Systems Aging

Lecture 8 - Nutrition and Longevity

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Recommended reading:
Rules for body fat interventions based on an operating point mechanism Bar et al. iScience. 2023

Attia, Outlive. 2023, chapters on nutrition

Today is lecture seven and the topic's really great
We'll explore longevity reflected in your plate
There's feedback loops and circuits
That are beautiful to watch
And today we'll study them alot
but not too much

Aging aging aging here and there
Agingx4 aging everywhere

Nutrition and longevity is a topic that is hard to study in humans

We are what we eat, but the transformation is complex and individual. Nutrition has long fascinated people as a way to health and longevity. Specific diets raise strong emotions and polarized convictions (paleo, vegan, keto, low carb, low fat, mediterranean and so on), almost like warring schools of thought. Weakly powered studies and poor reporting abound on questions like is coffee good or bad for health? Will eating a low fat diet reduce risk of cancer? Unlike exercise where evidence is repeated, strong and of coherent directionality, evidence about the effect of specific diets on longevity is fraught with biases, of generally low effect size and conflicted direction.

Here is what seems well supported: eating not too many or too few calories is important for health and lifespan. The composition of these calories is less important. What is important about composition is macronutrients - eating enough protein to the tune of about 1g/kg of weight (fat and carbs are both ok, alcohol should be minimized), avoiding toxins (mercury), minimizing ultra processed foods and getting enough micronutrients (vitamins, minerals) can suffice for good health. In cases of metabolic disorders like type 2 diabetes, fatty liver disease, or intolerance to certain foods, diets like low carb diets are warranted, but need to be individualized.

Why is the evidence so poor in general? Humans are hard to study when it comes to their plate. Nutrition research uses two main tools, epidemiology and experiment. Epidemiology has a problem of self reporting because food questionnaires (what did you eat over the past week, month, year) are inaccurate, and self reporting apps help a little bit. Studies have a big 'healthy user' bias- overall health for reasons other than nutrition is confounding. For example, low socioeconomic status is associated with ultra processed foods (unhealthy) but also with poor health for other reasons; Rich exercising people tend to eat differently, and so on. These studies show small effect sizes (typically less than hazard ratios of 1.5) and different studies often show opposite directions.
One consistent and small longevity effect is for vegetarian diet. However it is hard to control for confoundering factors. People that eat a vegetarian diet which is quite restrictive are often health conscious and make better lifestyle
Choices on things like
Smoking and other factors that are hard to control for. A counter example is the post ww2 Study that compared bus drivers to conductors who walk across the bus all day. Conductors had 50% lower risk of death than drivers- and there is no reason to think they would make different lifestyle choices like smoking than drivers.

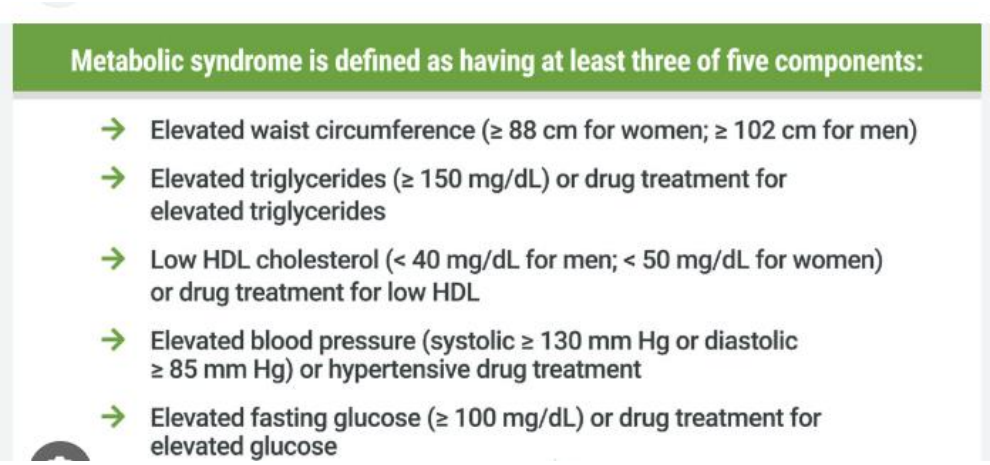
One of the studies considered best is PREDIMED about mediterranean diet.
PREDIMED (PREvención con DIeta MEDiterránea) was a Spanish trial of 7,447 people with risk factors for metabolic and heart disease randomized to either a Mediterranean diet with supplemental extra virgin olive oil, a Mediterranean diet supplemented with nuts, or a low-fat control diet. One arm got a liter of olive oil every week to promote cooking and eating olive-oil-related foods. The nut arm got nuts every week, and the control arm was instructed to eat a low fat diet and avoid certain foods like fish.

The trial was stopped early because the olive oil and nut arms had about 30% fewer severe cardiac events - and it was deemed unethical to continue the control arm. One criticism here is 'performance bias' - the oil and nut arms interacted more with the experimenters than the control arm, and such interactions are known to increase people's attention to nutrition and to affect behavior.
In addition to epidemiology, the other main tool is direct experiment. Experimenting directly on human nutrition is hard- requires admitting people to metabolic wards in a hospital and tracking what they eat, so the studies are short-term and have small sample size. They can still inform us about mechanisms as seen below.

We will build this lecture around three questions doctors consider

-Over/undernourished?
-Adequate muscle mass?

-Adequate metabolic health? That is- lack of metabolic syndrome which afflicts 20-30% of the global population, as defined by 3 of five criteria in this table.



Being over or under nourished raises risk of death and disease
Being over or undernourished means eating too many or too few calories. On a population level this can be seen by associating weight and death and disease risk. Weight is evaluated for research purposes as BMI - body mass index - the ratio of weight to height squared (in kg and meters). I weigh 90Kg and my height is 1.85m so my BMI is 90/1.85^2=26. A BMI of 20-25 is normal, 25-30 overweight, 30 and above obese.

Why height squared? It turns out our weight goes as height squared in humans on average, so BMI relates your weight to the weight that is ‘normal’ for your height. Another way to think about it is that BMI measures ‘width’.

Optimal BMI - the BMI with lowest hazard of death- is around 22 for men and slightly more for females. The optimal BMI rises slightly with age, creeping up to about 26 in 80- year olds.

But note an important caveat- **this graph does not tell us the direction of causality**. It is well established that high BMI is causal for many diseases. At low BMI the direction is often opposite- those with diseases often have reduced weight due to wasting or cachexia.

A BMI below 18.5 is considered underweight for adults. A BMI below 16 is classified as dangerously underweight and can pose health risks like osteoporosis, anemia, weakened immune system, and fertility problems.

Different ethnic groups have different ‘optimal’ BMI - for example about 2 BMI points lower in studies of East Asian populations and 4 points lower in South Asian populations, who have higher risk of diabetes in lean individuals.

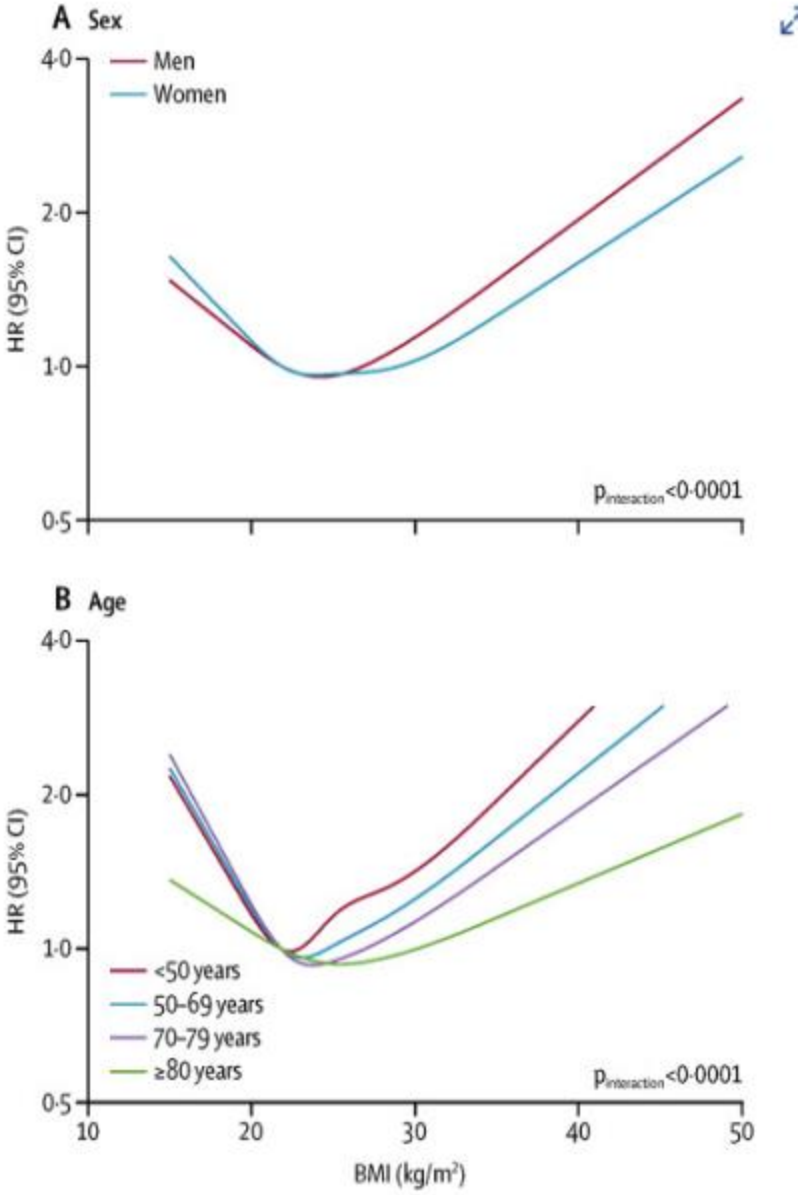


Fig. 7.1 Association between BMI and all-cause mortality among never-smokers, by sex (A) and age (B)

It's important to note that BMI is fine for cohort studies but should be taken with a hefty grain of salt for each individual- BMI does not take into account lean mass (muscle) versus fat mass (for reference ranges see https://doi.org/10.1038/s41430-020-0596-5) - you need to know both to correctly assess risk . High BMI due to elevated muscle mass is healthier.

Risk of diabetes and many cancers rise in obese individuals. Below is data from UK biobank in which hundreds of thousands of people at different ages contributed their medical data and did a standard set of lab tests - an amazing, publicly available resource for research.

High fat content has several dangerous effects. The body is designed to store fat, since we evolved when food was
far more scarce than today. Fat is best stored right under the skin (subcutaneous fat) especially in the legs and glutes.
However subcutaneous fat has a finite capacity - the cells expand to store more fat, but do not increase in number in adults. When there is overflow, fat begins to be stored in inner organs - this is abdominal fat and especially **visceral fat.** It is stored in lipid droplets in the cells of the liver, in muscles, in the pancreas and more.
When this happens the body triggers inflammation and insulin resistance. Inflammation and elevated insulin promote cancer, diabetes and heart disease. For example, liver cancer (a deadly cancer due to late detection) occurs only after liver fibrosis - in the past this was primarily due to alcoholism, but today there is an alarming rise due to fatty liver disease which transitions to scarred liver (cirrhosis) with a high risk of liver cancer.

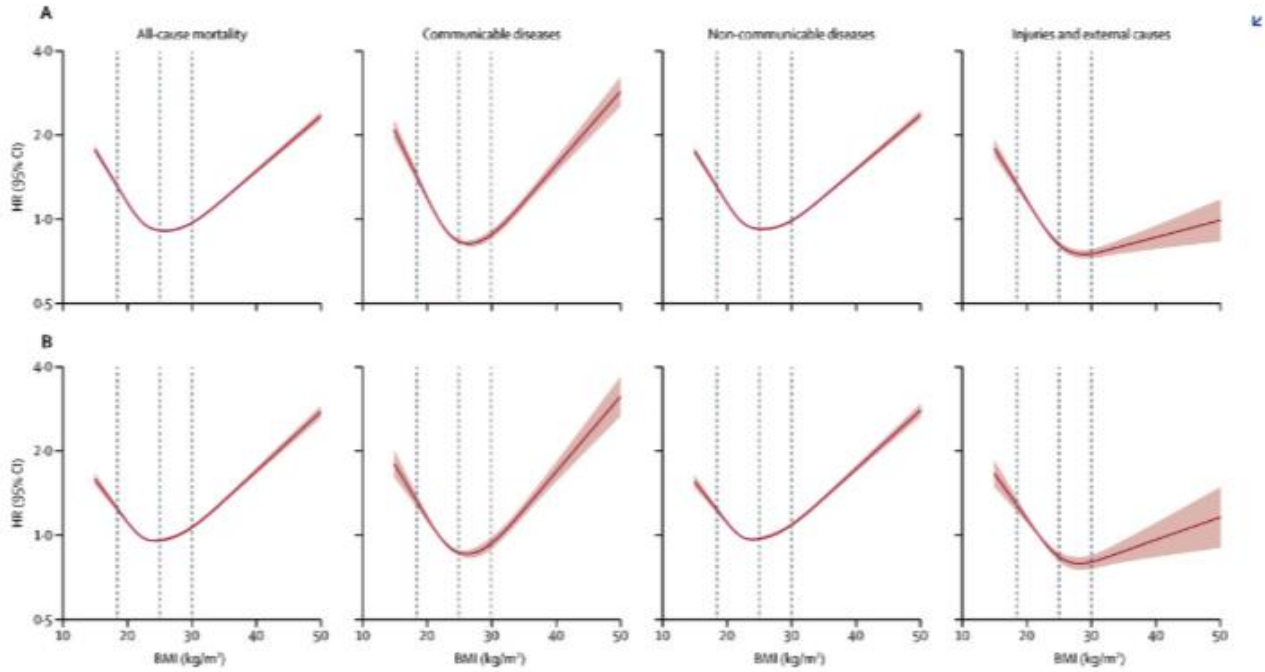


Fig. 7.2 All-cause mortality and cause-specific mortality outcomes in total study populations (A) and in never-smokers only (B).

