

Caloric restriction

Caloric restriction (CR) means reducing the total calories you eat, usually by 10% to 30%.

CR effects on lifespan and disease:

- Extends lifespan by 10% to 50% in animal models
- Greatly reduces the incidence of
 - cancer
 - heart disease
 - stroke
 - diabetes
 - many other disease

CR effects on brain:

CR Improves

- memory
- learning
- reaction time
- balance

CR Increases

- Long-Term Potentiation (LTP), a mechanism of learning
- production of the NMDA neurotransmitter receptor, key component in learning
- glucose production (energy supply for the brain)
- resistance to neurodegeneration

CR Decreases

- Neuron death in the hippocampus
- Free radical production
- Apoptosis (cell death)
- Toxin-induced neuron loss

CR effects on diabetes, cardiovascular disease and stroke risk factors:

CR causes

- Lower fasting levels of blood sugar and insulin
- Increased sensitivity to insulin
- Lower levels of cholesterol, triglycerides, bad LDL
- Increased good HDL

Not everyone should restrict calories. There are potential health risks (Le Bourg 2005, Dirks and Leeuwenburgh 2006). CR is not recommended if

- the individual is too young, pregnant, or otherwise at risk
- CR is too extreme (more than 30%)
- the individual has anorexia or bulimia associated with food consumption

First experiments in CR: Osborne, Mendel, Ferry 1917

During experiments on nutrition, selected rats were fed a calorie restricted diet ("stunted") over various period of time.

Here are the results.

- More than 2/3 of normally-fed rats died within 2 yrs.
- Four female rata were calorie restricted
- All four CR females lived longer than 2 years
- All four were breeding at a time when rats are typically in menopause.
- All produced from 3 to 6 litters; all offspring as vigorous as from younger mothers.

Osborne knew he couldn't make any firm conclusions from an experiment with only four rats. But he thought the observation was interesting and published it in the journal Science (which Thomas Edison had founded a few years earlier). In that Science article Osborne said, "it appears as if the preliminary stunting period lengthened the total span of their life."

That same year, J. Northrop showed that he could extend the lifespan of fruit flies when he restricted their food intake during the larval stage.



CR results have been replicated in many other species.

Spider life span

- Normal diet
 - average: 50 days
 - maximum: 100 days
- Caloric restriction
 - average: 90 days
 - maximum: 139 days



Guppy life span

- Normal diet
 - average: 33 months

- maximum: 54 months
- Caloric restriction
 - average: 46 months
 - maximum: 59 months

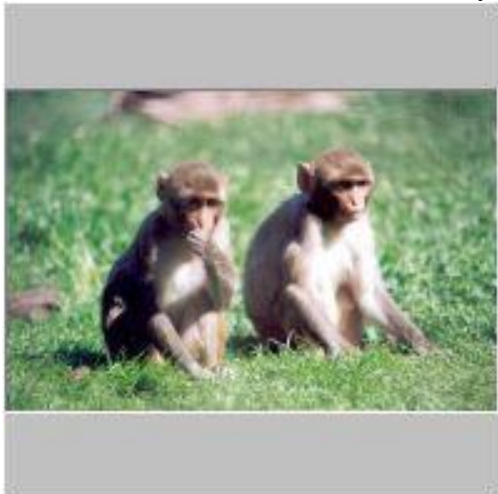


Rat life span

- Normal diet
 - average: 23 months
 - maximum: 33 months
- Caloric restriction
 - average: 33 months
 - maximum: 47 months



Calorie Restriction in Rhesus Monkeys





Average lifespan of rhesus macaque monkey ~ 25 to 30 years
Long term CR studies now underway in rhesus

CR in monkeys improves biomarkers of aging

- lower fasting glucose and insulin levels
- lower body temperature
- lower body fat
- higher levels of DHEA

Lower incidence of chronic diseases such as

- cancer
- cardiovascular disease
- diabetes
- ulcers
- cataracts
- kidney failure

Survival advantage not yet clear.

