

# Calorie Restriction

From Wikipedia, the free encyclopedia (5/10/09)

**Calorie restriction**, or **caloric restriction** (CR), is a dietary regimen thought to improve health and slow the aging process in some animals and fungi by limiting dietary energy intake below the average needs. CR is the only dietary intervention which has been documented to increase both the median and maximum lifespan in a variety of species, among them rodents, yeast, fishes and dogs. The life extension is varied, for mice and rats there is an 30-40% increase<sup>[1]</sup>. Even though there has been research on CR for over 70 years the mechanism by which CR works is still not well understood.<sup>[2][3]</sup> There are currently ongoing studies on primates to show if CR works on primates, and even though they are showing positive indications<sup>[2] [4]</sup>; it is still not certain if CR has a positive effect on longevity for primates and humans.<sup>[2][4]</sup> The effect of CR on IGF-1 serum levels seen in rodents has not been replicated in human trials.<sup>[5]</sup>

Recent research has been in favour of the hypothesis that CR works by decreasing the insulin levels and thereby upregulating autophagy,<sup>[6]</sup> but CR affects many other health indicators and whether insulin is the main concern is still undecided.<sup>[1]</sup>

Calorie restriction is a common measure found in several dietary regimens, including the Okinawa diet<sup>[7]</sup> and the CRON-diet.

## Effects on humans

### Positive effects

In human subjects, CR has been shown to lower cholesterol, fasting glucose, and blood pressure.<sup>[citation needed]</sup> In CR, energy intake is minimized, but sufficient quantities of vitamins, minerals and other important nutrients must be eaten.

A small-scale study in the US at the Washington University School of Medicine in St. Louis studied the effects following a calorie-restricted diet of 10-25% less calorie intake than the average Western diet. Body mass index (BMI) was significantly lower in the calorie-restricted group when compared with the matched group; 19.6 compared with 25.9. The BMI values for the comparison group are similar to the mean BMI values for middle-aged people in the US.<sup>[8]</sup>

All those on calorie-restricted diets experienced reductions in BMI after starting their diet. Their BMIs decreased from an average of 24 (range of 29.6 to 19.4) to an average of 19.5 (range of 22.8 to 16.5) over the course of their dieting (3-15 years). Nearly all the decrease in BMI occurred in the first year of dieting. It was found that the average total cholesterol and LDL (bad) cholesterol levels for calorie-restricted individuals were the equivalent of those found in the lowest 10% of normal people in their age group. It was found that the average HDL (good) cholesterol levels for calorie-restricted individuals

were very high—in the 85th to 90th percentile range for normal middle-aged US men. These positive changes in calorie-restricted individuals were found to occur mainly in the first year of dieting.<sup>[8]</sup>

"The calorie-restricted group also fared much better than the control group in terms of average blood pressure (100/60 vs. 130/80 mm Hg), fasting glucose, fasting insulin (65% reduction), body mass index ( $19.6 \pm 1.9$  vs.  $25.9 \pm 3.2$  kg/m<sup>2</sup>), body fat percentage ( $8.7\% \pm 7\%$  vs.  $24\% \pm 8\%$ ), C-reactive protein, carotid IMT (40% reduction), and platelet-derived growth factor AB."<sup>[9]</sup>

It was found that the calorie-restricted group had remarkably low triglyceride levels. In fact, they were as low as the lowest 5% of Americans in their 20s. This is more remarkable when it is noted that the calorie-restricted individuals were actually aged between 35 and 82 years. Both systolic and diastolic blood pressure levels in calorie-restricted group were remarkably low, about 100/60, values normally found in 10-year-old children. Fasting plasma insulin concentration was 65% lower and fasting plasma glucose concentration was also significantly lower in the calorie-restricted group when compared with the comparison group." The comparison group's statistics aligned approximately with the US national average on the dimensions considered.<sup>[10]</sup> Fasting plasma insulin levels<sup>[11]</sup> and fasting plasma glucose levels<sup>[12]</sup> are used as tests to predict diabetes. The researchers also found that "excessive calorie restriction causes malnutrition and can lead to anemia, muscle wasting, weakness, dizziness, lethargy, fatigue, nausea, diarrhea, constipation, gallstones, irritability and depression". The study was published in the March 2007 issue of the Journal of American Medical Association.<sup>[8]</sup>

While compelling, these studies used borderline overweight (BMI>25) subjects as controls, which is the average in some countries but not in others. It remains unclear whether the same effects would also be observed if non-overweight subjects were used as controls.