Fig. 7.3 BMI and the risk of disease Source: UKbiobank data (2018), **Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK** Bhaskaranet al.
The Lancet Diabetes & Endocrinology, Volume 6, Issue 12, 944 - 953

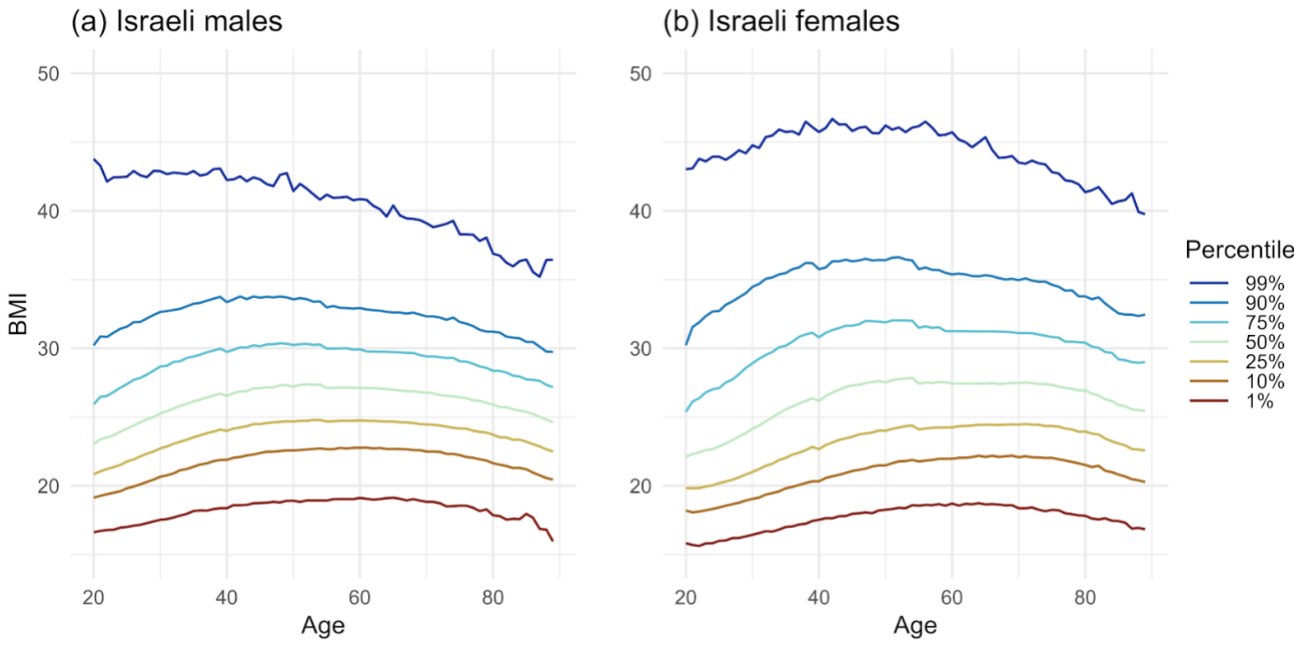
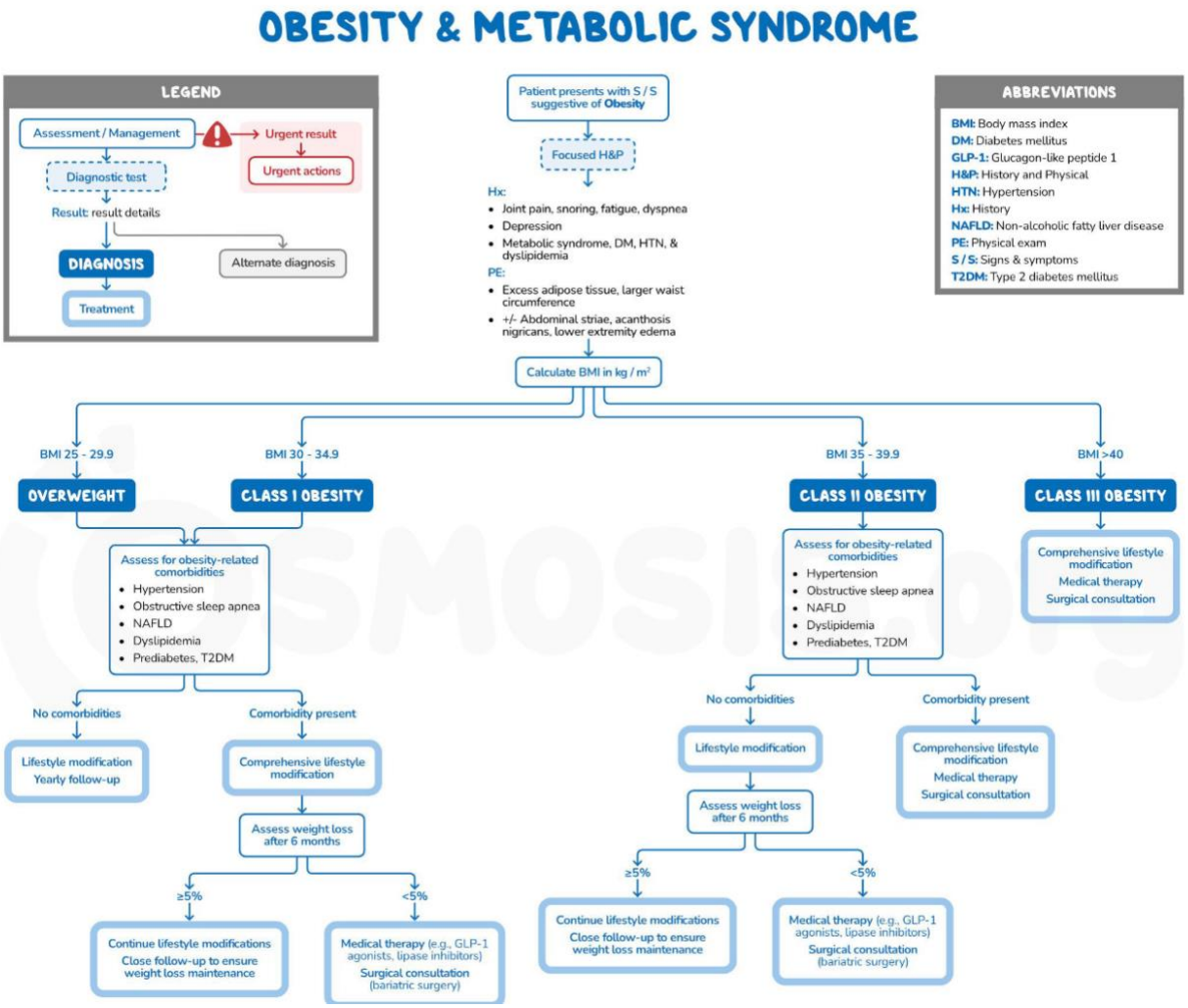


Fig 7.4 BMI data for the Israeli population from the Clalit HMO dataset. Source: doi: 10.1038/s43587-023-00536-5

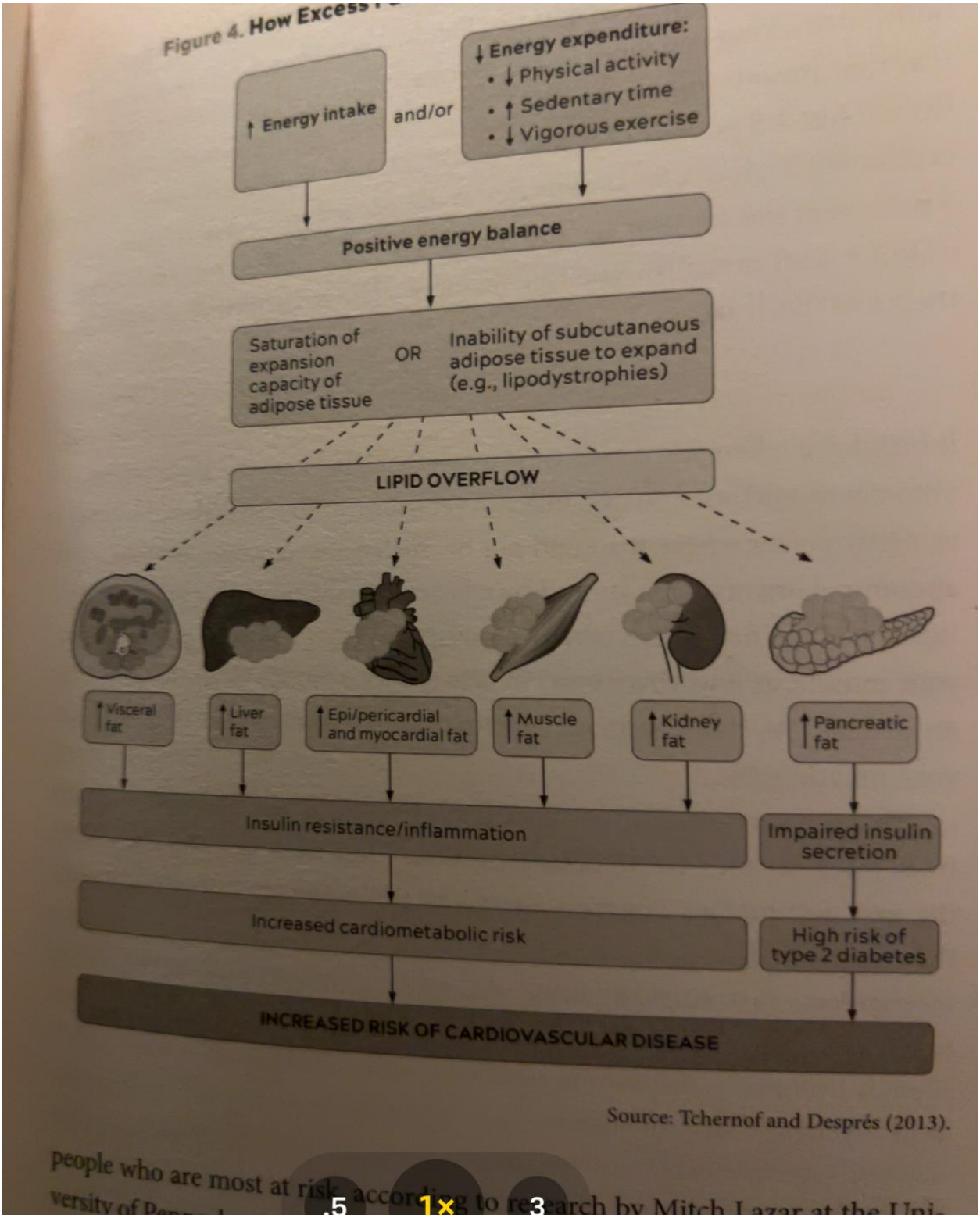


notes to self(Peter Attia) Metabolic disorder- more details: We have 5g of glucose in our blood - that's about a teaspoon. This is maintained by the liver producing glucose and storing it and by insulin enhancing the storage of glucose in the fat and muscle. Just a little bit more- 7g of glucose- means diabetes- a teaspoon and a half- emphasising the precision of this feedback controller
Muscle (mostly) and liver can store 1600 calories in glycogen- after about 2h of vigorous exercise it's used up and we "hit a wall" which is not pleasant.

Subcutaneous fat is healthy storage. But it has a carrying capacity (90k calories) . Generally people of Asian descent have lower carrying capacity. When the carrying capacity is exceeded fat is stored in inner organs as visceral fat. It is inflammatory and triggers insulin resistance.

People with low carrying capacity (thin with metabolic disorder) have 3 fold mortality risk; obese people without metabolic syndrome are generally healthy. It is metabolic syndrome more than being overweight that is crucial to address.

Insulin resistance begins when fat carrying capacity is approached and fat is stored between muscle cells and then within them. Beta cell mass grows to supply More insulin. Insulin causes more glucose into fat cells and thus more visceral fat (cortisol the stress hormone also enhances visceral fat- so stress and lack of sleep enter here)- inflammation leads to more insulin resistance/ Insulin is all About fat storage. High insulin also promotes cancer, atherosclerosis (leading to heart disease) and dementia including Alzheimer. Pancreatic visceral fat eventually leads to loss of insulin production (as does glucotoxicity) and then insulin-dependent type 2 diabetes. That's why metabolic syndrome is often upstream to the other three horsemen (even though diabetes itself is "only" killer number 7)



Source : Peter Attia outlive

Three approaches to reduce calories (dieting) - restricting calorie number, composition or feeding time

All diet strategies use one of these three or a combination- calorie restriction CR,dietary restriction DR and time restricted dressing TRF

Caloric restriction - counting calories - is hard for most people. It is very efficacious for weight control for those that can pull it off (e.g. athletes), but CR is not effective in the sense that it is unsustainable for most of the population.

Caloric restriction increases lifespan across the tree of life

In the field of longevity, caloric restriction is not only for dieting - some people consider and even practice it for lifespan extension even if their (original) weight is normal. It'simportant to say there is no good evidence this extends life in humans, and there is good reason to think that severe underweight is bad for health.

The reason for the allure of caloric restriction is it increases the lifespan of animals kept in lab conditions. Here, restriction is usually defined as reduction of 20% or more in caloric intake while keeping all essential nutrients.

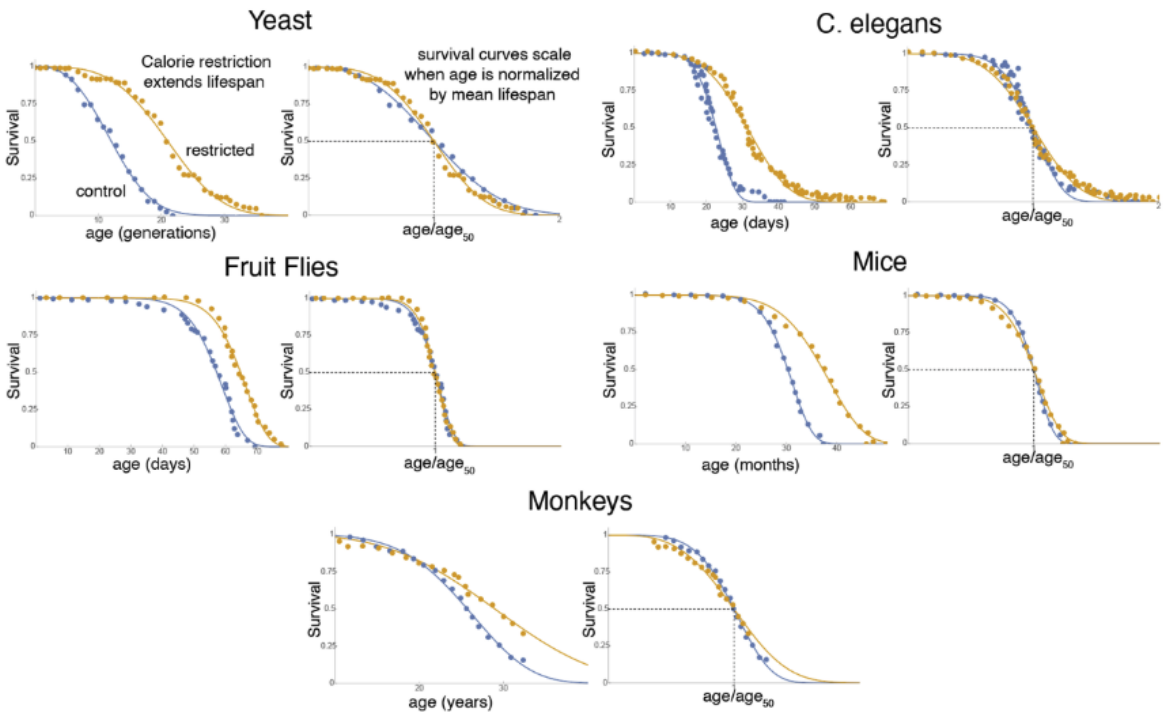


Fig 7.4 Caloric restriction increases lifespan with scaling of survival curves in different species. Adapted from (Conn's Handbook of Models for Human Aging (Second Edition) Chapter 19)

This experiment has been repeated many times, showing lifespan extension in worms, flies, mice and even yeast (growing on synthetic medium with 0.5% or 0.05% glucose instead of rich YPD medium). It also extended life in one of two long-term studies on monkeys.

Notably there's a trend where the longer lived the animal, the smaller the percent life extension.

Caloric restriction shows survival curves that collapse nearly onto the same curve when age is normalized by median lifespan (Fig 7.4).
As mentioned in the last lecture, the shape of the survival curve gives us clues about mechanisms- houses, trucks ,Xc and noise all change the shape in characteristic ways.

The SR model provides the scaling property to an excellent approximation only for perturbations that affect the houses - the production rate parameter η (Figure 7.5 A). Reducing η lengthens lifespan but preserves the shape of the survival curve. Median and maximal lifespan extend by the same factor. Mathematically, lowering eta effectively stretches time like a rubberband (since eta multiplies t in the equations).