How much CR is needed?

In animal studies, for every 2% reduction in total calories, we see about a 1% to 2% extension of lifespan. So reducing calories by 20% gives about a 10% to 20% extension in lifespan. There is a limit: 100% reduction doesn't work. Up to 50% CR appears to extend lifespan. For humans, a 20% to 30% reduction is quite doable, as we'll see shortly.

The effects of caloric restriction on preventing diseases such as cancer, stroke, and heart disease are even more dramatic. In caloric restricted animals, the rates of these diseases in caloric restricted animals are a fraction of those of control animals.

The Okinawa study

There are very few long-term studies of the effects of caloric restriction in humans. However, on the island of Okinawa, in southern Japan, a natural experiment has been underway for many decades.



More people live to over 100 years of age in Okinawa than anywhere else in the world. Their rates of stroke, cancer, dementia and other age-associated diseases are among the lowest in the world. Why? While many factors may contribute, caloric restriction appears to be one of the most important.

Here's a description from Bradley Willcox and Craig Willcox, who have published many scientific articles and two books describing their studies (Willcox 2002, 2005)

"Low caloric intake was first reported in the Okinawan population by Hokama et al. (1967) who showed that Okinawan school children consumed only 62% of the calories of other Japanese school children. Kagawa (1978) confirmed low caloric intake (83% of Japan average) in the Okinawa adult population from the 1972 Japan National Nutrition Survey and documented anthropometric and morbidity data from older Okinawans that were consistent with CR. Kagawa (1978)

hypothesized that this may have been partly responsible for the long and healthy lives of Okinawans.

Death rates from heart disease, cancer and cerebral vascular disease were found to be only 60 to 70% of that of the Japan average and the allcause mortality rate for 60–64 year olds was only half that of other Japanese. A later study published by Chan et al. (1997) also reported dietary and phenotypic data in Okinawan septuagenarians and centenarians consistent with CR.

"Our recent analysis of long-term trends in whole population caloric intake and energy balance for the years beginning in 1949 demonstrates that the Okinawan septuagenarian population appeared to be in a relative "energy deficit" consistent with CR until the late 1960s, eating approximately 11% fewer calories (approximately 1,785 kcal per day) than would normally be recommended for maintenance of body weight according to the Harris-Benedict equation (Willcox et al. Unpublished data).

"Moreover, nutritional studies suggest that the traditional Okinawan diet, with its high intake of green leafy and yellow root vegetables, sweet potatoes as a dietary staple, and soy as a principle protein supplemented by small amounts of fish and meat, was adequate in most nutrients and particularly high in antioxidant vitamins (Sho 2001; Suzuki et al. 2001; Todoriki et al. 2004; Willcox 2005).

Okinawan septuagenarians, who would have undergone CR until at least middle age according to the previous population data, exhibit higher DHEA levels when compared to age-matched Americans not subjected to CR

"... based on life table data for the year 1995 Average lifespan (measured as 50th percentile survival) and maximum lifespan (measured as 99th percentile survival) in the Okinawan, Japanese and U.S. populations were 83.8 and 104.9 years, 82.3 and 101.1 years, and 78.9 and 101.3 years, respectively

"... age-adjusted mortality for specific agerelated diseases (especially cardiovascular diseases) is extremely low in elderly Okinawans compared to other age-matched Japanese or Americans (Kagawa 1978; Suzuki et al. 2001). Thus, life expectancy at older ages is extremely long in Okinawa.

For the septuagenarian cohort, life expectancy from age 65 is the longest in Japan, and possibly the world, at 24.1 years for females and 18.5 years for males (Japan Ministry of Health, Labor and Welfare, 2005). This compares to 22.5 years and 17.6 years for the same birth cohort in mainland Japan (Japan Ministry of Health, Labor and Welfare 2000) and 19.3 years and 16.2 years for corresponding U.S. birth cohorts of females and males respectively (U.S. Centers for Disease Control and Prevention 2003).

