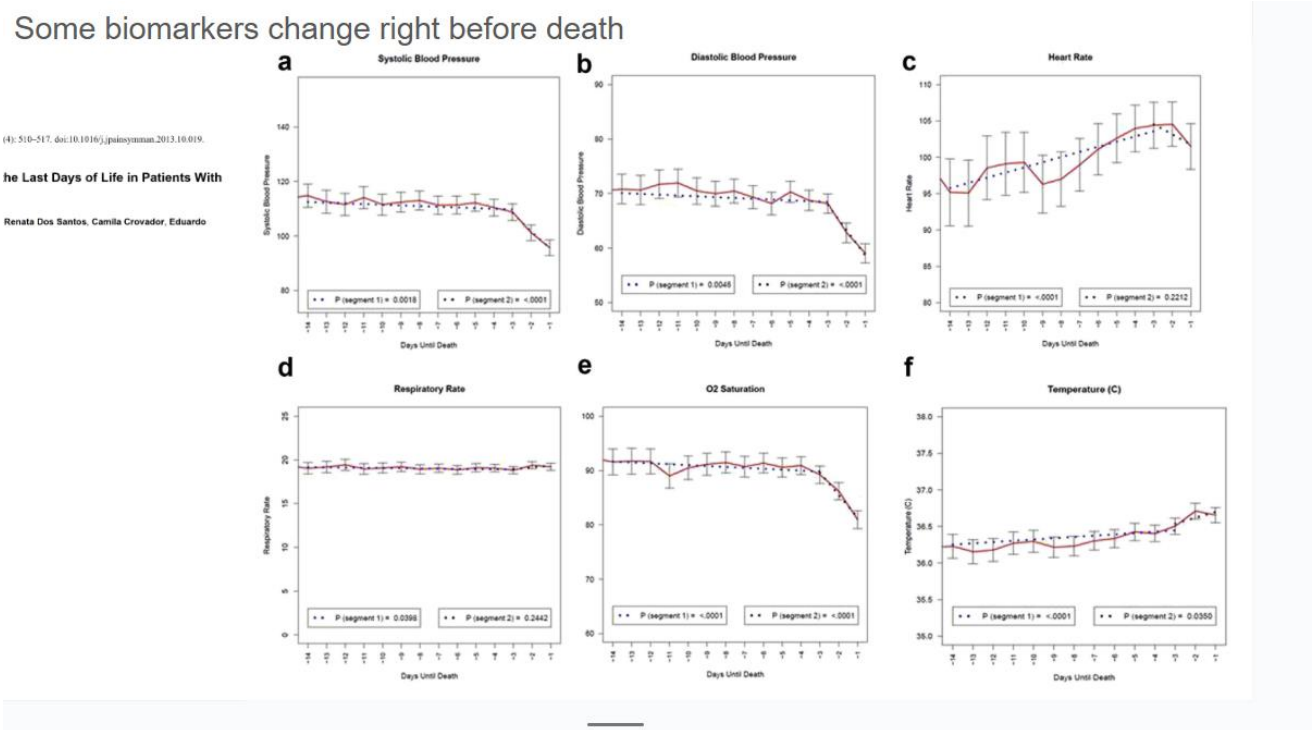
feel sad or depressed," says Choi. This study aimed to find out. "We wanted to see if there might be a causal connection, in either direction, between physical activity and depression," says Choi. "Does physical activity protect against depression? Or does depression simply reduce physical activity? Our study allowed us to untangle those questions in a powerful new way using genetic data.

To do this, the study applied a technique known as Mendelian randomization, using data from two large genetic databases that included hundreds of thousands of people. Having access to genetic data allowed researchers to use genetic variations between people as a kind of natural experiment to better see how exercise affects depression, and vice versa, says Choi. What they found is that exercise was able to independently reduce the risk for depression. People who moved more, they found, had a significantly lower risk for major depressive disorder — but only when the exercise was measured objectively using a tracking device, not when people self-reported how much exercise they performed. A 26% reduced risk per standard deviation of motion activity measured by devices."