### **Improved memory**

A 2009 research paper showed that a calorie restricted diet can improve memory in normal to overweight elderly. The diet as well resulted in decreased insulin levels and reduced signs of inflammation.<sup>[13]</sup> Scientists believe memory improvement on that experiment was caused by the lower insulin levels, because high insulin levels are usually associated with lower memory and cognitive function.<sup>[14]</sup> However, that relation seems to be age specific since another study, when analyzing people older than 65, those who were underweight had a higher dementia risk than normal or overweight people, where the latter had a lower risk than the other two conditions.<sup>[15]</sup>

### **Negative effects**

#### **Mortality**

Being on a CR diet can lead to an individual becoming underweight. One study has shown that having a BMI lower than 18 is associated with significantly increased mortality from noncancer, non-cardiovascular disease causes. The results were the same when not accounting for those who were underweight because they might have been already sick or were smokers. However, the study focused solely on BMI and did not look specifically at diet.<sup>[16]</sup>

When the body is faced in a condition, generally a disease or slower metabolism associated with age, where it can not digest or metabolize nutrients properly or have higher energy needs, the lack of enough stored energy can aggravate that condition.

### **Starvation**

When in prolonged periods of severe caloric restriction the body burns lean tissue (including but not limited to muscle and collagen) along with its remaining fat reserves.<sup>[17]</sup> The combination of starvation and the associated lethargy and decreased physical activity can result in muscular atrophy which leads to lower quality of life.<sup>[18][19]</sup> In the final stages of starvation the breakdown of tissues to supply energy can have its own adverse effects on the body.<sup>[citation needed]</sup>

Beyond using lean tissue as energy source, the presence of catabolic hormones, like cortisol, and lack of anabolic ones, like Insulin, disrupts protein synthesis and amino acid uptake.

### **Lack of essential nutrients**

When reducing calorie intake, intake of essential nutrients may also be reduced, especially fat-soluble vitamins, which require fat for proper absorption and others nutrients generally associated with high calorie foods, like oils, nuts, meat and dairy products.

### **Abnormal hair growth**

When undernourished the body slows the growth rate of hair and nails.<sup>[20]</sup>

### **Neuroglycopenia**

Hypoglycemia can lead to neuroglycopenia.

## **Research history**

In 1934, Mary Crowell and Clive McCay of Cornell University observed that laboratory rats fed a severely reduced calorie diet while maintaining vital nutrient levels resulted in life spans of up to twice as long as otherwise expected. These findings were explored in detail by a series of experiments with mice conducted by Roy Walford and his student Richard Weindruch. In 1986, Weindruch reported that restricting the calorie intake of

laboratory mice proportionally increased their life span compared to a group of mice with a normal diet. The calorie-restricted mice also maintained youthful appearances and activity levels longer and showed delays in age-related diseases. The results of the many experiments by Walford and Weindruch were summarized in their book *The Retardation of Aging and Disease by Dietary Restriction* (1988) ([ISBN 0-398-05496-7](#)).

The findings have since been accepted and generalized to a range of other animals. Researchers are investigating the possibility of parallel physiological links in humans. In the meantime, many people have independently adopted the practice of calorie restriction in some form.

Trials were set up at [Washington University](#) in 2002 and involved about thirty participants. Dr. Luigi Fontana, clinical investigator, says CR practitioners seem to be aging more slowly than the rest of us. "Take systolic blood pressure," he says. "Usually, that rises with age reliably, partly because the arteries are hardening. In my group, mean age is 55, and mean systolic blood pressure is 110: that's at the level of a 20-year-old."