The rate of house production has two parts- building houses and garbage production per house. It's the latter that caloric restriction affects (we know that from shift experiments between normal and restricted diets in mid life flies, where the hazard changes immediately - changing the rate of house production would only change the hazard slope).
Caloric restriction is indeed thought to reduce the rate of damage production by slowing down the 'rate of living' so that there is less metabolic activity. It also shifts the cells into increased (in-house) repair and recycling. This should reduce the rate of toxicity per house, reducing η.

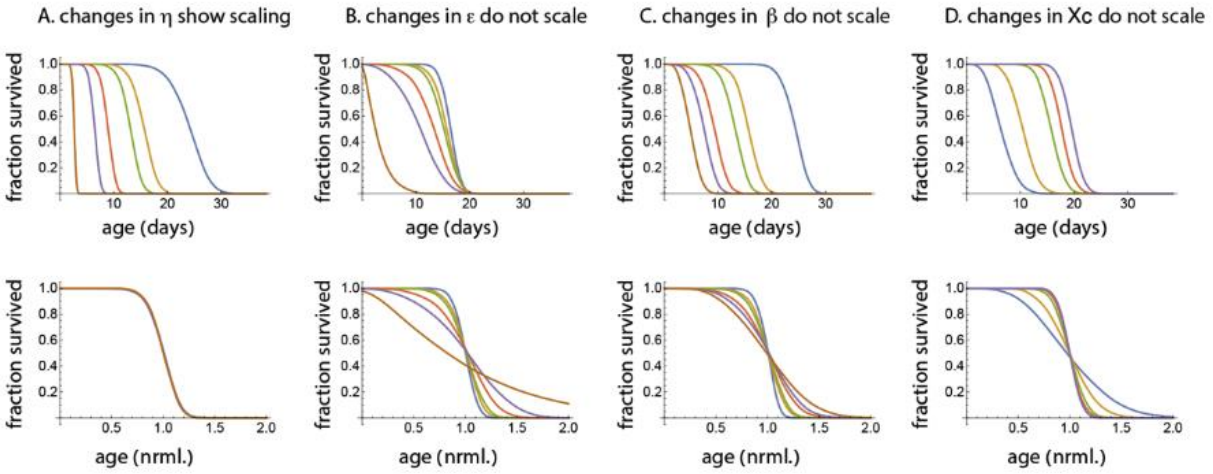


Fig 7.5 Scaling is found in the saturating removal model upon changes in damage production slope, but not changes in other parameters, the removal rate, noise, or death threshold XC

The evolutionary reason that cr extends life across organisms is a tradeoff between reproducing when food is plentiful, and waiting when food is scarce. Like Herman Hesse's character Siddhartha who has learned to meditate, wait and starve, an advantage over the other hungry men who come to town and take the first job they find.

The pathways for the effects of caloric restriction include the IGF1 pathway. Lifespan extension by mutations in this pathway, such as daf-2 mutations in worms, were among the first life-span-extending mutations found, as you can read in the history by pioneer aging researcher Cynthia Kenyon (Kenyon 2011). These mutations shift the entire survival curve to longer lifetimes but maintain its shape showing scaling (Fig 7.6). Similar longevity and scaling is seen in IGF1 mutations across organisms. Even human centenarians are enriched for mutations that lower IGF1 or its receptor (Barzilai, age later book). Calorie restriction does not extend the lifespan of these mutants further- indicating that the igf1 pathway mediates the effect of CR.

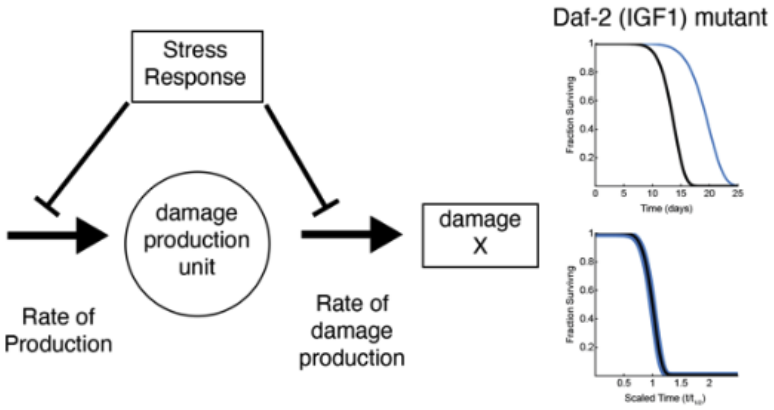


Fig 7.6 Inhibiting the IGF1 pathway affects production of damage, increasing lifespan with survival-curve scaling.

Interestingly, there is no scaling in the SR model when a perturbation affects other parameters, such as removal rate β (Fig 7.5 C). Thus, there is no scaling when the trucks are affected. When removal rate β is increased - more trucks - the model predicts that lifespan increases and the survival curve becomes steeper. The reason for the steeper curve is that damage has a shorter half-life due to faster removal, and thus there is less time for noise to randomize things. Survival becomes more deterministic, and organisms die at more similar times.

Mathematically, adding trucks makes the curve shift to the right parallel to itself as if the same number of years are added to both median and maximal lifespan. An intuitive explanation is that in the SR model when damage is high and trucks are saturated, the equation is approximately $dx/dt = \eta t - \beta = \eta(t - \beta/\eta)$, and a change in beta to $\beta + \Delta\beta$ is thus like a shift in t to $t - \Delta\beta/\eta$. A change in threshold Xc causes a more severe steepening, changing median lifespan much more than maximum lifespan. High threshold affects early deaths making them much more unlikely. High Xc makes less of a difference to old deaths since damage rises quickly at old ages.

Similar steepening effects are found with changes in noise epsilon, which changes the slope but has minor effects on median lifespan. The lower the noise the steeper the survival curve as the dynamics become more deterministic.
Thus the SR model suggests that caloric restriction In longevity experiments works on the houses primarily.

Dietary restriction means not eating certain foods

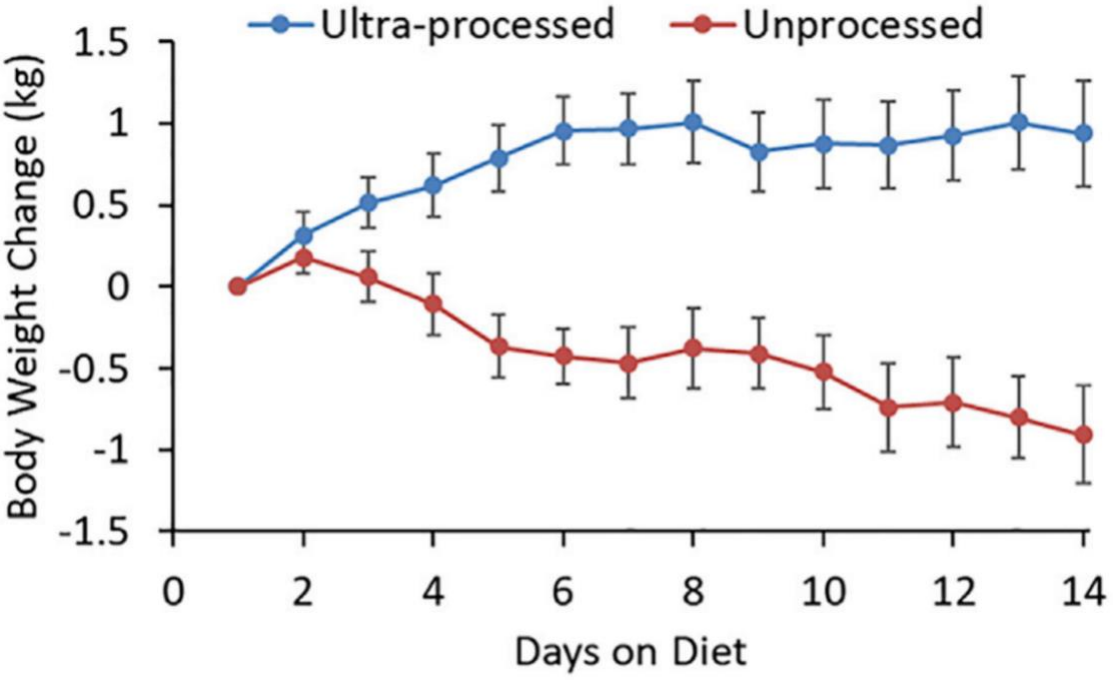
Dietary restriction means avoiding certain foods. Most diets are in this category. The idea is that not eating certain foods will reduce calories. There is experimental evidence that it is important not to eat ultra-processed food (junk food), because it increases hunger. Also sugar and other simple carbs increase hunger. It is good to eat enough protein - about 1g/kg of body weight (no evidence for benefit of double or triple that amount as advocated sometimes), and to do resistance training so as not to lose muscle mass with age.

A case in point is the monkey caloric restriction experiments performed since the 80s by two groups. One study found life extension, the other did not. The two groups published a joint paper discussing the differences in the studies. The main difference is the type of food: Wisconsin feed had 28% sugar in ultra processed commercial monkey feed. Here CR extended life and health compared to controls that eat as much as they wanted (ad libitum).

L In contrast the NIH food had only 4% sugar and the rest of the carbs from whole grains because the food was made in-house from unprocessed products - and this study did not find lifespan extension in caloric restriction. The natural food controls indeed ate 10% less than the Wisconsin junk food controls, since processed food and sugar increase appetite. Sicker controls in the junk food study, which indeed seemed to have more metabolic disorders and cancer, were helped a lot by restricting calories of this food.

This disagreement of two experiments is lucky (they were not designed for this comparison) - it may have taught us that eating less junk food is good; but if already eating at the salad bar there is no need to restrict calories and you'll be fine.

Dietary restriction is effective and prescribed for people with metabolic disorder or other conditions, restricting carbs, saturated fats and eating lots of fiber, vegetables. Together with exercise and enough protein, muscle mass can be preserved as well. In fact early type 2 diabetes can be reversed by lifestyle changes, though few can pull this off.


Ultra-processed
Unprocessed
Body Weight Change (kg)
1.5
1
0.5
0
-0.5
-1
-1.5
0
2
4
6
8
10
12
14
Days on Diet

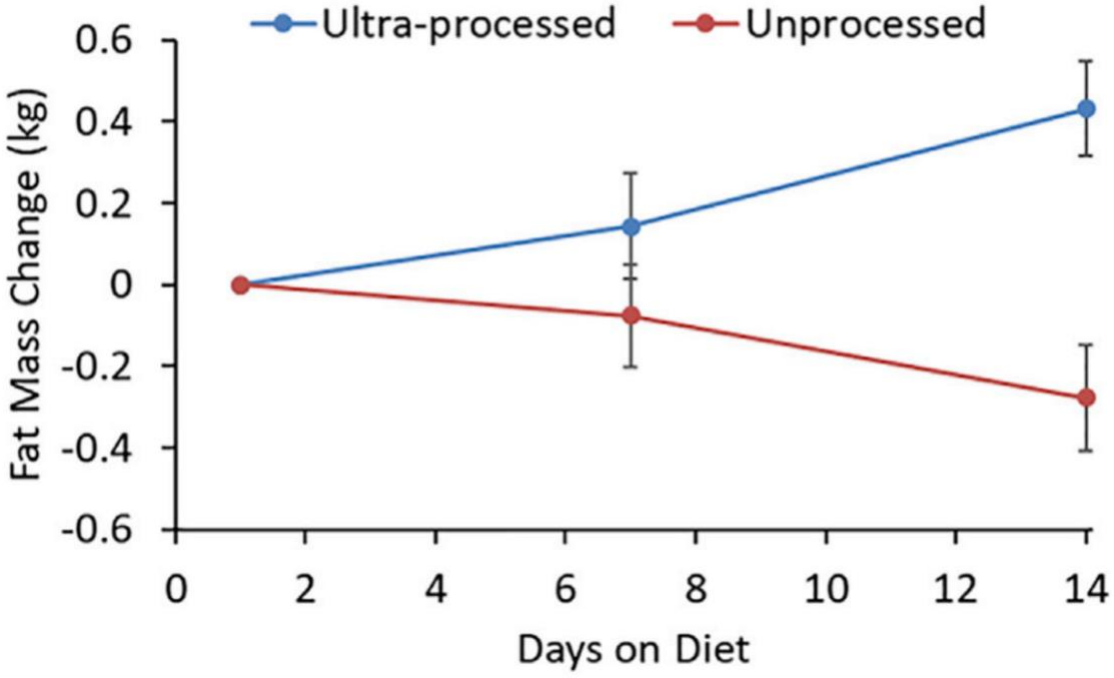

Ultra-processed
Unprocessed
Fat Mass Change (kg)
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
0
2
4
6
8
10
12
14
Days on Diet

Fig 7.7 An example of a clinical trial which investigated whether ultra-processed foods affect energy intake. 20 weight-stable adults, aged (mean ± SE) 31.2 ± 1.6 years and BMI = 27 ± 1.5 kg/m2 were admitted to the NIH Clinical Center and randomized to receive either ultra-processed or unprocessed diets for 2 weeks immediately followed by the alternate diet for 2 weeks. Meals were designed to be matched for presented calories, energy density, macronutrients, sugar, sodium, and fiber. Subjects were instructed to consume as much or as little as desired. Energy intake was greater during the ultra-processed diet (508 ± 106 kcal/day; $p = 0.0001$), with increased consumption of carbohydrate (280 ± 54 kcal/day; $p < 0.0001$) and fat (230 ± 53 kcal/day; $p = 0.0004$), but not protein (-2 ± 12 kcal/day; $p = 0.85$). Weight changes were highly correlated with energy intake ($r = 0.8$, $p < 0.0001$), with participants gaining 0.9 ± 0.3 kg ($p = 0.009$) during the ultra-processed diet and losing 0.9 ± 0.3 kg ($p = 0.007$) during the unprocessed diet. Limiting consumption of ultra-processed foods may be an effective strategy for obesity prevention and treatment. Source: https://pubmed.ncbi.nlm.nih.gov/31105044/