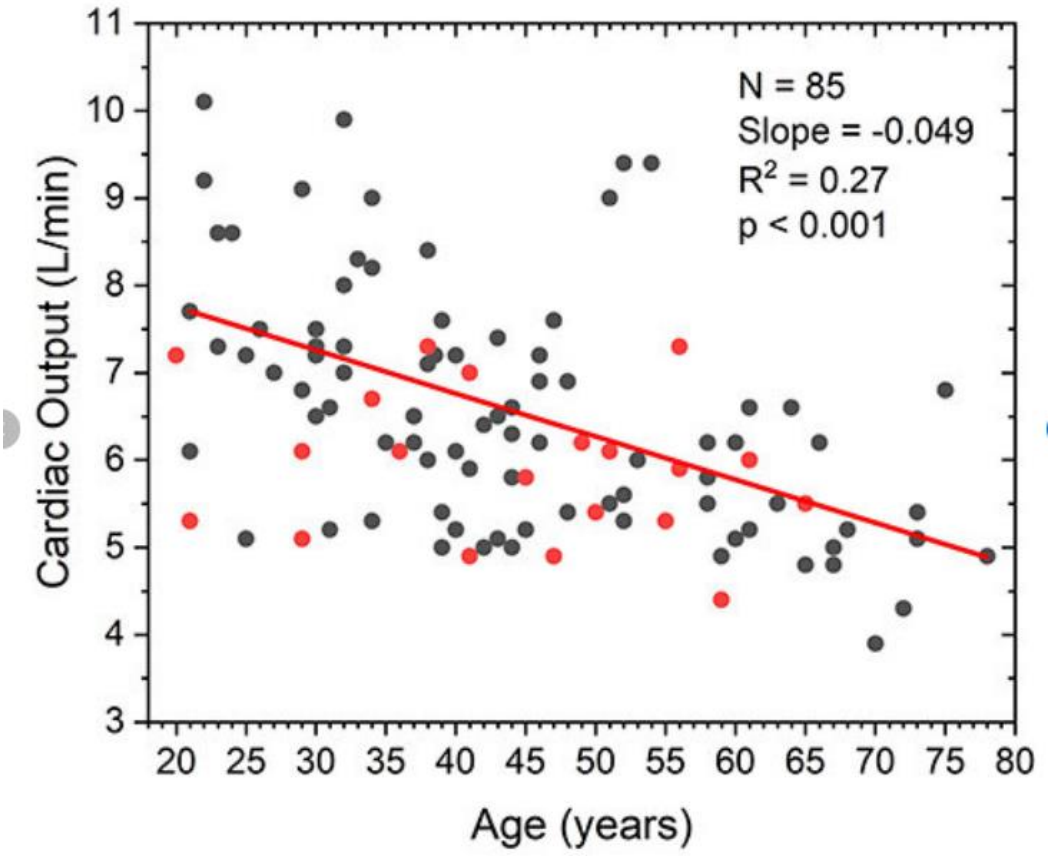
Source: [https://www.health.harvard.edu/mind-and-mood/more-evidence-that-exercise-can-boost-mood]

Appendix 3

Last days of life in cancer patients show changes in some biomarkers.