"We cite the following reasons for a more optimistic view of the potential benefits of the CR lifestyle for human beings:

First, the accumulated evidence of 70 years of CR studies suggests that CR is an extremely ancient and very important survival mechanism which appeared early in the evolution of eukaryotes. Therefore it appears to be strongly conserved throughout the phylogenetic scale (from yeast to mammals). As such, it would be unusual if it did not work in some positive capacity in humans as well.

Second, studies in progress with non-human primates (who share over 95% of our genes and have similar reproductive physiology) on a CR regimen, while not yet conclusive, are showing early results consistent with previous animal data.

Third, short-term and longer-term studies of humans under a true CR paradigm have shown dramatic changes in physiology and metabolic shifts similar to other animals.

"Calories in the Okinawan population were approximately 11% fewer than what would usually be recommended for their body weight and activity levels (based on the Harris-Benedict equation)

"Yet, even with this mild CR-like regimen older Okinawans have gained an additional 6% survival time from age 65 (1.3 years) versus other Japanese and an additional 20% survival time (3.6 years) versus Americans.

Given the large number of factors that influence human lifespan, this is also surprisingly similar to the gain in lifespan observed in prior animal studies (i.e. 10–20% calorie reduction leads to a 10–20% increase in lifespan).

Most importantly, the Okinawans appear to have gained an increased health span, with almost a decade of disability-free life expectancy beyond what typical Western populations experience." (Willcox 2006)

In the USA, if you live to 85 years old, your risk of dementia is 25% to 30%.

In Okinawa, your risk is about 15% (Willcox 2002).

What does CR do to the brain, synapses and neurogenesis?

Contestabile (2009) and Fontán-Lozano (2008) review the experiments to understand the molecular mechanisms of caloric restriction's effects on the brain. Here are some examples of the findings:

- CR in rats completely prevents age related deficits in long term potentiation, the basis of learning and memory (Eckles-Smith 2000)
- CR in rats and mice increases the number of newly generated neurons in the dentate gyrus in the hippocampus (Lee 2000, Bondolfi 2004)
- CR enhances neurotrophin expression and neurogenesis in the hippocampus of adult mice (Lee 2002)
- Brain-derived neurotrophic factor (BDNF) is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice (Lee and Duan 2002)
- CR significantly counteracted DNA fragmentation, a specific marker of apoptosis, in the cerebral cortex of aged rats (Shelke 2003)
- CR promotes neuronal survival against naturally-occurring apoptosis, by restoring physiological levels of a central enzyme in DNA repair (Hiona 2004)
- CR preserves the shape and density of dendritic spines on neurons, compared to 38% loss in controls (Moroi-Fellers 1989)
- CR maintains both motor coordination and learning compared to controls (Ingram 1987, Stewart 1989, Pitsikas 1990, Magnusson 1998)
- In older CR rats, improved motor learning is correlated with improved neurotransmitter function (Gould 1995)

There are many theories for exactly how CR slows down aging and protects against age-related neurodegenerative diseases. CR's beneficial effects appear to involve lowering reactive oxygen species and increased production of antioxidants, among a variety of mechanisms. We'll return to this topic later.

CR: stroke, Alzheimer's, and Parkinson's disease

CR appears to protect against stroke, Alzheimer's, and Parkinson's disease. Contestabile (2009) gives a very good review, which I'll summarize here.

CR and Alzheimer's disease

In humans, CR reduces risk for AD (Stranahan 2008), and may delay and reduce symptoms (Pasinetti 2007).

Mutated human beta-amyloid precursor protein (APP) induces progressive development of amyloid plaques in the cortex and hippocampus in transgenic mice, a mouse model of AD. Long-term CR significantly protected against this damage. (Patel 2005, Wang 2005)

CR gave greater protection to double transgenic mice in which the gene for the Alzheimer's disease related protein, presenilin-1, was mutated, in addition to the one for beta-amyloid precursor protein (Patel 2005).