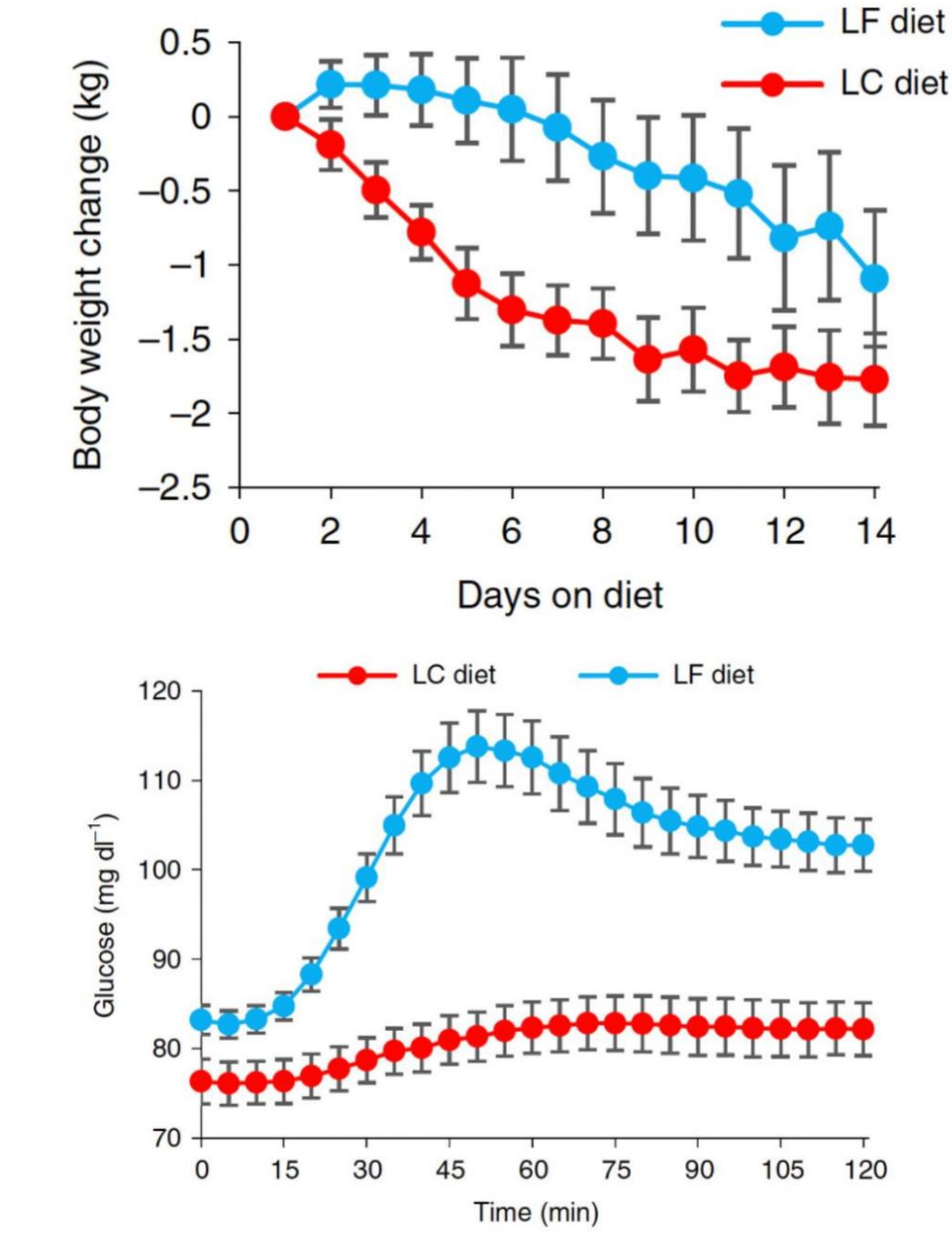


Fig 7.8 a clinical trial showing how mLow carb (keto) diet lowered weight and improved glucose response compared to low fat plant based diet. The carbohydrate–insulin model of obesity posits that high-carbohydrate diets lead to excess insulin secretion, thereby promoting fat accumulation and increasing energy intake. Thus, low-carbohydrate diets are predicted to reduce ad libitum energy intake as

compared to low-fat, high-carbohydrate diets. To test this hypothesis, 20 adults aged 29.9±1.4 (mean±s.e.m.) years with body mass index of 27.8±1.3kgm−2 were admitted as inpatients to the National Institutes of Health Clinical Center and randomized to consume ad libitum either a minimally processed, plant-based, low-fat diet (10.3% fat, 75.2% carbohydrate) with high glycemic load (85g1,000kcal−1) or a minimally processed, animal-based, ketogenic, low-carbohydrate diet (75.8% fat, 10.0% carbohydrate) with low glycemic load (6g1,000kcal−1) for 2 weeks followed immediately by the alternate diet for 2 weeks. One participant withdrew due to hypoglycemia during the low-carbohydrate diet. The primary outcomes compared mean daily ad libitum energy intake between each 2-week diet period as well as between the final week of each diet. We found that the low-fat diet led to 689±73kcald−1 less energy intake than the low-carbohydrate diet over 2 weeks ($P<0.0001$) and 544±68kcald−1 less over the final week ($P<0.0001$). Therefore, the predictions of the carbohydrate–insulin model were inconsistent with our observations. This study was registered on ClinicalTrials.gov as NCT03878108. Source: https://doi.org/10.1038/s41591-020-01209-1.

Time-restricted feeding does not have much evidence in humans yet

A current fad is to restrict feeding time to 8h so 16h are spent fasting, or even 6/18 or 4/20 schedules with longer fasting periods. This has shown efficacy in animal models, but strong data in humans to my knowledge is lacking. It's probably easier to maintain than counting calories for most people.

It is quite plausible that eating at night is bad for metabolic health. This is due to the circadian clock which makes beta cells secrete less insulin in response to glucose at night than in the morning, and other adaptations that make eating at night less metabolically favourable. According to this it is better to eat your carbs at breakfast.

Now let's dive into how to control fat mass. We begin with the puzzle of how weight stays so nearly constant over decades?

The weight setpoint circuit

Weight song (Streets of london)

Have you ever wondered how our weight stays nearly constant
Give or take 5 kilos
Over decades it's the same
Of course there are exceptions, there are times we fluctuate
But overall it seems that there's a setpoint for our weight

So if you want to know the answer
And you have a curious mind
Let me take you by the hand and walk you through the leptin circuit
I'll show you you something that may help you understand

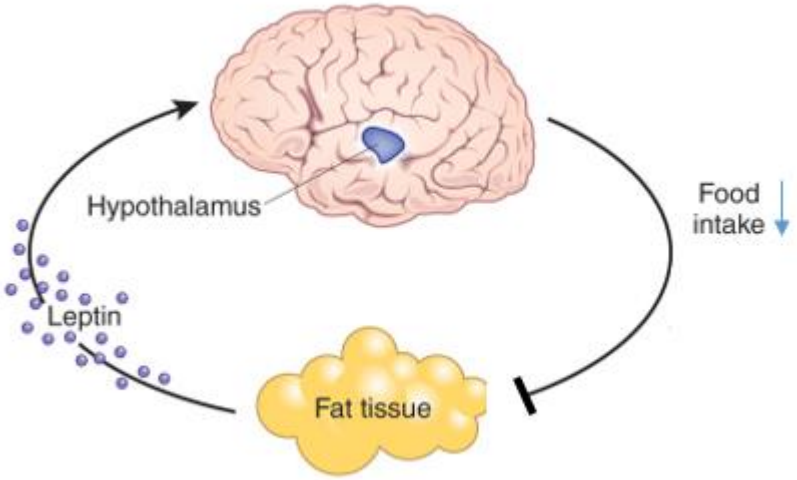
Leptin and weight control

It seems we have a weight setpoint. I weighed about 85 kilos from age 25 to age 53. Where is this weight setpoint written down in our body? For a setpoint, we need to *exactly* balance our energy intake and energy expenditure, which is remarkable given that we eat about a million calories per year.

Weight control is an important basic question of biological control, and an example of more general principles of homeostatic feedback. It is also a major health concern. Overweight is growing in the world, including children. In 2016, more than 1.9 billion adults aged 18 years and older were overweight. Of these over 650 million adults were obese. The worldwide prevalence of obesity nearly tripled between 1975 and 2016. And the most recent twist is the emergence of safe drugs against obesity- glp1 receptor agonists and its friends- which turn out to have many health benefits.

What causes obesity and overweight?

The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. Globally, there has been an increased intake of energy-dense ultra processed foods that are high in fat and sugars (junk food); and an increase in physical inactivity due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization.



No discussion of weight is complete without talking about dieting. When we diet we lose weight, but when we stop the diet, we overeat and return to the setpoint. We will understand why in this lecture.

Human beings have a weird effect that if you diet for 6 months or more, you start to regain weight despite the diet and go about halfway back to where you were before.and when diet is stopped people sometimes go to a higher weight than before the diet. Part of this is due to loss of muscle mass, where diets typically lose fat and muscle mass in a 2:1 ratio.

So we need to consider the weight set point, how it arises and how it changes.

Weight is controlled by feedback loops whose general idea is: the more you eat, the more signals that reduce appetite and food seeking behavior (Fig. 2).

One of the basic feedback loops was discovered when obese mice mutants were studied. These mice eat voraciously and have 250% more fat mass than normal mice. It turned out they were missing a hormone called **leptin**, or were missing the receptor for leptin.

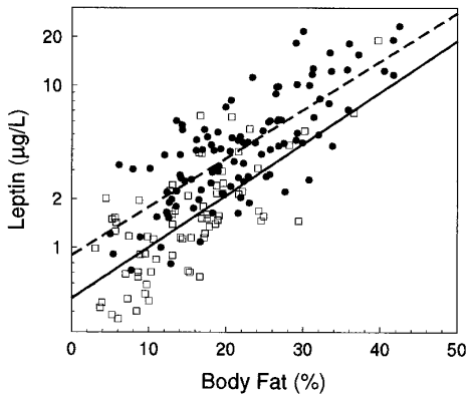
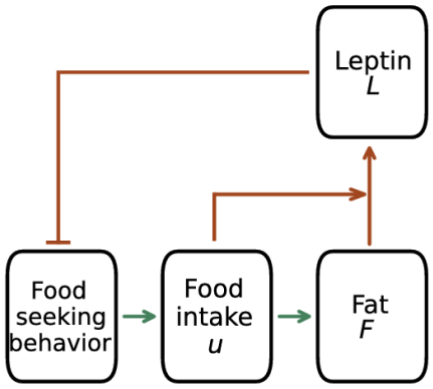


Fig 7.9 Leptin rises quadratically with body fat.

Leptin is a hormone - a molecule made by one organ and secreted to the blood to affect other organs. Leptin is predominantly produced by white adipose tissue (the scientific name for fat) and secreted into the circulation. Leptin regulates metabolism and appetite by inhibiting food intake, lowering body weight and increasing metabolic rate. Circulating leptin levels grow about quadratically with body fat percentage and body mass index (BMI) (Fig. 3). Leptin also responds to acute changes in energy balance: fasting decreases leptin levels and feeding increases leptin levels. Obese people have high circulating leptin levels suggesting decreased sensitivity to leptin, which is referred to as leptin resistance.



So this feedback loop specifically controls the amount of fat (Fig. 4). Fat cells used to be considered as simple containers for fatty acids, a storage depot that can deploy fatty acids for use as fuel for the body in times of need. The discovery of leptin promoted fat to the status of an endocrine organ- a smart organ capable of communicating with the brain. We now know that there are many other such adipokine hormones talking with other organs.

The way that leptin acts in the brain is, like most questions about the brain, largely shrouded in mystery. Leptin interacts with neurons in the hypothalamus, a brain region we will see is like the body's thermostat that integrates many signals to keep our physiology balanced.
In this lecture we will elegantly sidestep the brain by discussing this feedback loop in a graphic analysis based on two curves that can be readily measured experimentally.
We will also avoid the complications of human psychology and culture linked to weight, and begin with data from rodents - mice and rats.

The leptin feedback loop evolved because it is important for fat amounts to be kept under control. Too low fat levels make the organism vulnerable to starvation. Too low fat levels also prevent

reproduction. On the other hand, too much fat makes the organism prone to predation. There is a sweet spot in the middle, and the job of the feedback loop is to maintain that sweet spot.

To understand the feedback loop, we break it down into two arms. One arm is how eating raises fat, the other is how fat reduces eating. We then unleash these two effects together and see how they reach a set point.
The first arm is the way that food affects fat percentage. Suppose we keep an animal on a given amount of food intake, u grams/day. After a few weeks we measure its fat percentage. The more food, the more fat. So we can plot this curve, steady state fat level on an imposed diet of u, on an important plot called a **phase portrait** (Fig. 7.10)**.** The axes are food intake u versus fat percentage F.
This line, which we call the energy line (marked diet line in the figure) intersects the x axis at a minimal food needed to support basic metabolic costs. Below this we go to zero fat - the animals starve to death.
The energy line thus describes the food-->fat arm of the feedback loop.

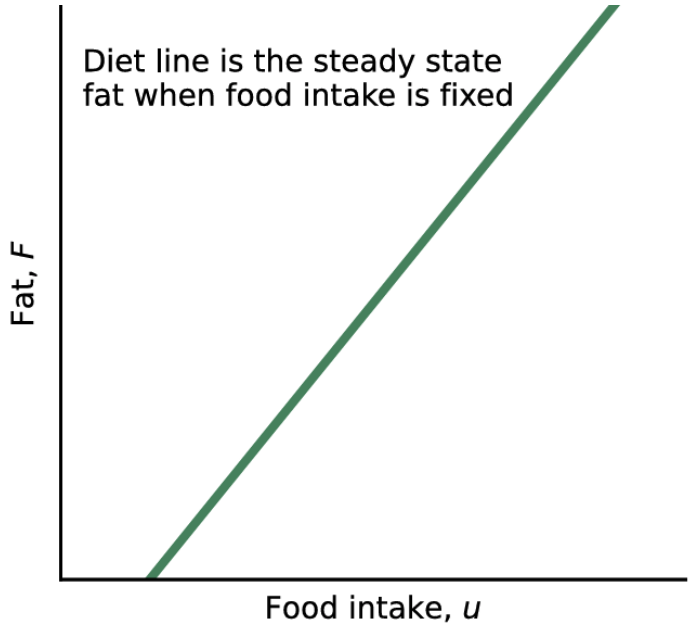


Fig 7.10 The energy line is steady state fat at a given level of food intake. **dF/dt = 0,.**

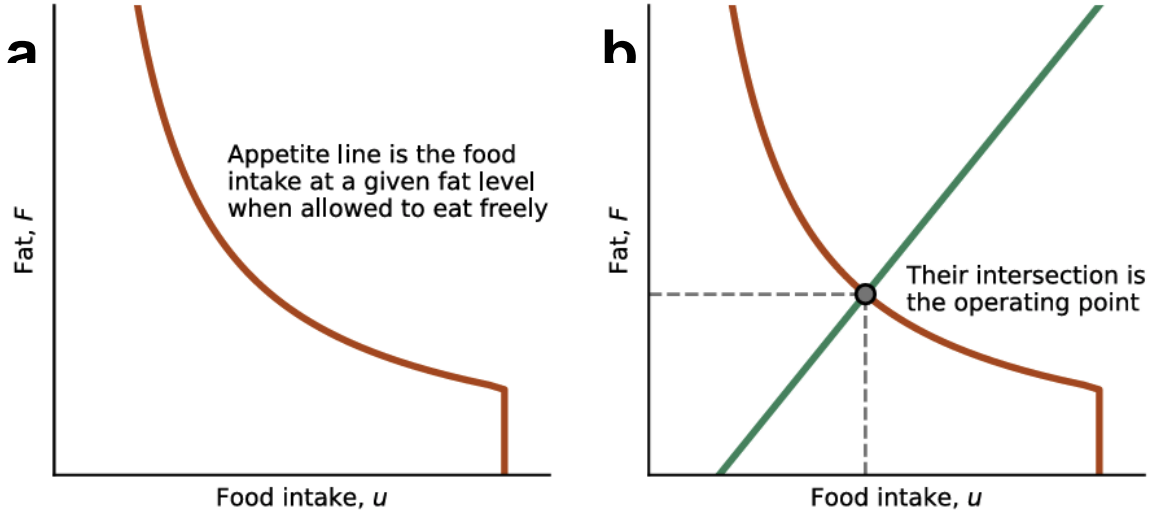


Fig 7.11 a) The appetite line du/dt = 0,is the steady-state u levels when F is constant. **b)** Intersection of the two lines is the set point..