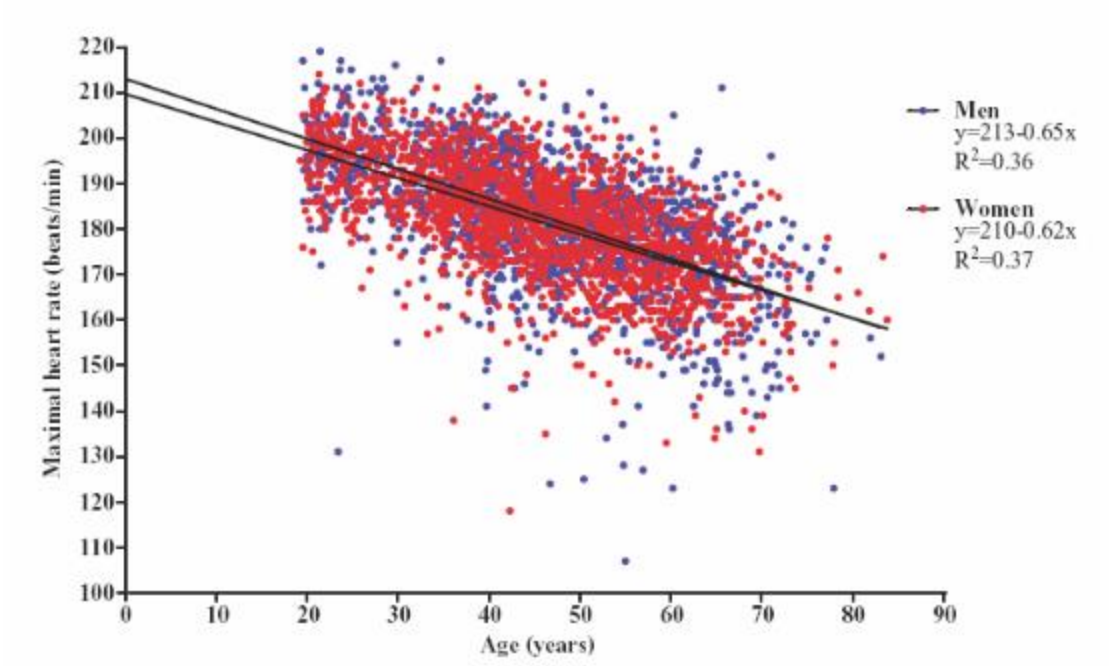


Some functions vary more and some less across population,
Some declienlienarly and some slow then fast

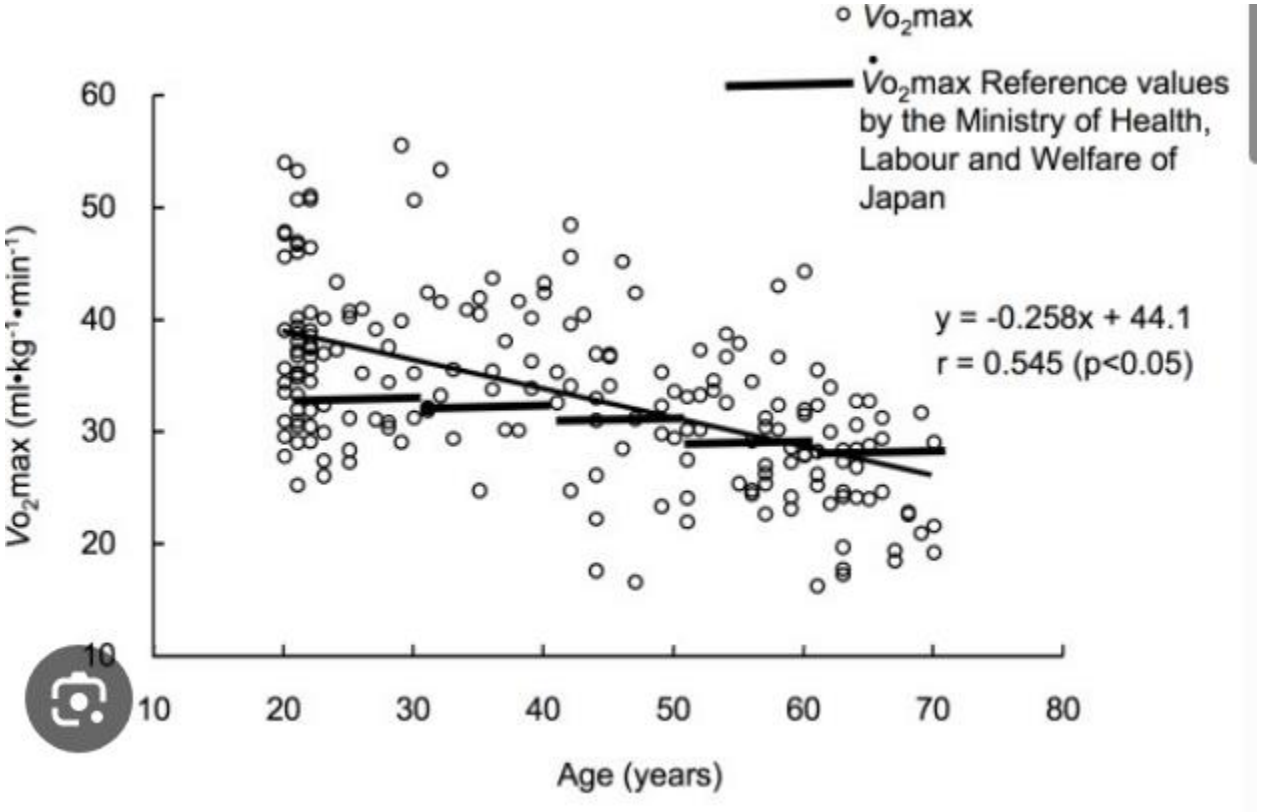


Decline in resting cardiac output as a function of age in men (black) and women (red). Measurements obtained 5–10 minutes after subjects assumed a semi-reclined position using an earpiece dye-dilution method. In this cohort study, cardiac output peaks near age 20, then declines continuously with increasing age at an approximate rate of 50mL per year. (After Katori, 1978).[20]