In a triple transgenic mouse, (mutation of APP, presenilin-1 and tau protein), CR reduced development of the AD markers amyloid deposition and tau protein phosphorylation, and gave improvement of cognitive deficits (Halagappa 2007)

CR and stroke

CR reduced brain damage and improved behavioral recovery in a rat model of stroke (Yu 1999).

In a rat model of stroke model, 3-months CR did not protect neurons in the hippocampus, but CR animals performed better than controls in radial arm maze task and showed less stress behavior. Despite equivalent damage to neurons in hippocampus, suggests that CR rats recovered better (Roberge 2008).

CR and Parkinson's disease

In a mouse model of Parkinson's disease, CR reduced both the loss dopaminergic neurons and the motor deficits (Duan 1999)

CR in a monkey model gave similar neuroprotection and improved motor activity (Maswood 2004).

Caloric restriction: how to

How can you

- reduce total calories?
- not feel hungry?
- enjoy what you eat?

Food substitution

The first key idea is food substitution:

Let's assume you eat a typical diet of about 2,000 calories per day, and drink one Classic Coke per day.

- Medium-size Classic Coke: 210 calories.
- Replace it with a Diet Coke: 0 calories.

If you replace one Classic Coke with one Diet Coke per day, you have just achieved 10% caloric restriction. You will likely extend your lifespan by 5% to 10%, and reduce your risk of cancer, heart disease, diabetes, stroke, dementia and many other diseases.

Burning off those 210 calories by exercising would take about

- 40 minutes of Bicycling
- 30 minutes of Swimming
- 20 minutes of Running

Here are some examples of easy ways to restrict calories by substituting. This doesn't mean portion control: they are all the same amount of food.

| Regular food | Calories | Substitution | Calories |
|--|-------------|---|------------|
| Breakfast cereal, 30 g | 100 | Fiber One cereal, 30 g | 60 |
| Milk, 2%, 8 oz | 130 | Almond milk, 8 oz unsweetened, Blue Diamond | 40 |
| Starbucks Grande Vanilla Latte, 2% milk, vanilla syrup | 250 | Starbucks Grande Skinny Vanilla Latte, non-fat milk, sugar-free vanilla syrup | 130 |
| Hamburger, ¼ pound (169 g) | 410 | Salmon, wild, ¾ cup (168 g) | 180 |
| Large French fries (154 g) | 500 | Cottage cheese, non-fat, 1 cup (145 grams) | 123 |
| Classic Coke, medium, McDonalds | 210 | Diet Coke | 0 |
| Tortilla, flour, 62g | 160 | Tortilla, low-carb, 62g, La Tortilla Factory | 80 |
| Cheese, cheddar, 1 oz | 114 | Cheese, cheddar, non-fat 1 oz | 45 |
| Apple pie, slice, 180 grams | 420 | Apple, 1 medium 3" diameter, 180 grams | 95 |
| Jell-O, regular, 3.5 oz | 70 | Jell-O, sugar-free, 3.5 oz | 10 |
| Total calories | 2364 | | 763 |

If you eat the regular food in the left column, you are likely gaining weight.

If you eat the alternative food in the right hand column, *you can actually eat twice as much* and still be caloric restricted!

Caloric density

The second key idea is caloric density.

To feel satiated (not hungry), most people need about 2 to 3 pounds of food per day.

Food labels give information in grams, so we need convert pounds to grams:

- 2.2 pounds = 1 kilogram = 1000 grams.
- 1 pound = 450 grams

So, to be satisfied and not hungry, we need to eat 900 to 1400 grams per day.

- 900 grams * 2.2 pounds/1000 grams = 3.08 pounds of food per day.
- 1400 grams * 2.2 pounds/1000 grams = 1.98 pounds of food per day.

Now, suppose you eat 3 pounds (1400 grams) of food that averages 1 calorie per gram. You would be eating about 1400 calories per day, and you would feel pretty stuffed.