The second arm describes how fat inhibits food seeking behavior, namely fat--|food, where --| is our symbol for inhibition. We'll call this the **appetite line** (Fig. 7.11A)**.**

Experimentally, we start with an animal that has a fat level F, perhaps reached after a specific diet. We then let it eat as much and as often as it wants over a 24h period, technically called eating *ad-libitum*. The more fat, the more leptin, and thus the smaller the appetite, and the less the animal eats. Plotting this on the phase plane we have a decreasing curve shown in red here.

Now the interesting point to watch is where the two lines intersect. This is the **fat setpoint** (Fig. 7.11B). At this point, the food intake and the appetite match exactly. It defines a steady-state fat level F_{st}, and a steady-state food intake level, u_{st}.

So our concept here is that negative feedback can be broken into two arms. Each arm can be measured by keeping one variable constant and measuring the other at steady-state. In the language of dynamic systems these lines are called **nullclines**, and their intersection is the fixed point, where the system does not change, a set point.

Good order : obesity from eating junk food shifts appetite line, then stomach distention increases shifting umax, and after time leptin resistance. Then glp1. Then exercise. Then hypothyroid and aging. Then dynamics - overshoot.

The dynamics of dieting include an overshoot of eating

Now let's discuss dynamics and dieting. Suppose we diet for a while, eating less than our normal intake u_{st}. The amount we eat is u_{diet}. We move away from our set point. After a few weeks, fat drops to a new steady state fat F_{diet} which is lower than our normal fat setpoint. We know what F_{diet} is from the energy line - after all we are enforcing the diet without regard for the appetite line. That is how the energy line is defined in the first place. Great. What happens when we stop dieting?

To understand this we need the concept of **separation of timescales.** The two processes, weight gain and appetite, have very different timescales. Fat changes over weeks, much more slowly than appetite which happens over the course of a day. Leptin changes over a timescale of an

hour. So after we stop dieting, and allow ourselves to freely eat, our intake in the next 24h will be determined by our current fat level as per the appetite line. Because fat is low after the diet, appetite is higher than our setpoint. We eat more than we used to before the diet- we overshoot. That day we gain a bit of fat so that the next day we are a little fatter. Our appetite drops accordingly, crawling along the appetite line. We crawl along the appetite line until we return to the setpoint (Fig. 7.12). We can say the set-point is defended by the feedback loop against changes. It is globally stable.

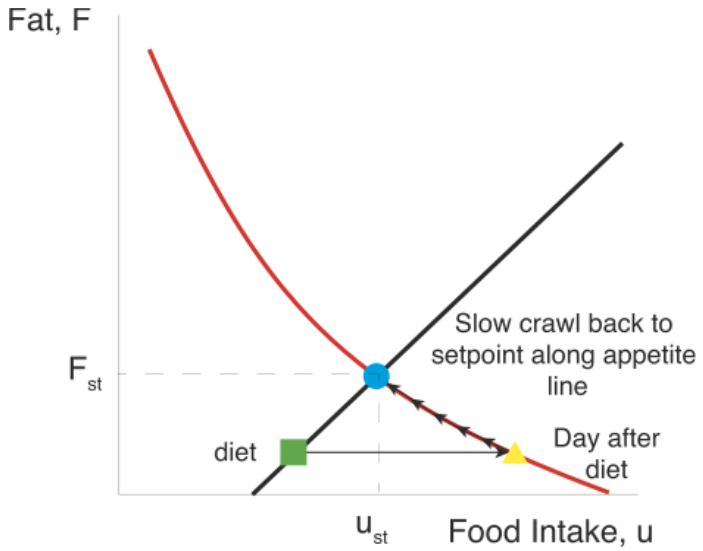


Fig 7.12 Dynamics of dieting show overshoot of intake when diet is stopped

To see this in a different way, we can plot our food intake as a function of time to see the overshoot and then return to baseline food intake (Fig. 7.13). Fat rises monotonically and slowly back to its baseline level.

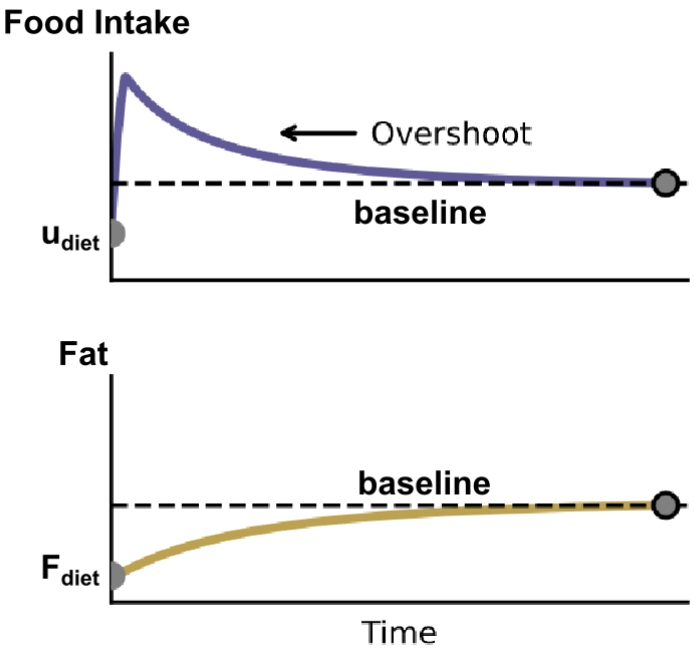


Fig 7.13 After dieting, food intake overshoots before returning to baseline.

After the diet there is an overshoot in eating, and then food intake crawls back to baseline. Fat drops slowly during the diet, then climbs back slowly to the setpoint after the diet is over. This is exactly what is seen in experiments.
The phase portrait can also show us what happens when instead of a diet, we overfeed the animal for some time, as in tube feeding experiments. After overfeeding is stopped, and the animal can eat freely, there is an undershoot in food intake. And this is what is seen in experiments on rodents. We use separation of timescales extensively in this course. It is nature's gift to theorists.

Physical exercise shifts the setpoint

Let's use our phase portrait to analyze some interventions. We start with exercise (Fig. 7.14). Exercise increases the metabolic rate due to activity (e.g. running 10Km uses about 700 calories), and builds lean body mass, namely muscle. The extra muscle burns more energy even when we rest. This affects the energy line: if we keep an animal on a certain daily food intake, and let it run on the wheel, it will have less fat than an animal without a wheel. Thus chronic exercise shifts the energy line downwards. In fact it shifts it to the right as we will see later.
The set point- the crossing point of the appetite and energy lines - also shifts. It shifts to less fat but more food intake. Eat more and lose fat. And that is precisely what happens when rats are given a running wheel: they lose 30% fat and eat 20% more!
In fact, any intervention that moves the energy line will have a paradoxical effect in which eating and fat move in opposite directions. For example in hyperthyroidism, when we have too much thyroid hormone, our metabolic rate is too high- heart beats fast and we feel hot. A common symptom is ‘I eat more but I'm losing weight’. This is because the energy line shifts in a way similar to exercise.

The opposite condition, hypothyroidism in which there is too little thyroid hormone (a common disease causes this in about 2% of the human population mostly in women), metabolism is

slowed. There is often constipation and sensitivity to cold. The diet line shifts up (opposite of exercise). There is a paradoxical effect where we gain weight despite having lower appetite.

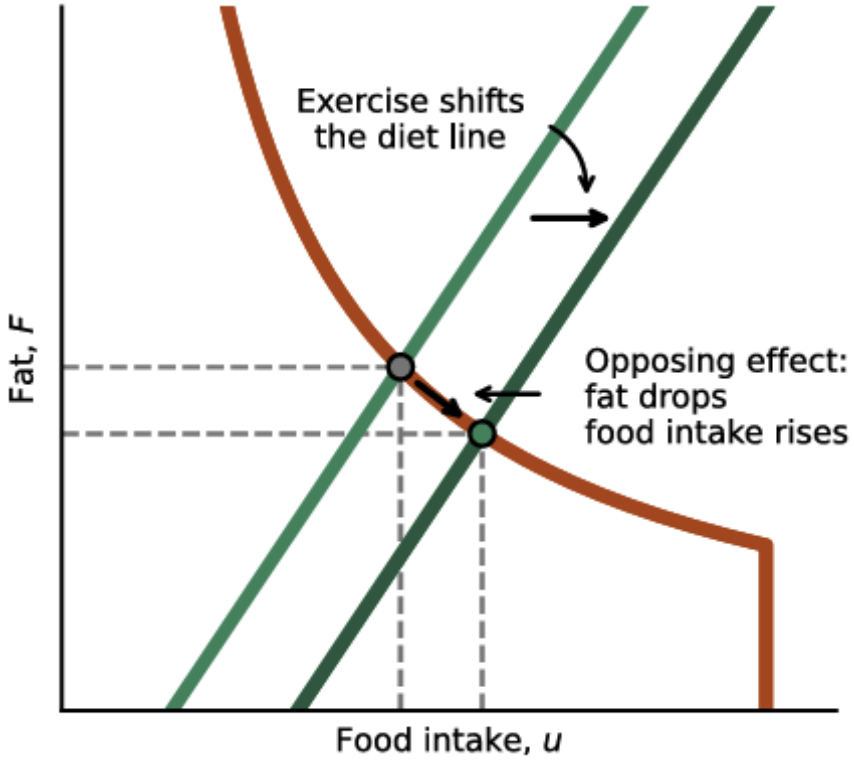


Fig 7.14 Exercise shifts the diet line.

Obesity is due to a shifted appetite line caused by leptin resistance

What happens when we shift the other line, the appetite line? This can happen when leptin works less effectively, a phenomenon called leptin resistance (Fig. 7.15). Leptin is a hormone, a molecule that flows in the blood. It is sensed by its target cells, mainly neurons in the brain, by nanometer sized sensors called **receptors**. Receptors are proteins that stick out the cell across its membrane. They can bind a specific molecule like a lock and key, and activate processes inside the cell.

Leptin is sensed by the leptin receptor on specific neurons. Each Of these neurons has tens of thousands of leptin receptors. The effect of leptin depends on its concentration, the higher the concentration, the more receptors it binds on the cell surface. The more lepin-bound receptors, the more they affect the brain to reduce food seeking behavior. Plotting the output, food seeking behavior, as a function of leptin concentration gives us a decreasing curve. Its halfway point is at a leptin concentration denoted K_L, the binding coefficient of the leptin receptor.

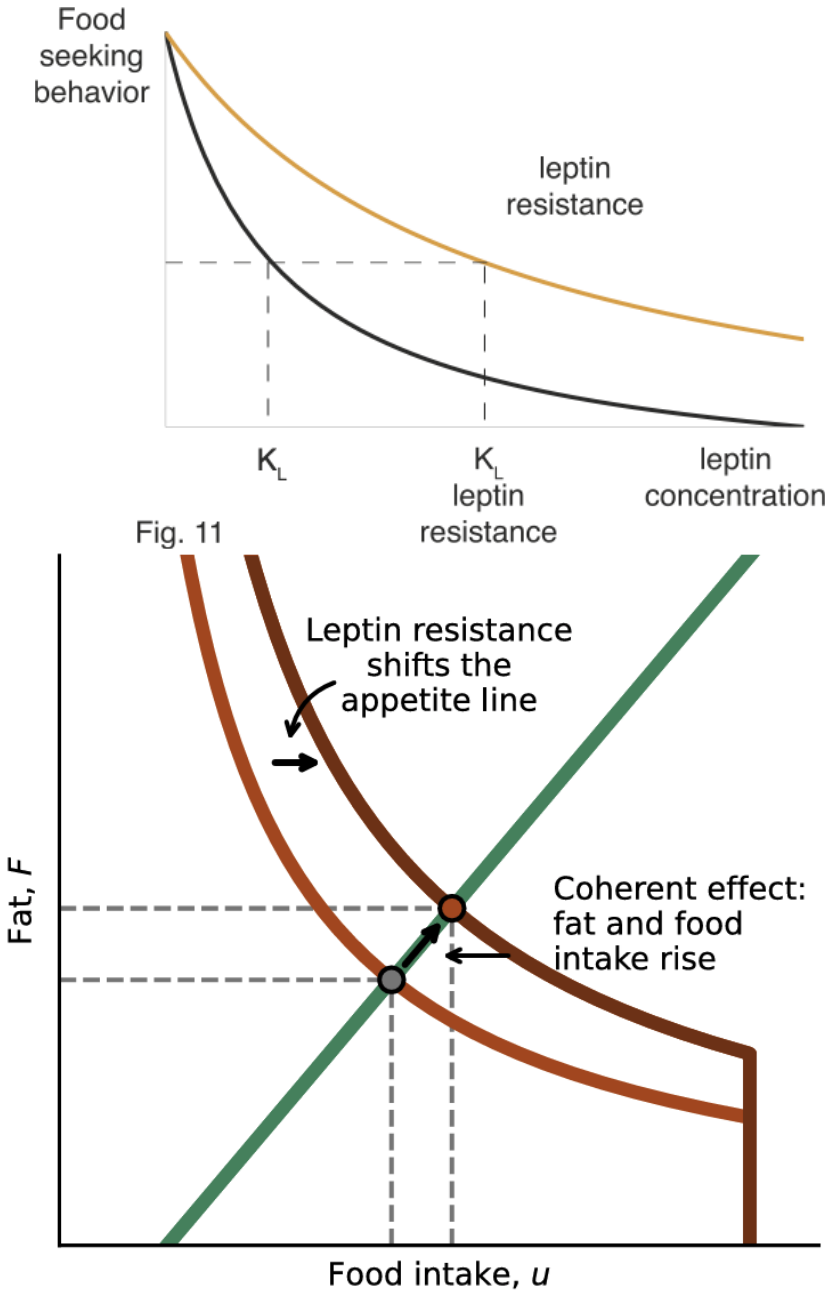


Fig 7.15 Leptin resistance.

For reasons not fully clear, people can develop leptin resistance. Their K_L rises, and it takes more leptin to have a given effect. Each unit of leptin, the buzz-kill for food, is less effective. Since leptin is secreted by fat, this means that at a given fat level, appetite is higher. The appetite line shifts to the right (Fig.7.15).

One physiological role of leptin resistance is during healthy pregnancy, where it causes increased appetite in the mother to supply the fetus.

Notice the effect on the weight setpoint. Both food intake and fat increase. This is what is seen in leptin-resistant rodents. In fact, when the leptin receptor is mutated and made dysfunctional, which is the ultimate resistance, the animal is 250% of its normal weight.

In general, any perturbation that affects the appetite line will have a coherent effect on eating and fat: both rise or both fall. This is in contrast to shifting the energy line which has opposite effects on fat and eating. The difference is due to the upward and downward slope of the lines. Thus, seeing the effects on eating and fat can help diagnose an intervention to see which nullcline it affects.
Another rule concerns overshoots: changes in the appetite line cause overshoots in food intake similar to the effect of stopping a diet we saw above(Fig 7.13). Changes in the energy line do not. That is why stopping Ozempic causes an overshoot in eating.
Leptin resistance was a source of disappointment for researchers and clinicians who originally hoped that leptin would be a good treatment for obesity. When leptin is injected to obese mouse mutants who can't make leptin, the mice lose weight dramatically. Similarly, in very rare human patients with a mutation in the leptin gene (congenital leptin deficiency, CLD found in about 100 people on earth) leptin injection is a life-saving treatment: individuals with CLD eat huge amounts of food and have morbid obesity and immune problems, which leptin injections resolve. However, for the vast majority of obese people, leptin has almost no effect due to leptin resistance.
Some perturbation can shift both lines, for example High levels of hormones like estrogen. This can cause effects like rise in fat without changes in food intake.