A study conducted by the [Salk Institute for Biological Studies](#) and published in the journal *Nature* in May 2007 determined that the gene PHA-4 is responsible for the longevity behind calorie restriction in animals, '***with similar results expected in humans***'.<sup>[21]</sup> The discovery has given hope to the synthesising of future drugs to increase the human lifespan by simulating the effects of calorie restriction. However, [MIT](#) biologist [Leonard Guarente](#) cautioned that "(treatment) won't be a substitute for a healthy lifestyle. You'll still need to go to the gym".<sup>[22]</sup>

## Effects of CR on different organisms

### Primates

Researchers at New York's Mount Sinai School of Medicine reported in 2006 that compared to monkeys fed a normal diet, squirrel monkeys on a life-long calorie-restrictive diet were less likely to develop Alzheimer's-like changes in their brains.<sup>[23]</sup> Since squirrel monkeys are relatively long-lived, definitive conclusions regarding whether or not they are aging slower are not yet available. A study on rhesus macaques was started in 1989 at the [University of Wisconsin-Madison](#). Preliminary results show lower fasting insulin and glucose levels as well as higher insulin sensitivity and LDL profiles associated with lower risk of atherogenesis in dietary restricted animals.<sup>[24]</sup>

### Mice

Studies in female mice have shown that estrogen receptor-alpha declines in the pre-optic hypothalamus as they age. The female mice that were given a calorically restricted diet during the majority of their lives maintained higher levels of ER $\alpha$  in the pre-optic hypothalamus than their non-calorically restricted counterparts.<sup>[25]</sup> Studies in female mice have shown that both Supraoptic nucleus (SON) and Paraventricular nucleus (PVN) lose about one-third of IGF-1R immunoreactive cells with normal aging. Old calorically

restricted (CR) mice lost higher numbers of IGF-1R non-immunoreactive cells while maintaining similar counts of IGF-1R immunoreactive cells in comparison to Old-AI mice. Consequently, Old-CR mice show a higher percentage of IGF-1R immunoreactive cells reflecting increased hypothalamic sensitivity to IGF-1 in comparison to normally aging mice.<sup>[26][27]</sup>

## Rats

Seventy years ago, McCay CM, *et al.*, discovered that reducing the amount of calories fed to rats nearly doubled their lifespan. For the last seventy years, scientists have proposed hypotheses as to why. Some explanations included reduced cellular divisions, lower metabolism rates, and reduced production of free radicals generated by metabolism.

## Yeast

Fungi model are very easy to manipulate and many crucial steps toward the understanding of aging has been done with it. Many studies were published in budding yeast and fission yeast to analyse the cellular mechanisms behind the increased longevity due to calorie restriction. First, calorie restriction is often called dietary restriction because the same effects on life span can be reached only by changing the nutrient quality without changing the amount of calorie. The data from Dr Guarente, Dr Kennedy, Dr Jazwinski, Dr Kaeberlein, Dr Longo, Dr Shadel, Dr Nyström, Dr Piper and others showed that genetic manipulations in nutrient signaling pathways could mimic the effects of dietary restriction. In some case dietary restriction needs mitochondrial respiration to increase longevity (chronological aging) and in some other case not (replicative aging). Nutrient sensing in yeast controls stress defense, mitochondrial functions, Sir2 and others. These functions are all known to regulate aging. Genes involved in these mechanisms are : TOR, PKA, SCH9, MSN2/4, RIM15, SIR2,...<sup>[28] [29] [30] [31] [32]</sup>

## Drosophila

Research in 2003 by Mair et al. showed that calorie restriction extends the life of fruit flies of any age with instantaneous effects on death rates.<sup>[33]</sup>

## *Caenorhabditis elegans*

Recent work in *Caenorhabditis elegans* has shown that restriction of glucose metabolism extends life span by primarily increasing oxidative stress to exert an ultimately increased resistance against oxidative stress, a process called (mito)hormesis.<sup>[citation needed]</sup>

## Why might CR increase longevity?

There have been many theories as to how CR works, and many of them have fallen out of favor or been disproved. These include reduced basal metabolic rate, developmental delay, the control animals being gluttons, and decreased glucocorticoid production.