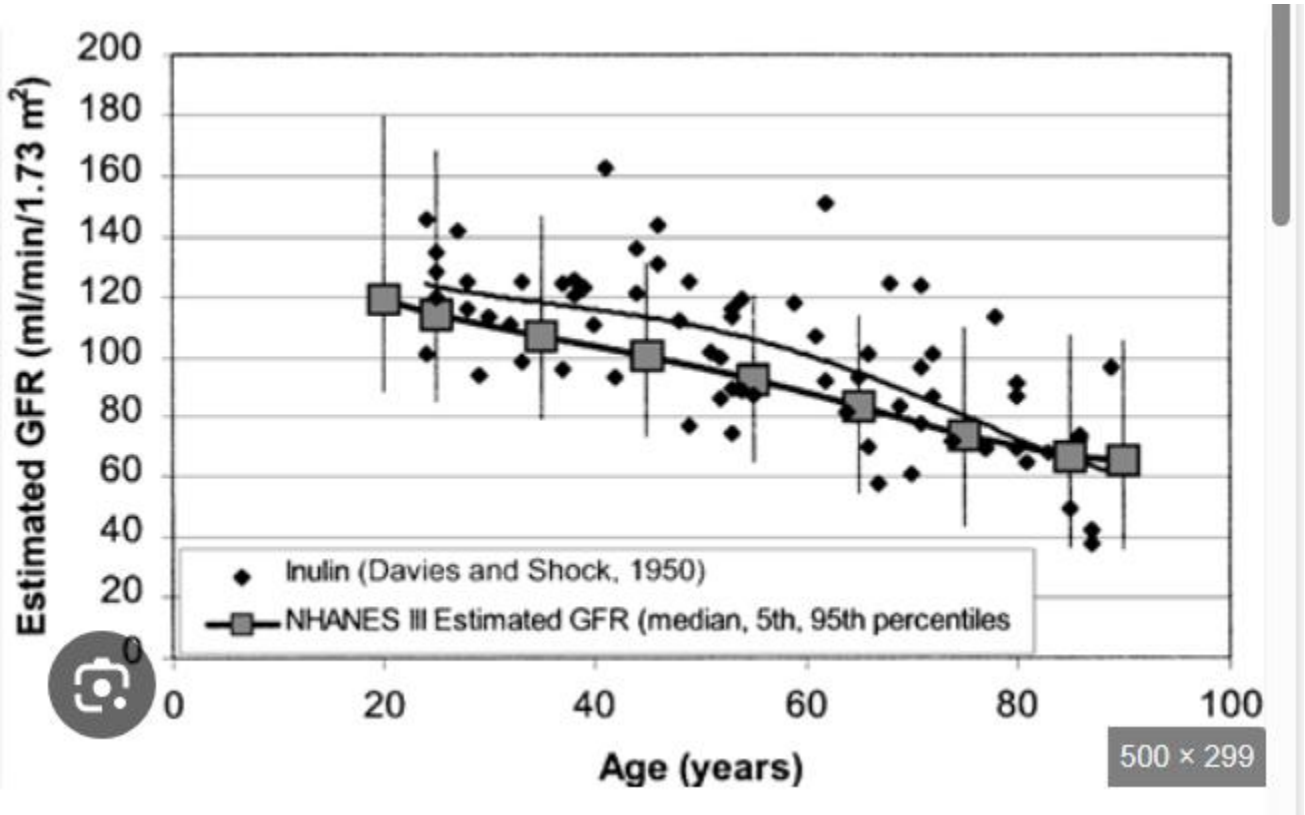
DOI: 10.2147/CIA.S447665



Source: Age-predicted maximal heart rate in healthy subjects: The HUNT Fitness Study



VO2max shows a factor of 2 at age 20, and also cardiac output.
Incontrast max heart rate varies by factor of 20% (40/220)



GFR also varies by about 40% between individuals (80-120)/100 at age 50

Changes in amplitude with age for common nerves with R correlation values. The graph highlights the significant negative correlation between amplitude and age for individual nerves in both adult males and females. The mean amplitude was calculated for each age group. The age group was created by rounding age to the nearest 5 years. The blue line is a Loess-smoothed curve far the trimmed mean (1%). The gray area around the smooth line represents the 95% confidence interval. The dashed line represents the females' trimmed mean values, and the dotted line represents the males' trimmed mean values. Age groups with fewer than five records were omitted (age groups 0, 90, and 5 in some cases). Supplementary Table 2 lists the number of records in each age group.