Weight song part 2

So how can I tell you that I lost weight
And I finally fit those jeans?
Yes I know I'll keep those brown sacks
Pretty soon I'll gain those pounds back
It's a cycle that never really ends.

Mathematical analysis of the energy line
So far we used a graphic approach, with the phase portrait and the energy and appetite lines. In this course we back up our graphical approaches with equations. The reason is that equations can help you ask new questions, and make more precise predictions. The equations we will use are the simplest ones that capture the essence of the system; many details with more minor effects are ignored for the sake of understandability.

So let's write an equation for the control of fat mass by food intake- an equation for the diet line. Fat mass F is increased by food when fatty acids are stored in fat cells. The cells get bigger. Fat mass is reduced when fatty acids are secreted from the fat cells, in order to supply the body with fuel. Thus fat mass is a balance of storage and of use for the body's energy needs. The rate of change of fat, dF/dt obeys

dF/dt=(fat gain from food) - (fat removal for the body's energy needs).

The rate of fat gain from a food intake of u grams/day is $\alpha_F u$. The parameter $\alpha_F$is the rate of fat production from a gram of food, and depends on the type of food - $\alpha_F$is higher for food rich in fat, for example, than for low-fat food. The rate of fat removal has two parts: there is the energy cost of the body, for muscles needed to breathe and digest, and the functions of the liver, brain, kidneys and other organs, denoted γ_E. This is like unconditional love - it's unconditional energy expenditure just because you exist.

Incidentally, the organs use energy in the following order: liver (30%), brain (20%), muscle (20%), kidneys (10%), heart (10%) others (20%).
Together with this **basal metabolic rate** (BMR) when the body is at rest, about 2000 Kcal/day, we can add the energy needed to move and exercise. The exercise cost is usually smaller than

the BMR, for example as mentioned above 10Km run costs about 700 Kcal. BMR is high in children and drops with age, becoming roughly constant from age 20-50, dropping again at ages above 50 (Fig. 13).
The second part of the energy cost is the metabolic cost of fat itself, which is proportional to the amount of fat $\gamma_F F$. Putting this all together we obtain:

$$dF/dt = \alpha_F u - \gamma_F F - \gamma_E \quad (1)$$

To calculate the energy line, recall that we fix food intake (eg by imposing a diet) and we wait until steady-state, which means until fat stops changing. Steady-state thus means zero rate of change, namely that dF/dt=0. Solving (1) at steady state, $dF/dt = 0 = \alpha_F u - \gamma_F F - \gamma_E$, provides an equation for fat as a function of intake u, the diet line:

$$F = \alpha_F/\gamma_F \, u - \gamma_E/\gamma_F$$

The Energy line

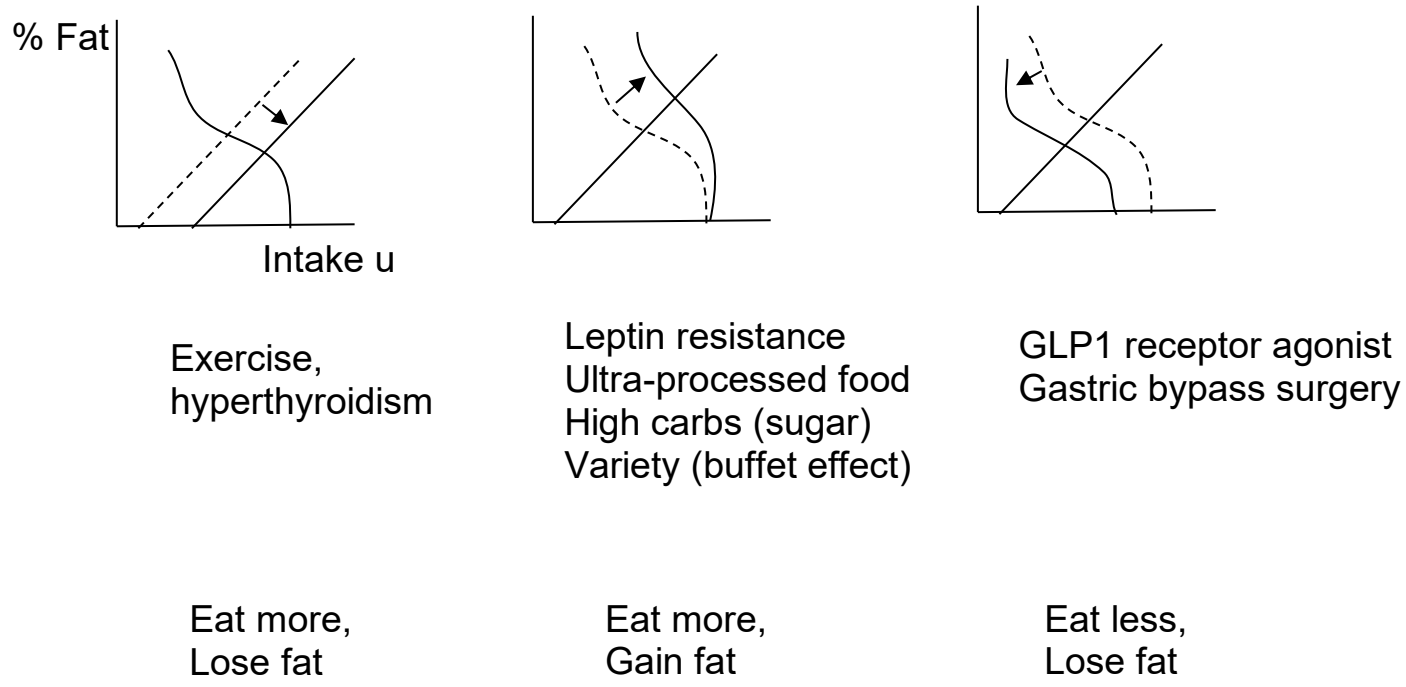


Fig 7.16 The energy and appetite lines can help understand different interventions. In these sketches, interventions move one of the lines from
Its original dashed state to a new state as denoted by the arrow.

This is a straight line that has slope α_F/γ_F. It intersects the x axis at a point where food intake balances the energy cost γ_E, namely $u = \gamma_E/\alpha_F$. Thus, if we exercise, we increase the energy cost γ_E, the intersect point gets larger (moving the line to the right) but the slope doesn't change. The shifts just as shown in Fig. 14.
Interestingly, switching to high-fat food (increasing α_F) increases the slope of the diet line and pushes the intersect point to the left, making the diet line steeper. The weight setpoint rises to

higher fat. Makes sense- fatter food, you get fatter. But to understand the set point completely means we need to think also about the appetite line. How does it shift? Does high-fat food affect it too? What about exercise? To understand this, we need to have an equation also for the appetite line. For these and other weighty questions, stay tuned.

Weight song part 3

So what can we do if we can't diet,
And we don't have a weight loss pill*?
Exercise and eat good food,
and maybe walk the golden path:
accept your setpoint,
and learn to love your weight.

*I wrote this lyric around 2021 before GLP1 receptor antagonists (**Ozempic**) for weight loss became the world's 5th top selling drug.

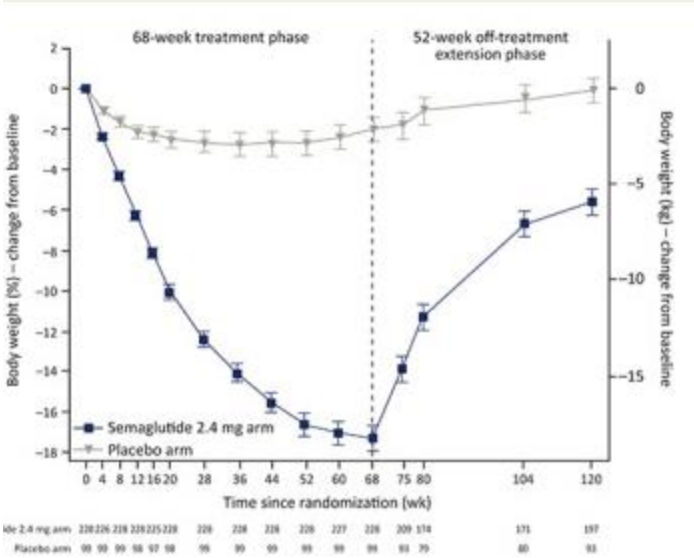


Fig 7.17 Ozempic (semaglutide) has become a widely used drug since 2021, clinical trial shows loss of more than 15% body weight in a year, with weight gain once the drug is stopped. Source:Wilding 2022 PMID: 35441470. Recent studies suggest that tapering rather than stopping abruptly can reduce the weight rebound effect.

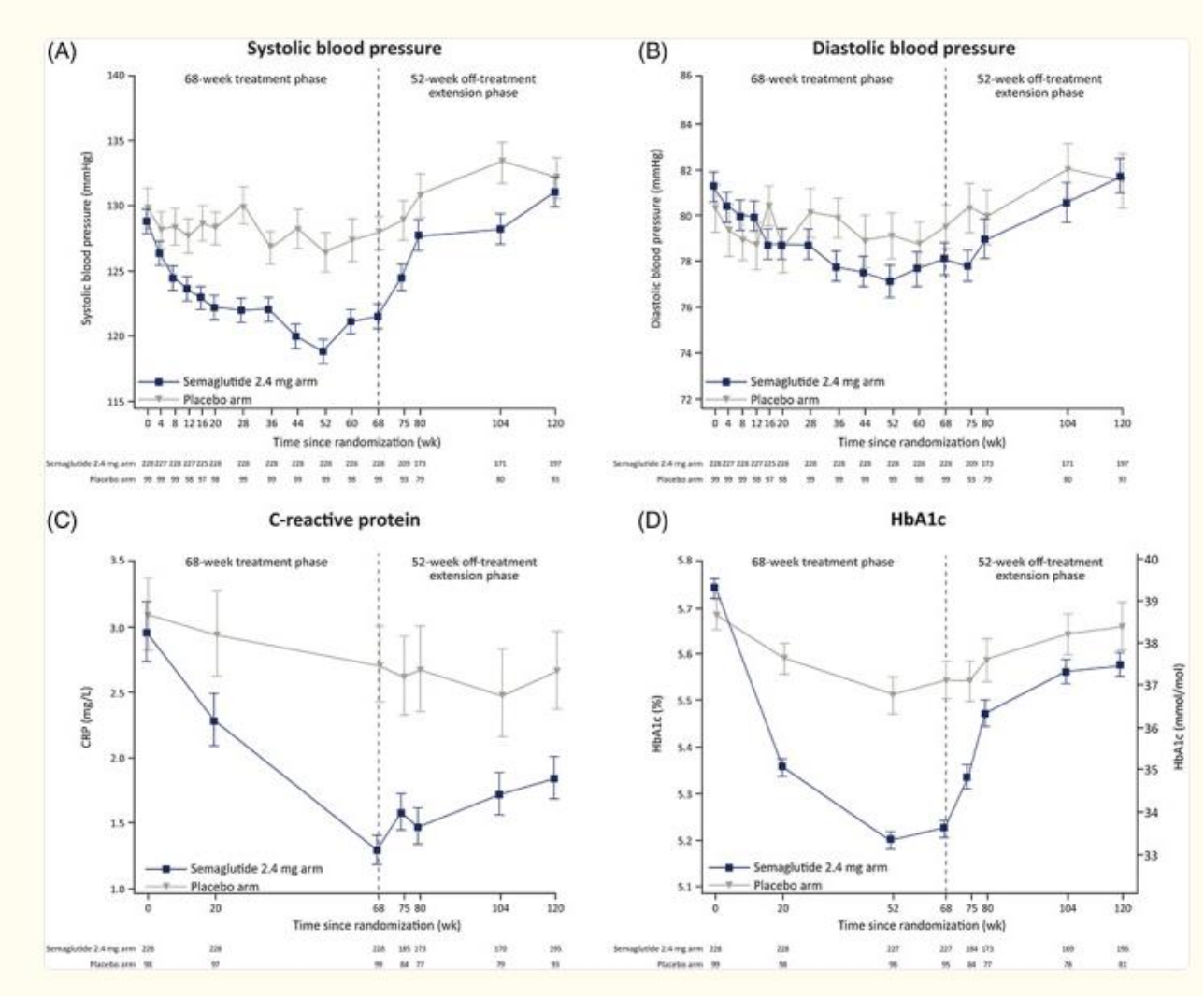


Fig 7.18 Ozempic treatment improves blood pressure, inflammatory marker CRP and blood glucose marker HbA1c, with gains lost once treatment stops.

nice deep sigh of relief

A glimpse into how we work with models and experimental data

The content of this part on the weight setpoint is research from my lab (Bar 2023). It started with PhD student Omer Karin, and the torch was taken up by PhD student Alon Bar, who got inspired to compare the model to data from rats. This is how we do research on physiology- write minimal models, compare them to a century of experiments that were usually done for other reasons. We also compare the models to large medical datasets. When possible, we test the theory with new experiments.

Alon Bar considered the rat feeding experiments of Ruth Harris, Thomas Kasser and Roy Martin (1986) . The experimenters aimed to find how body composition (fat, proteins) changes when feeding changes. Their temporal data is so precise it can be reused for our purposes here. When rats were put on 40% of their normal diet for a few weeks, they lost fat mass (Fig. 1). This

restrictive diet was then stopped, and the rats were allowed to eat ad-libitum (freely). At first they ate more than normal (overshoot), and every day ate less and less until they returned to their normal fat and food intake.
Conversely, when overfed by tube feeding at 160% of their normal food intake, they fattened (Fig. 2). After tube feeding was stopped, the rats ate less than normal (undershoot) and gradually returned to their normal weight and food intake.

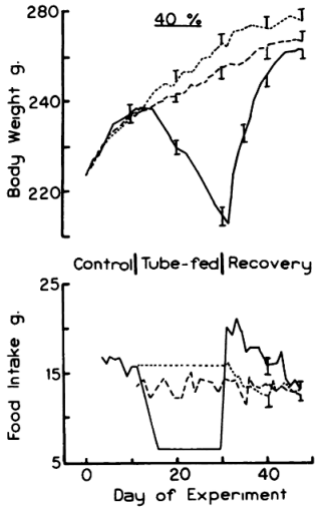


Fig. 1 Rats weight and intake dynamics at 40% food restriction

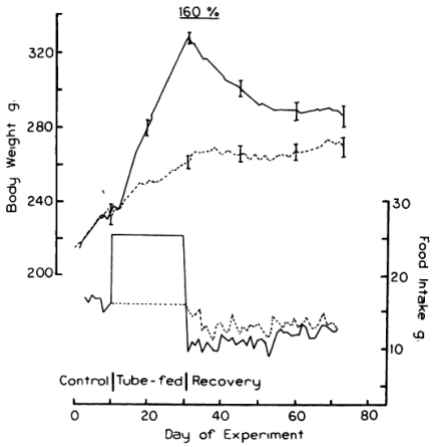


Fig. 2 Rats weight and intake dynamics at 160% food overfeeding

The experiment thus has two parts: forced feeding, and then recovery. The forced feeding part can be used to test and calibrate the energy line. The recovery provides the appetite line.
We can get the energy line from the steady state fat in the different conditions. Let's draw the data on a phase portrait of food intake u versus fat F. Rats restricted to 40% of normal food intake (u=6g/day) end up with almost zero fat. This is one point on the diet line. Rats overfed to 160% their normal intake reached fat of about 2.5 times higher than normal. This is another point on the diet line. It looks pretty much like a straight line as expected.
The appetite line can be seen directly from the recovery trajectory. After underfeeding is stopped, mice overshoot to eat about 20g per day, about 30% higher than their normal intake of 15g/d. They then slowly over weeks trace out a line in the phase portrait as they lose fat and eat less, until approaching the normal level.
After the overfeeding condition, rats eat less, about 10g/day. They drop rapidly in fat but keep eating about the same, which gives the nullcline a concave shape that drops vertically in this region, before starting to eat less and converging back to the setpoint. We gain a nice

experimental picture of the diet and appetite lines (Fig. 3).