## **(Mito)hormesis**

Main article: Hormesis

A small number of researchers in the CR field are now proponents of a new theory known as the "Hormesis hypothesis of CR" also known as the "Mitohormesis hypothesis of CR" due to the likely involvement of mitochondria. Southam and Ehrlich (1943) reported that a bark extract that was known to inhibit fungal growth, actually stimulated growth when given at very low concentrations. They coined the term "hormesis" to describe such beneficial actions resulting from the response of an organism to a low-intensity biological stressor. The word "hormesis" is derived from the Greek word "hormaein" which means "to excite".

The (Mito)hormesis hypothesis of CR proposes that the diet imposes a low-intensity biological stress on the organism, which elicits a defense response that helps protect it against the causes of aging. In other words, CR places the organism in a defensive state so that it can survive adversity, and this results in improved health and longer life. This switch to a defensive state may be controlled by longevity genes (see below).

While the (Mito)hormesis hypothesis of CR was a purely hypothetical concept until late 2007, recent work by Michael Ristow's group in a small worm named Caenorhabditis elegans has shown that restriction of glucose metabolism extends life span by primarily increasing oxidative stress to exert an ultimately increased resistance against oxidative stress.<sup>[34]</sup> This is probably the first experimental evidence for hormesis being an essential cause for extended life span following CR.

## **Insulin signaling**

See also: Insulin#Physiological effects

Lowering of the concentration of insulin and substances which are related to insulin, e.g Insulin-like growth factor 1 and Growth hormone has been shown to upregulate autophagy, the repair mechanism of the cell<sup>[35]</sup>

Early work in C. elegans (see Cynthia Kenyon) and more recent research in mice has suggested (see Matthias Bluher, C. Ronald Kahn, Barbara B. Kahn, *et al.*) that it is not only reduced calorie intake which influences longevity. This was done by studying animals which have their metabolism changed to reduce activity of the hormone insulin or downstream elements in its signal transduction, consequently retaining the leanness of animals in the earlier studies. It was observed that these animals can have a normal dietary intake, but have a similarly increased lifespan. This suggests that lifespan is increased for an organism if it can remain lean and if it can avoid any excess

accumulation of adipose tissue: if this can be done while not diminishing dietary intake (as in some minority eating patterns, see e.g. Living foods diet or Joel Fuhrman) then the 'starvation diet' anticipated as an impossible requirement by earlier researchers is no longer a precondition of increased longevity.<sup>[citation needed]</sup>

The extent to which these findings may apply to human nutrition and longevity is as noted above under investigation. A paper in the Proceedings of the National Academy of Sciences, U.S.A. in 2003 showed that practitioners of a CR diet had significantly better cardiovascular health.<sup>[36]</sup> Also in progress are the development of CR mimetic interventions.<sup>[37]</sup>