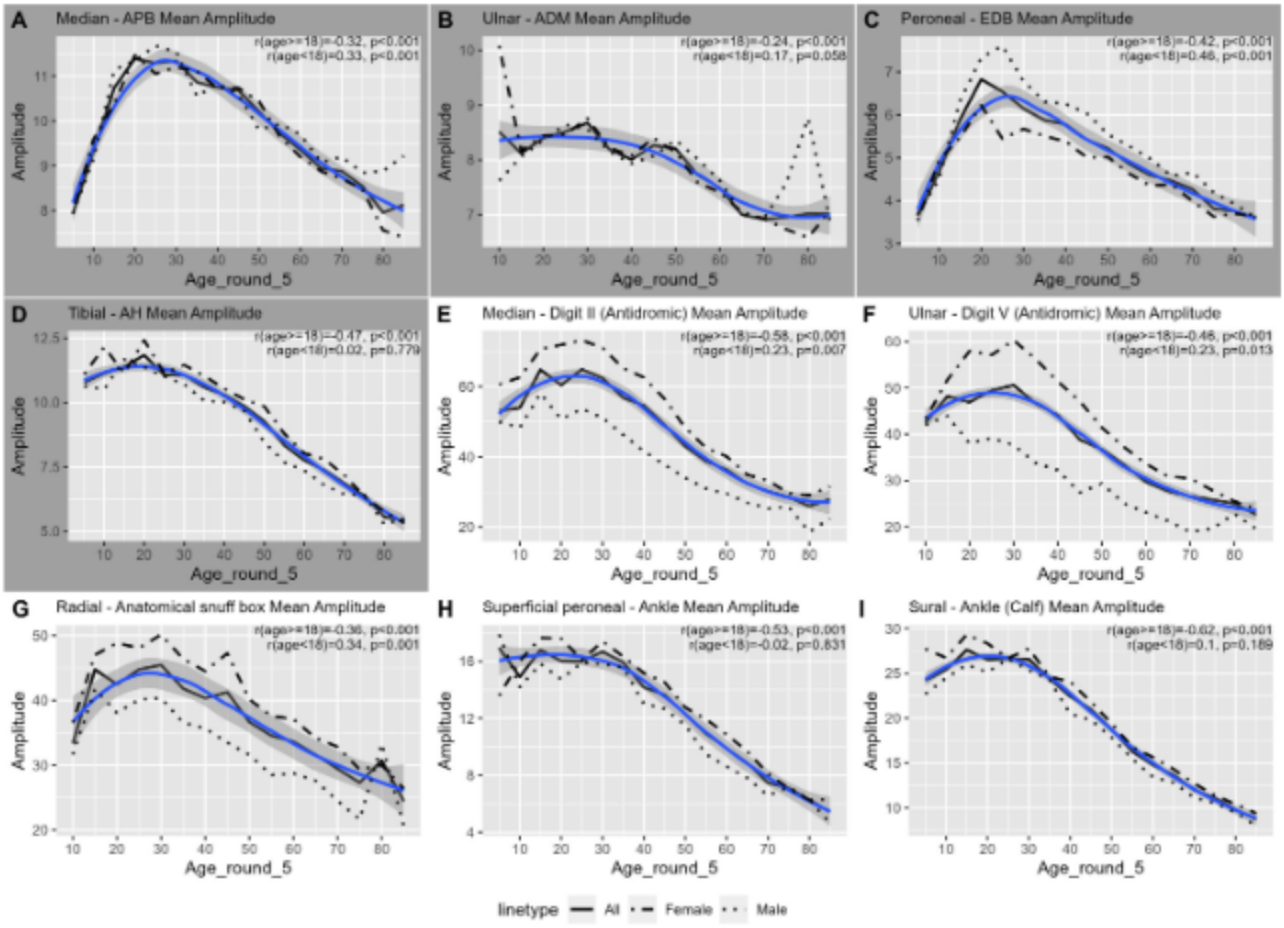


Fig. 3

Changes in velocity with age for common nerves with correlation values. The graph highlights the velocity dynamics for individual nerves in both adult males and females. The mean velocity was calculated for each age group. The age group was created by rounding age to the nearest 5 years. The blue line is a Loess-smoothed curve for the trimmed mean (1%). The gray area around the smooth line represents the 95% confidence interval. The dashed line represents the females' trimmed mean values, and the dotted line represents the mates' trimmed mean values. Age groups with fewer than five records were omitted (age groups 0, 90, and 5 in some cases). Supplementary Table 3 lists the number of records in each age group.