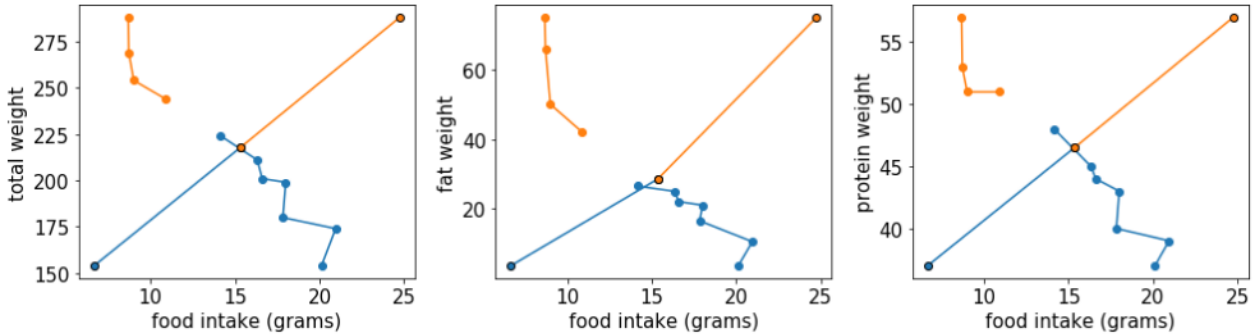


Fig. 3 experimental construction of the diet and appetite

Equations for fat determine the rate of dieting

Above we wrote down an equation for the rate of change of fat, a conservation equation for bioenergetic balance: fat changes due to food intake, metabolic costs, and the cost of fat itself:

$$(1)\ dF/dt = \alpha_F u - \gamma_E - \gamma_F F$$

. Solving this at steady state yielded the energy line:

$$(2)\ F_{st} = \alpha_F/\gamma_F\, u - \gamma_E/\gamma_F$$

Namely steady-state fat when u is constant.

nice deep sigh of relief

How quickly does fat reach its steady state? We can solve Eq (1) over time. This is a solution of an ordinary linear differential equation, which is always of the form

$$F(t) = Ae^{-\gamma_F t} + B$$

To make sure this is really a solution, we take the time derivative dF/dt, to find Eq 1 back again. We can determine A and B by making sure that $F(t)$ starts at its initial condition $F(0)$ at $t = 0$, and ends up at F_{st} at infinite time. To do so, note that at $t \to \infty$, the exponent goes to zero $e^{-\gamma_F t} \to 0$, so that $B = F_{st}$. When t=0 the exponent is $e^{-\gamma_F 0} = 1$and thus $A = F(0) - F_{st}$. We obtain therefore:

$$(3)\ F(t) = (F_{st} - F(0))(1 - e^{-\gamma_F t}) + F(0)$$

This solution compares well with the experiments of Harris et al (Fig. 4).

From this comparison we can find the rate at which fat changes- how long do I need to diet if I'm a rat before I get halfway to the steady state? The half-life for fat, as always in a differential equation like this, is determined by the constant that multiplies the variable- on our case F, namely γ_F. The $\gamma_F$parameter has units of $1/time$, and indeed the half-life which has units of time is proportional to $1/\gamma_F$. To find it precisely, we need to find when $e^{-\gamma_F t_{1/2}} = 1/2$,which, when taking log of both sides, results in:

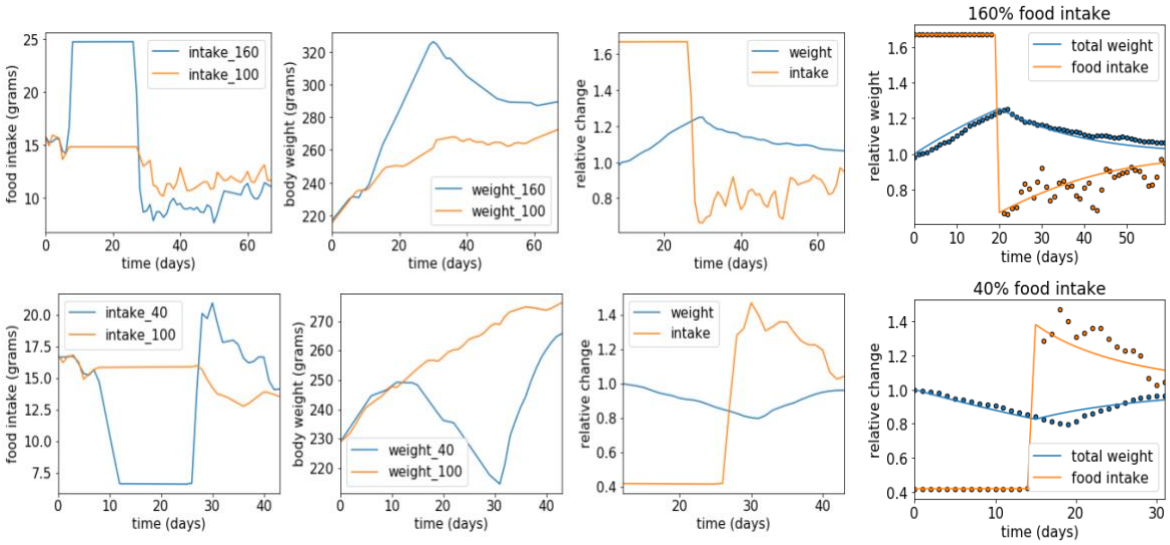


Fig. 4 Daily food intake and weight dynamics of rats constrained to 40% or 160% daily food intake. Data is normalize to relative change from control group.

$$(4)\ t_{1/2} = ln(2)/\gamma_F \quad \textbf{fat half-life}$$

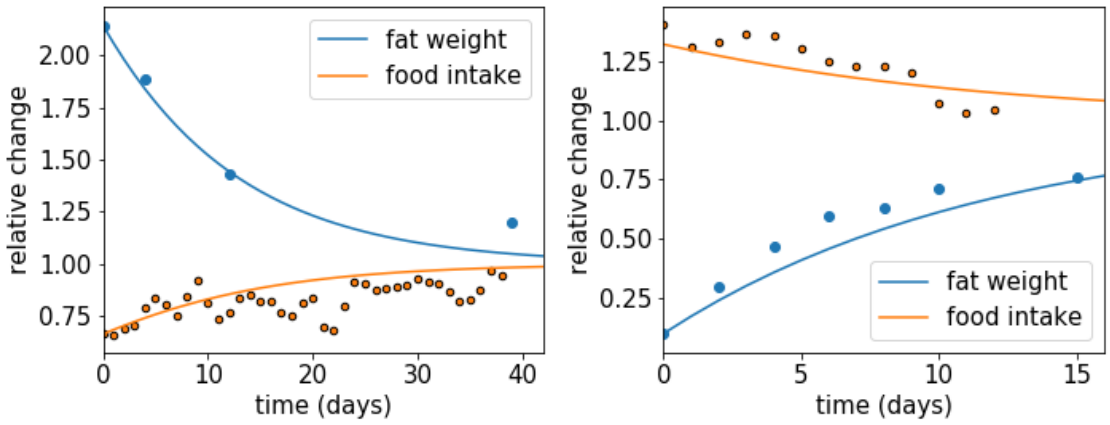


Fig. 5. Fat recovery to steady state dynamics

Since the fat half-life depends only on γ_F, and not on the initial or final fat levels, we can see that the half-way time from one steady state to another steady state is always the same. This applies to loss or gain of fat.
Our differential equation, Eq 1, describes the rat data very well (Fig. 5). The timescale for changes in fat shows a half-life in rats of about 10 days, giving $\gamma_F = 0.07\ d^{-1}$.

Mathematical model for the appetite line
Lets next consider the appetite line. This is slightly harder than the diet line, but hopefully we will be fine.

nice deep sigh of relief

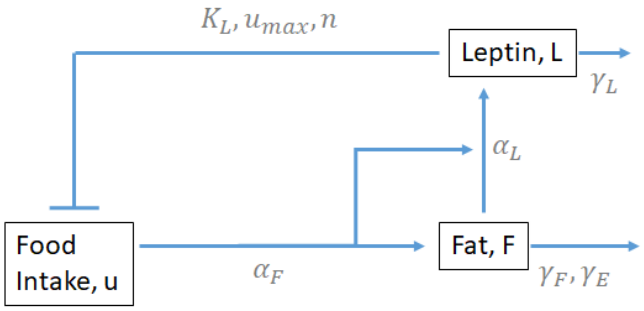


Fig. 6 Leptin hormone circuit controls food intake and weight

OK. Appetite is controlled by leptin (Fig. 6). Leptin, L, is secreted by fat at a rate enhanced by food intake[1] . For example, in starvation for a day, less leptin is secreted by a given amount of fat than during a fed state, which is a great way to make the animal eat more when it is starved.

Since leptin production rate grows with both fat and with food intake, it can be modeled as a product of fat mass F times food intake u , with a rate parameter α_L placed in front: $\alpha_L \boldsymbol{u} \cdot F$. Leptin is removed by clearance in the kidney, which gives each molecule of leptin a removal rate γ_L, making a total removal of $\gamma_L L$molecules per unit time. The difference between production and removal gives an equation for the rate of change of leptin:
(5) $dL/dt = \alpha_L \boldsymbol{u} \cdot F - \gamma_L L$

The removal of leptin is rapid, with a half-life of about 40 minutes. As always, leptin half-life is determined by the removal parameter γ_L, so that $ln(2)/\gamma_L \sim 40min$. Leptin dynamics are thus much faster than the fat dynamics which change over many days. We can therefore safely assume that leptin is at steady-state, $dL/dt = 0$, which is again a use of the principle of separation of timescales.

Plugging in dL/dt=0 to Eq 5, we find $L = \alpha_L \boldsymbol{u} \cdot F/\gamma_L$. To get leptin as a function of fat, we can use the diet line (Eq 2) to express food intake u in terms of F. This shows that at steady-state, leptin rises with fat:

$$L = \alpha_L / \boldsymbol{\alpha_F \gamma_L} (\boldsymbol{\gamma_F F} + \boldsymbol{\gamma_E}) \cdot F$$

Now for a simplification to make our life easier. Except at very high fat levels, we can ignore the $\boldsymbol{\gamma_F F}$ term in the parentheses, to a good approximation, because most of the metabolic cost comes from the basal metabolic rate due to the lean mass $\boldsymbol{\gamma_E}$, and not from the cost of fat $\boldsymbol{\gamma_F F}$. This approximation results in a linear dependence of leptin on fat:

$$(6)\ L = \alpha_L \gamma_E / \boldsymbol{\alpha_F \gamma_L} F = a\, F$$

nice deep sigh of relief

Now we are ready for the appetite line. Food intake is suppressed by leptin, as we saw. This inhibition has a halfway effect when leptin concentration is K_L. Thus, the appetite, defined as the

[1] How food intake controls leptin secretion is unclear. For experts: it seems not to be due to post-meal rise in insulin, but instead to be more related to average insulin over a few days.

food intake over a day in ad-libitum conditions, can be written as a decreasing function of leptin $u = f(L/K_L)$. Using our linear law for leptin as as function of fat, Eq. 6, we can replace leptin L with $a\ F$:

$$(7)\ u = f(aF/K_L)$$

This is the appetite line.

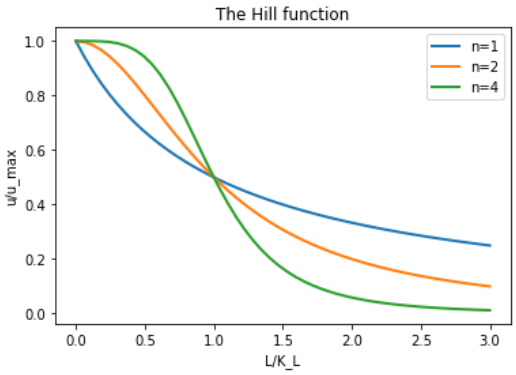


Fig. 7 leptin control of food intake is described by hill function

We can be more concrete by giving a specific form to the function f. As before, we use an excellent biochemical model for the effect of a hormone when binding to a receptor. This is the **Hill function** (Fig. 7), derived in Appendix A, where:

$$(8)\ u/u_{max} = 1/(1 + (L/K_L)^n)$$

The half-way point is K_L, and the steepness is determined by the Hill coefficient n. In this function, when there is no leptin, eating is at its maximal "satiety" value, u_{max}. This maximal satiety is due to stomach distention, hormones like *ghrelin* and *glp1*, and other factors. Our function is a decreasing function since leptin decreases appetite, The more leptin, the less appetite.
Plugging in our expression for L in terms of fat, $L = \alpha_L\gamma_E/\boldsymbol{\alpha_F\gamma_L}\,F$, we can invert the Hill function to write the appetite line:

$$(9)\ F^n = (\qquad)^n(u_{max}/u - 1) \quad \textbf{\textit{the appetite line}}$$

The appetite line is a decreasing function as expected: the more fat the less food intake. It intersects the x-axis at the maximal food intake u_{max}. The appetite line curves at high fat and has a distinctive concave shape. The larger K_L, that is the higher the leptin resistance, the more this curve shifts to the right, pivoting around u_{max}.

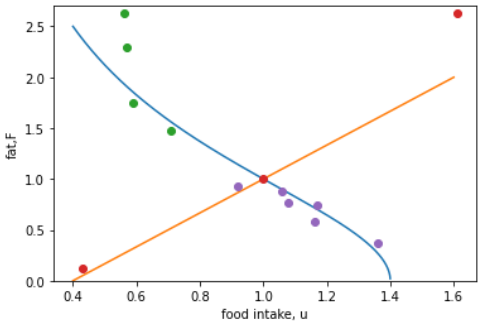


Fig. 8 Rat data compares well with diet and appetite lines

The appetite line has a parameter α which is a combination of parameters for leptin production and removal, and for fat removal and production from food. For example, the appetite line depends on food composition through the parameter α_F.
With the two nullclines in hand, we can compare the model to the experiments on rats when they recover from over- and under-feeding (Fig. 8). The experimental data shows behavior that is similar to the model. The diet line rises linearly and intersects the x-axis at a certain intake rate. The appetite line drops in a curved way.

nice deep sigh of relief

Normalized variables help to reduce the number of free parameters
If we use the rat data and set the normal rat food intake and fat both to 1, we can have a model with fewer parameters.