## **Sir2/SIRT1 and resveratrol**

Sir2 or "silent information regulator 2" is a longevity gene, discovered in baker's yeast cells, that extends lifespan by suppressing DNA instability (see Sinclair and Guarente, Cell, 1997).<sup>[38]</sup> In mammals Sir2 is known as SIRT1. Recent discoveries have suggested that the gene Sir2 might underlie the effect of CR. In baker's yeast the Sir2 enzyme is activated by CR, which leads to a 30% lifespan extension. David Sinclair at Harvard Medical School, Boston, showed that in mammals the SIRT1 gene is turned on by a CR diet, and this protects cells from dying under stress.<sup>[39]</sup> An article in the June 2004 issue of the journal Nature showed that SIRT1 releases fat from storage cells.<sup>[40]</sup> Sinclair's lab reported that they have found small molecules (e.g. resveratrol) that activate Sir2/SIRT1 and extend the lifespan of yeast,<sup>[41]</sup> nematode worms, fruit flies,<sup>[42]</sup> and mice consuming a high caloric diet.<sup>[43]</sup> The effect of resveratrol on lifespan in *C. elegans* and *Drosophila* was recently re-investigated by D. Gems and L. Partridge. After performing the experiment numerous times, it was concluded that the lifespan extending effects of resveratrol are not consistent, and the previously reported lifespan increases were in fact due to natural variability in *C. elegans* lifespans (Effects of resveratrol on lifespan in *Drosophila melanogaster* and *Caenorhabditis elegans*. *Mech Ageing Dev.* 2007 Oct;128(10):546-52. Epub 2007 Aug 14. PMID: 17875315 [PubMed - indexed for MEDLINE]). No lifespan extension in *Drosophila* was reported. A more recent study from Sinclair and De Cabo also concluded that resveratrol does not extend lifespan of normal mice (Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. *Cell Metab.* 2008 Aug;8(2):157-68. Epub 2008 Jul 3.) An Italian group headed by Antonio Cellarino showed that resveratrol extends the lifespan of a vertebrate fish by 59%.<sup>[44]</sup> In the yeast, worm, and fly studies, resveratrol did not extend lifespan if the Sir2 gene was mutated. A group of researchers headed by Matthew Kaeberlein and Brian Kennedy (who just like Sinclair, were trained in the lab of L. Guarente) at the University of Washington Seattle believe that Sinclair's work on resveratrol is an artifact and that the Sir2 gene has no relevance to CR.<sup>[45]</sup>

Guarente has recently published that behavior associated with caloric restriction did not occur when Sirt1 knockout mice were put on a calorie restricted diet, the implication being that Sirt1 is necessary for mediating the effects of caloric restriction. However, the same paper also reported that the biochemical parameters thought to mediate the lifespan extending effects of caloric restriction (reduced insulin, igf1 and fasting glucose), were

no different in normal mice and mice lacking Sirt1. Whether the lifespan-extending effect of CR was still evident in Sirt1 knockout mice was not reported in that study.

According to Sinclair's data, Sirtuins (SirT1, Sir2, ...) are involved in calorie restriction-mediated effects on longevity and so are beneficial for longevity<sup>[46]</sup> but in some case these enzymes can be pro-aging and appeared detrimental for longevity. That was seen by Valter Longo and coworkers in yeast and mammals.<sup>[47] [48] [49]</sup>

Sirtris Pharmaceuticals, Inc., a GlaxoSmithKline-owned biotechnology company based in Cambridge, MA co-founded by Sinclair, is developing resveratrol and other SIRT1 activators for human use. Because life-span extension is not an FDA-approvable indication, the company is developing SIRT1 activators for the treatment of diseases associated with aging including type 2 diabetes and cancer.

## **DHEA**

While calorie restriction has been shown to increase DHEA in primates (PMID 12543259), it has not been shown to increase DHEA in post-pubescent primates (PMID 15247063).

## **Free radicals and glycation**

Two very prominent theories of aging are the free radical theory and the glycation theory, both of which can explain how CR could work. With high amounts of energy available, mitochondria do not operate very efficiently and generate more superoxide. With CR, energy is conserved and there is less free radical generation. A CR organism will be less fat and require less energy to support the weight, which also means that there does not need to be as much glucose in the bloodstream. Less blood glucose means less glycation of adjacent proteins and less fat to oxidize in the bloodstream to cause sticky blocks resulting in atherosclerosis. Type II Diabetics are people with insulin insensitivity caused by long-term exposure to high blood glucose. Obesity leads to type 2 diabetes. Type 2 diabetes and uncontrolled type 1 diabetes are much like "accelerated aging", due to the above effects. There may even be a continuum between CR and the metabolic syndrome.