Compare that to a typical American caloric intake per day:

- 2,666 calories per day (men)
- 1,877 (women)

Let's look at an average American male eating 2,666 calories. Cutting that to about 2,000 calories per day is 25% caloric restriction.

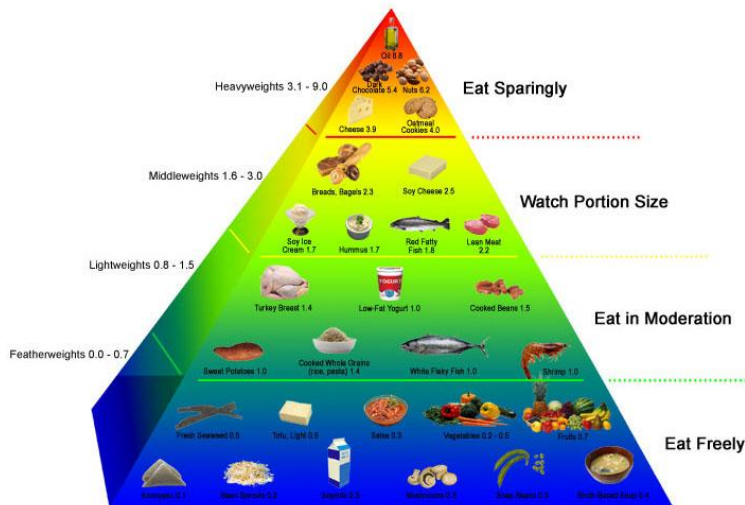
Here are foods with less than one calorie per gram (caloric density < 1.0). You can pretty much eat as much of these as you want. To reach 2000 calories, you would have to eat more than 2,000 grams * 2.2 pounds/gram = 4.4 pounds. That's way beyond what most people can eat.

- Vegetables
- Fruit
- Soups with clear broth (not cream-based)
- Cottage cheese
- Tofu
- Low-fat yoghurt
- Most fish (baked, boiled, or stir fried. Not deep fried)
- Sweet potato (yam) and purple yams

To make it all taste good, sprinkle some fruit (like fresh raspberries or sliced apple), some non-fat feta, a little olive oil and some balsamic vinegar on a salad. Try a bowl of blueberries and cottage cheese as a snack. Stir fry some veggies and tofu, throw in some green onion and mushrooms, add some interesting spices.

There are some very tasty, healthy dips with caloric density around 1.0. You can use these in a wrap with spinach, as extra flavor in a salad, or for dipping veggies.

- Trader Joe's "Tomato & Basil Hummus Dip": 30 grams, 35 calories
- East & West Gourmet Afghan Food "Basil Pesto": 28 grams, 32 calories
- East & West Gourmet Afghan Food "Sun-Dried Tomato Hummus": 28 grams, 20 calories



The Okinawa food pyramid is a good guide.

You still need glucose to make your brain function well. But you want to deliver the glucose at an even rate, spread over hours, not minutes.

Poor choices are white bread, white rice, white pasta, white potatoes or simple sugars (from soda). These all deliver sugar too quickly and make your blood sugar and insulin levels spike. High insulin levels in your blood causes the liver and other tissues to remove the sugar quickly (converting most of it to fat), and leave you hungry again within a couple of hours. Restrict these to small amounts when you need a shot of glucose to get your brain working, and mix them with protein and a little healthy oil to slow their absorption.

Better choices are yams (sweet potatoes), purple yams, brown rice, or oatmeal. Whole wheat bread and pasta have caloric density around 1.1, and break down more slowly than the white versions.

White bread, bagels, muffins, crackers, donuts, cookies, and so on have caloric density of 2.5 to 3 and higher. So they don't fill you up. They also contain lots of simple sugars that cause the insulin spike that soon make you hungry again.

Salmon and tuna have caloric density around 1.8. But the omega-3 fatty acids are beneficial, and they have little saturated fat. So substitute these for other meats.

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