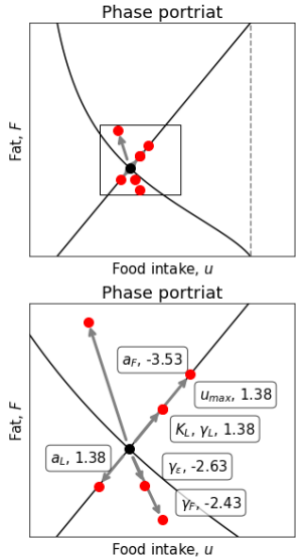


Fig. 9 Analyzing the effect of each parameter on the steady state

The energy nullcline is a straight line that intersects the x axis at u_0=0.4 and goes through (1,1), and thus is

$$(10)\ F = (u - u_0)/(1 - u_0)$$

The appetite nullcline intersects the x axis at u_{max} =1.4, and thus

$$(11)\ F^n = (u_{max}/u - 1)/(u_{max} - 1)$$

These scaled nullclines seem to agree with the rat data, with one free parameter, the Hill coefficient n of leptin action. A value of n=7 gives reasonable agreement.

Difference in weight setpoint between individuals:
Importantly, since different individuals have different parameters, the appetite line and the diet line differ from individual to individual. In humans, such parameters vary with age, especially BMR which is high in children and low after age 50. Our lifestyles, including food quality and exercise levels, also vary. As a result, we each have our own weight set point. The model can now help us evaluate the effects of different parameters and different interventions (Fig. 9). The effects are clearly seen when we draw arrows around the set point indicating the effect of changing each parameter.

Two parameters increase both fat and intake: increase in leptin resistance $\boldsymbol{K_L}$ and in the satiety level $\boldsymbol{u_{max}}$. These parameters shift only the appetite line.
The rest of the parameters shift both diet and appetite lines. Increasing food 'fatness', α_F, the parameter which determines the rate at which food is converted to fat, causes a large rise in fat and a small drop in food intake.
Increasing exercise or metabolic rate raises γ_E, which causes a reduction in fat and an increase in food intake; the relative increase in intake is smaller than the relative increase in fat. This

agrees with experiments in which rodents are given a running wheel, which lowers fat by 30% and increases food intake by 20%. The major parameters that increase weight setpoint are thus: food fatness, satiety, reduced metabolic rate and leptin resistance.

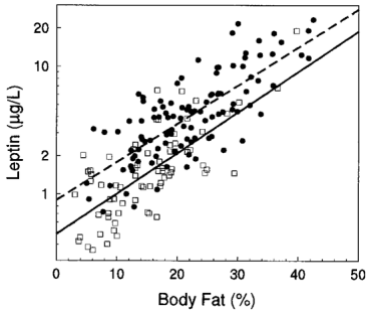


Fig. 10 The relation between leptin and fat across the population is quadratic

Differences in leptin between people: We can go from rodents to humans for a moment, even though the model is not guaranteed to apply precisely. In humans, leptin varies widely between people, and so does percent fat. In fact, leptin goes approximately as percent fat squared, $L \sim F^2$ (Fig. 10). In mice as well, mutants with a dysfunctional leptin receptor (db/db mice) have 250% more fat and 6 times more leptin, matching the square dependence since $2.5^2 \sim 6$. This square dependence seems to contradict a step in our thinking, where we said that leptin goes proportional to fat, not fat squared (Eq 3). This proportionality applies, however, for a given individual with a given set of parameters: twice the fat, twice the leptin.

When comparing different individuals, we need to remember they have different parameter sets. It turns out that variation in one of the model parameters can give the square relation between leptin and fat (Fig. 11). This parameter is $\boldsymbol{u_{max}}$, the satiety point, the maximal food intake. This analysis predicts umax to be a major cause for difference between individual leptin levels. Other factors such as exercise, food quality and basal metabolic rate have important but smaller effects. Thus, treatments that lower $\boldsymbol{u_{max}}$, such as GLP1 hormone receptor agonists (Ozempic) that causes satiety, or surgical treatments such as gastric bypass, are expected to have a large effect on the weight setpoint. And they do indeed.

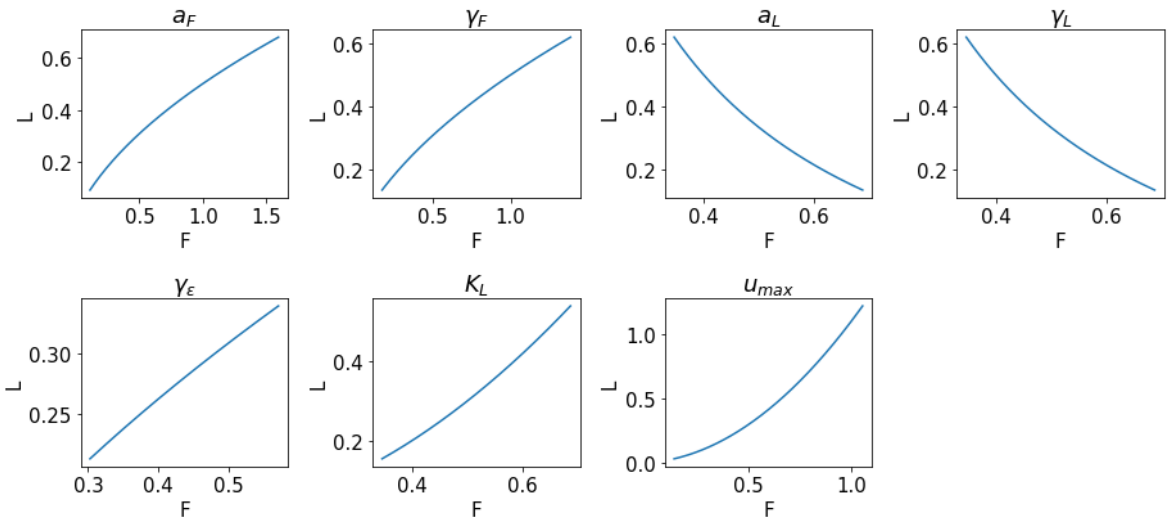


Fig. 11 Fat and Leptin sensitivity to 16-fold change in each parameter

Gastric bypass is surgery that helps you lose weight by changing how your stomach and small intestine handle the food you eat. After the surgery, your stomach will be smaller. You will feel full with less food. The food you eat will no longer go into some parts of your stomach and small intestine that absorb food. (source: wiki)

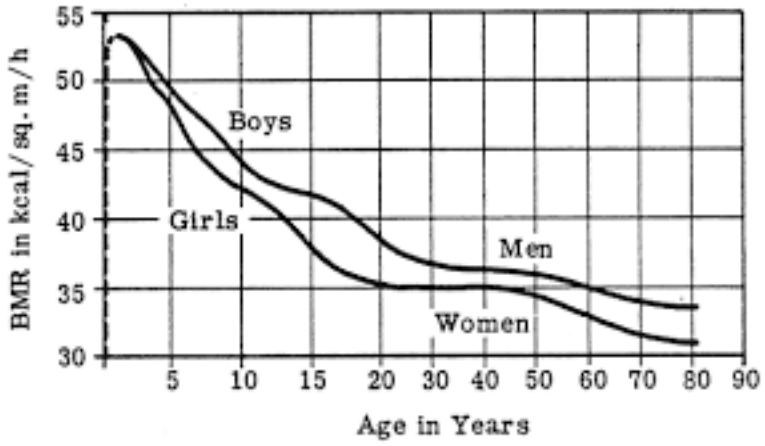


Fig. 12 BMR drops with age over childhood, and again at old age

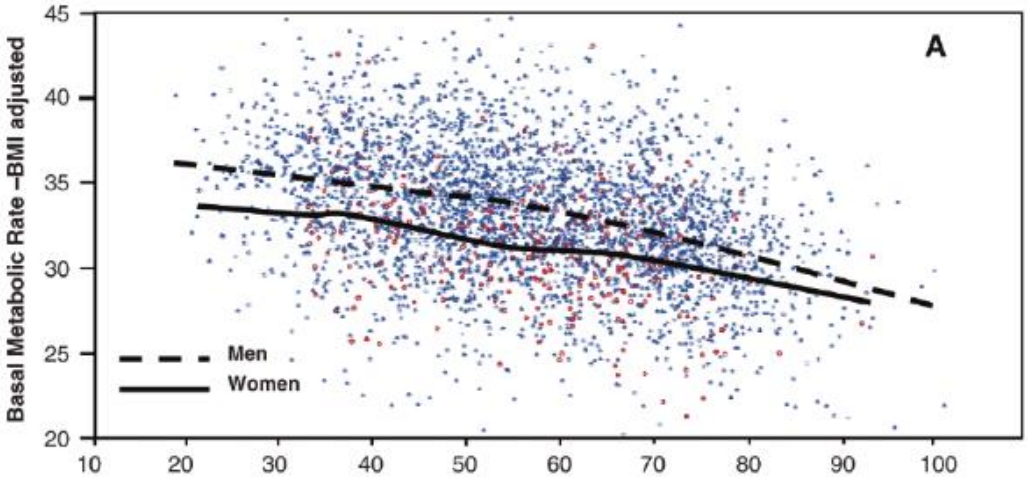


Fig 7.12 BMR drops with age from [https://www.fao.org/4/m2845e/m2845e00.htm] and from the Baltimore health study DOI:10.1093/gerona/63.7.698

Basal metabolic rate drops with age:
One parameter that changes with age is basal metabolic rate (BMR). This corresponds to the parameter γ_E (a sum of BMR and the cost of activity and exercise). BMR is high in young children and drops with age over childhood. It is roughly constant in the three decades from age 20-50, and drops again at ages above 50 (Fig. 7.12). Note the large variability between individuals. My 8 year old youngest daughter Carmel has a BMI of 14, and mine is 26. At ages 30-52 I was 85kg and now at 55 I am 90kg- despite exercise- perhaps my BMR is dropping?
At very old age weight can drop dangerously, a phenomenon known as wasting. This is related in part to sick behavior- many illnesses display reduced appetite and other withdrawal behaviors. The inflammatory changes at old age may set off such sick behaviors and wasting.

Why did the feedback loop evolve? Current theory is that the leptin system serves an important evolutionary function, by protecting individuals from the risks associated with being too thin

(starvation, infertility, poor immune function) or too obese (being eaten by predators). This hypothesis suggests that populations with low predation but high probability of famine and food insecurity (e.g. populations on small islands) will tend to accumulate genetic predisposition to obesity. Genetic predisposition collides with modernity, with its nutrition (high α_F, nearly unlimited access to food) and sedentary lifestyle (low γ_E), to generate the ongoing rise in childhood and adult obesity.

The take home message graphical and math models, calibrated by experiments, can explain mysteries like the weight setpoint and how different interventions affect it. Eat reasonable amounts of healthy food and show up for exercise.

Let's take a nice deep sigh of relief

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Appendix A: The Hill Function

Every biochemistry student learns to derive the Hill equation, named after Archibald Hill who used it in 1910 to describe oxygen binding to hemoglobin. Consider a receptor R binding n molecules of L with rate k_{on}, to form a complex [RLn], which falls apart at rate k_{off} . At steady-state the collisions of R with n molecules of L that make the complex, at rate k_{on} R L^n , are balanced by the complex falling apart, so that K_{on} R L= k_{off} [RLn]. Total receptor R_t concentration is a sum of free and bound R so that R+[RLn]= R_t. Putting this together yields $R = R_t /(1 + (L/K_L)^n)$where K_L=k_{off}/k_{on} is the concentration of L at which half of R are bound, and n is the Hill coefficient.
Additional processes inside the cell affect the hormone action, including signal transduction pathways that convey the information form the cell membrane to its nucleus. Therefore, in our course we will use the Hill equation often, where we understand that K_L is not necessarily k_{off}/k_{on} but instead the concentration of hormone needed for a half-maximal effect on its target organ.
When the hormone causes an increase in physiological output, rather than a decrease, the Hill equation is $u/u_{max} = (L/K_L)^n/(1 + (L/K_L)^n)$
This function rises from zero when the input hormone is L=0, to a maximum of 1 at high L, reaching 1/2 when L=K_L. It can be derived by asking for the amount of bound receptors.

Note to self: model muscle mass with axes of protein intake and muscle mass. Workout line: dM/dt=p f(a) - r - r1 M

where a is activity, r is body amino acid needs and r1 is muscle amino acid needs. Mst=p/r1 f(a)-r/r1
Appetite line: determined by fat. So we need fat muscle and intake (carb and protein) 3D phase space.
dF/st=c u -b(a)-e1 M-e2 F, with c determined by food composition, b energy output e1 and e2 energy costs of muscle and fat.
Appetite line determined by F. This creates a muscle fat intake operating point. Exercise will increase intake u and M and reduce F. Ozempic will reduce u and M
And F. It takes longer to recover muscle mass than fat mass. This should lead to overshoots and maybe explain the long term habituation effects of a diet where fat is regained after a year (as muscle is lost). Sarcopenia and wasting are quick when activity is zero:

Evolutionary Benefits of Visceral Fat

Visceral fat played a crucial role in human evolution, serving as a metabolically active energy reservoir that supported survival in unpredictable environments. Unlike subcutaneous fat, which acts primarily as long-term energy storage and insulation, visceral fat is more lipolytically active, meaning it can rapidly release free fatty acids (FFAs) to supply energy during fasting, physical exertion, or stress. This was particularly advantageous in early hunter-gatherer societies, where periods of feast and famine were common. Additionally, visceral fat contributes to endocrine regulation, secreting adipokines like leptin and adiponectin, which help modulate metabolism, appetite, and immune function. It also provides a localized immune response, with resident macrophages producing cytokines that help fight infections—an essential function in pre-modern environments where injury and pathogen exposure were frequent. Furthermore, the portal circulation connection between visceral fat and the liver allowed for rapid mobilization of energy, particularly beneficial during times of acute stress or starvation, enhancing survival in challenging conditions.

While visceral fat was an asset in evolutionary history, modern lifestyles have transformed it into a major pathophysiological risk factor. Chronic caloric excess, combined with reduced physical activity, leads to an overaccumulation of visceral adipose tissue (VAT), which is strongly linked to metabolic dysfunction. Unlike in evolutionary settings where periodic fasting and physical exertion would regulate fat stores, continuous energy surplus today results in low-grade systemic inflammation due to excessive secretion of pro-inflammatory cytokines (e.g., TNF-α, IL-6). This contributes to insulin resistance, hepatic steatosis, and increased cardiovascular risk. Additionally, visceral fat expansion is associated with dysregulated adipokine secretion, reducing protective factors like adiponectin while increasing leptin resistance, further exacerbating metabolic disease. The portal theory suggests that excess FFAs and inflammatory mediators from visceral fat impair hepatic insulin sensitivity, accelerating the progression of type 2 diabetes and atherosclerosis. What

was once a survival advantage has now become a driver of chronic disease, making lifestyle interventions essential to mitigate its harmful effects.

posed to the patient, but the memory still makes me cringe.

Even then, less than twenty years ago, we knew relatively little about why we sleep, what happens *while* we are asleep, and the importance of sleep to both short-term performance and long-term health. We now know that chronic sleep debt is a far more insidious killer than the acute sleep deprivation that results in falling asleep at stop signs. Many studies have found powerful associations between insufficient sleep (less than seven hours a night, on average) and adverse health outcomes ranging from increased susceptibility to the common cold to dying of a heart attack. Poor sleep dramatically increases one's propensity for metabolic dysfunction, up to and including type 2 diabetes, and it can wreak havoc with the body's hormonal balance. Looking back, I now suspect that at least some of my own health issues, in my thirties, had their roots in my cavalier disregard of sleep.

As important as sleep is for the body, it may
Good sleep, in terms of
tive functi