In examining Calorie Restriction with Optimal Nutrition, it is observed that with less food, and equal nutritional value, there is a higher ratio of nutrients to calories. This may lead to more ideal essential and beneficial nutrient levels in the body. Many nutrients can exist in excess to their need, without side effects as long as they are in balance and not beyond the body's ability to store and circulate them. Many nutrients serve protective effects as antioxidants, and will be at higher levels in the body as there will be lower levels of free radicals due to the lower food intake.

Calorie Restriction with Optimal Nutrition has not been tested in comparison to Calorie Excess with Optimal Nutrition. It may be that with extra calories, nutrition must be similarly increased to ratios comparable to that of Calorie Restriction to provide similar antiaging benefits.



Stated levels of calorie needs may be biased towards sedentary individuals. Calorie restriction may be no more than adapting the diet to the body's needs.

Although aging can be conceptualized as the accumulation of damage, the more recent determination that free radicals participate in intracellular signaling has made the categorical equation of their effects with "damage" more problematic than was commonly appreciated in years past.

### **Papers on CR in yeast: dismissing increased respiration**

In late 2005 Matt Kaeberlein and Brian Kennedy published two important papers on calorie restriction in yeast. In the first, they show that calorie restriction does not increase respiration in yeast (in contrast with the model proposed by Lenny Guarente). In the second, calorie restriction decreased the activity of TOR, a nutrient-responsive signaling protein already known to regulate aging in worms and flies. This paper is the first to directly link TOR to calorie restriction.

### **Papers on CR in *C. elegans*: promoting increased respiration**

In late 2007 Michael Ristow published a paper on calorie restriction in *C. elegans*.<sup>[34]</sup> Here the authors show that calorie restriction does increase respiration in *C. elegans* as previously described for yeast (in support of the model proposed by Lenny Guarente, although independent of Sir2.1).

### **Evolution**

It has been recently argued that during years of famine, it may be evolutionarily desirable for an organism to avoid reproduction and to upregulate protective and repair enzyme mechanisms to try to ensure that it is fit for reproduction in future years. This seems to be supported by recent work studying hormones.<sup>[50]</sup>

## **Objections**

### **No benefit to houseflies**

One of the most significant oppositions to caloric restriction comes from Michael Cooper, who has shown that caloric restriction has no benefit in the housefly.<sup>[51]</sup> Michael Cooper claims that the widely purported effects of calorie restriction may be because a diet containing more calories can increase bacterial proliferation, or that the type of high calorie diets used in past experiments have a stickiness, general composition, or texture that reduces longevity.

### **Catabolic damage**

A major conflict with calorie restriction is that adequate calorie intake is needed to prevent catabolizing the body's tissues. A body in a catabolic state promotes the degeneration of muscle tissue, including the heart.

### **Physical activity testing biases**

While some tests of calorie restriction have shown increased muscle tissue in the calorie-restricted test subjects, how this has occurred is unknown.<sup>[citation needed]</sup> Muscle tissue grows when stimulated, so it is possible that the calorie-restricted test animals exercised more than their companions on higher calories. The reasons behind this may be that animals enter a foraging state during calorie restriction. In order to control this variable, such tests would need to be monitored to make sure that levels of physical activity are equal between groups.

### **Insufficient calories and amino acids for exercise**

Exercise has also been shown to increase health and lifespan and lower the incidence of several diseases. Calorie restriction comes into conflict with the high calorie needs of athletes, and may not provide them adequate levels of energy or sufficient amino acids for repair, although this is not a criticism of CR per se, since it is certainly possible to be an unhealthy athlete, or an athlete destined to die at a young age due to poor diet, stresses, etc. Moreover, in experiments comparing CR to exercise, CR animals live much longer than exercised animals.<sup>[52]</sup>

### **Benefits only the young**

There is evidence to suggest that the benefit of CR in rats might only be reaped in early years. A study on rats which were gradually introduced to a CR lifestyle at 18 months showed no improvement over the average lifespan of the Ad libitum group.<sup>[53]</sup> This view, however, is disputed by Spindler, Dhahbi, and colleagues who showed that in late adulthood, acute CR partially or completely reversed age-related alterations of liver, brain and heart proteins and that mice placed on CR at 19 months of age show increases in lifespan.<sup>[54]</sup>

### **Possible contraindications**

Both animal and human research suggest BUD CR may be contraindicated for people with amyotrophic lateral sclerosis (ALS). Research on a transgenic mouse model of ALS demonstrates that CR may hasten the onset of death in ALS. Hamadeh *et al* therefore concluded: "These results suggest that CR diet is not a protective strategy for patients with amyotrophic lateral sclerosis (ALS) and hence is contraindicated."<sup>[55]</sup> Hamadeh *et al* also note two human studies<sup>[56][57]</sup> that they indicate show "low energy intake correlates with death in people with ALS." However, in the first study, Slowie, Paige, and Antel state: "The reduction in energy intake by ALS patients did not correlate with the proximity of death but rather was a consistent aspect of the illness." They go on to

conclude: "We conclude that ALS patients have a chronically deficient intake of energy and recommended augmentation of energy intake." (PMID 8604660)

Previously, Pedersen and Mattson also found that in the ALS mouse model, CR "accelerates the clinical course" of the disease and had no benefits.<sup>[58]</sup> Suggesting that a calorically dense diet may slow ALS, a ketogenic diet in the ALS mouse model has been shown to slow the progress of disease.<sup>[59]</sup> More recently, Mattson *et al* opine that the death by ALS of Roy Walford, a pioneer in CR research and its antiaging effects, may have been a result of his own practice of CR.<sup>[60]</sup> However, as Mattson *et al* acknowledge, Walford's single case is an anecdote that by itself is insufficient to establish the proposed cause-effect relation.

### **Negligible effect on larger organisms**

Another objection to CR as an advisable lifestyle for humans is the claim that the physiological mechanisms that determine longevity are very complex, and that the effect would be small to negligible in our species.<sup>[61]</sup>

## **Intermittent fasting as an alternative approach**

Main article: Intermittent fasting

Studies by Mark P. Mattson, Ph. D., chief of the National Institute on Aging's (NIA) Laboratory of Neurosciences, and colleagues have found that intermittent fasting and calorie restriction affect the progression of diseases similar to Huntington's disease, Parkinson's disease, and Alzheimer's disease in mice (PMID 1119686). In one study, rats and mice ate a low-calorie diet or were deprived of food for 24 hours every other day (PMID 12724520). Both methods improved glucose metabolism, increased insulin sensitivity, and increased stress resistance. Researchers have long been aware that calorie restriction extends lifespan, but this study showed that improved glucose metabolism also protects neurons in experimental models of Parkinson's and stroke.

Another NIA study found that intermittent fasting and calorie restriction delays the onset of Huntington's disease-like symptoms in mice and prolongs their lives (PMID 12589027). Huntington's disease (HD), a genetic disorder, results from neuronal degeneration in the striatum. This neurodegeneration results in difficulties with movements that include walking, speaking, eating, and swallowing. People with Huntington's also exhibit an abnormal, diabetes-like metabolism that causes them to lose weight progressively.

This NIA study compared adult HD mice who ate as much as they wanted with HD mice who were kept on an intermittent fasting diet during adulthood. HD mice possess the abnormal human gene huntingtin and exhibit clinical signs of the disease, including abnormal metabolism and neurodegeneration in the striatum. The mice on the fasting program developed clinical signs of the disease about 12 days later and lived 10 to 15% longer than the free-fed mice. The brains of the fasting mice also showed less

degeneration. Those on the fasting program also regulated their glucose levels better and did not lose weight as quickly as the other mice. Researchers found that fasting mice had higher brain-derived neurotrophic factor (BDNF) levels. BDNF protects neurons and stimulates their growth. Fasting mice also had high levels of heat-shock protein-70 (Hsp70), which increases cellular resistance to stress.

Another NIA study compared intermittent fasting with cutting calorie intake. Researchers let a control group of mice eat freely (ad libitum). Another group was fed 60% of the calories that the control group consumed. A third group was fasted for 24 hours, then permitted to free-feed. The fasting mice didn't cut total calories at the beginning and the end of the observation period, and only slightly cut calories in between. A fourth group was fed the average daily intake of the fasting mice every day. Both the fasting mice and those on a restricted diet had significantly lower blood sugar and insulin levels than the free-fed controls. Kainic acid, a toxin that damages neurons, was injected into the dorsal hippocampus of all mice. Hippocampal damage is associated with Alzheimer's. Interestingly, the scientists found less damage in the brains of the fasting mice than in those that ate a restricted diet, and most damage in mice with an unrestricted diet. But the control group which ate the average daily intake of the fasting mice also showed less damage than the mice with restricted diet.<sup>[62]</sup>

Another Mattson study<sup>[63]</sup> in which overweight adult asthmatics followed alternate day calorie restriction (ADCR) for eight weeks showed marked improvement in oxidative stress, inflammation, and severity of the disease. Evidence from the medical literature suggests that ADCR in the absence of weight loss prolongs lifespan in humans<sup>[64]</sup>.

## Notes

1. <sup>^ a b</sup> Mattson MP (2005). "Energy intake, meal frequency, and health: a neurobiological perspective". *Annu. Rev. Nutr.* **25**: 237–60. doi:[10.1146/annurev.nutr.25.050304.092526](https://doi.org/10.1146/annurev.nutr.25.050304.092526). PMID 16011467.
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3. <sup>^</sup> Bergamini E, Cavallini G, Donati A, Gori Z (2003). "The anti-ageing effects of caloric restriction may involve stimulation of macroautophagy and lysosomal degradation, and can be intensified pharmacologically". *Biomed. Pharmacother.* **57** (5-6): 203–8. PMID 12888255. <http://linkinghub.elsevier.com/retrieve/pii/S0753332203000489>.
4. <sup>^ a b</sup> Rezzi S, Martin FP, Shanmuganayagam D, Colman RJ, Nicholson JK, Weindruch R (May 2009). "Metabolic shifts due to long-term caloric restriction revealed in nonhuman primates". *Exp. Gerontol.* **44** (5): 356–62. doi:[10.1016/j.exger.2009.02.008](https://doi.org/10.1016/j.exger.2009.02.008). PMID 19264119.
5. <sup>^</sup> Fontana L, Weiss EP, Villareal DT, Klein S, Holloszy JO (2008). "Long-term effects of calorie or protein restriction on serum IGF-1 and IGFBP-3 concentration in humans". *Aging Cell* **7** (5): 681-687. PMID 18843793. <http://www3.interscience.wiley.com/journal/121398450/abstract?CRETRY=1&SRETRY=0>.
6. <sup>^</sup> Cuervo AM, Bergamini E, Brunk UT, Dröge W, French M, Terman A (2005). "Autophagy and aging: the importance of maintaining "clean" cells". *Autophagy* **1** (3):

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<http://www.landesbioscience.com/journals/auto/abstract.php?id=2017>.
7. <sup>^</sup> The Anti-Aging Plan: Strategies and Recipes for Extending Your Healthy Years by Roy Walford (page 26)
  8. <sup>^</sup> <sup>a</sup> <sup>b</sup> <sup>c</sup> Some Try Calorie Restriction For Long Life
  9. <sup>^</sup> Long-term Calorie Restriction Improves Cardiovascular Risk
  10. <sup>^</sup> Strict diet lowers heart risk
  11. <sup>^</sup> A high fasting plasma insulin concentration predicts type 2 diabetes independent of insulin resistance: evidence for a pathogenic role of relative hyperinsulinemia
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