



## Review

## Can we live longer by eating less? A review of caloric restriction and longevity

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## ABSTRACT

Caloric restriction, decreasing caloric intake by 20–30%, was first shown to extend life in rats nearly 80 years ago. Since that time, limiting food intake for longevity has been investigated in species from yeast to humans. In yeast and lower animals, caloric restriction has repeatedly been demonstrated to lengthen the life span. Studies of caloric restriction in non-human primates and in humans are ongoing and initial results suggest prolongation of life as well as prevention of age-related disease. There is also data in rodents suggesting that short term caloric restriction has beneficial effects on fertility. Although caloric restriction has many positive effects on health and longevity, quality of life on a restricted diet as well as the ability to maintain that diet long term are concerns that must be considered in humans.

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The more you eat, the less flavor; the less you eat, the more flavor. – Chinese Proverb

## 1. Introduction

The seminal study of caloric restriction (CR) was in 1935 in rats and revealed prolongation of life span [1]. Since that time, CR has been found to prolong life in many species including yeast, worms, flies, rodents, and monkeys [2]. CR has been found to ameliorate age-related diseases including diabetes, cardiovascular disease, cancer, and dementia in rodents, non-human primates, and humans [2–4]. Although there is limited scientific data in humans, people are practicing CR. The Calorie Restriction Society International has over 7000 members and encourages people to eat 25% fewer calories than recommended in order to attain a longer, healthier life [5,6]. People practicing CR aim to eat about 25% fewer calories than recommended while also attempting to eat a nutrient dense diet to fulfill all nutrient requirements [5]. There are several described methods of dietary therapy to achieve longevity including restriction of calories, alternate day fasting (fasting every other day and eating ad libitum on alternate days), creating an energy deficit by a combination of restricting intake and expending energy with exercise, and dietary restriction (restricting specific groups of food) [3]. This review will focus on restriction of calorie intake. Because of the success of CR for prolonging the life span in lower species, there are studies of CR ongoing in both non-human primates and humans [7,8]. This review will focus on the evidence for CR promoting longevity in lower animals, non-human primates, and humans as well as the effects of CR on fertility (Fig. 1).

## 2. Caloric restriction in lower animals

CR without malnutrition has been shown to increase the life span of yeast, worms, flies, and mice [2]. Decreasing glucose concentration, thereby causing CR, in the growth medium of yeast extends both reproductive life and life span [9]. A variety of methods to yield CR in *Caenorhabditis elegans* extends the life span [10]. Interestingly, in *Drosophila* CR by limiting the intake of amino acids is more effective in extending the life span than reducing sugars [11]. Regardless of the method used to restrict calories, it is thought that the mechanisms for life extension are the same across species [2]. Although the mechanisms are not fully elucidated, it appears that CR causes changes in nutrient-sensing pathways in all species studied [2].

The first evidence that CR extends life was in rats in 1935 [1]. CR has been studied extensively in mice and rats since that time. CR in rodents extends the life span by 60% [12]. Perhaps more importantly, 30% of the CR animals die without evidence of age-related disease (versus only 6% of control animals) [12,13]. It has been suggested that that prolongation of life by CR is also mediated by reduced activity of nutrient-sensing pathways, including amino-acids sensing as well as pathways on the utilization and storage of carbon sources (see review [2]).

## 3. Caloric restriction in non-human primates

Currently, there are three groups looking at CR in non-human primates (National Institute on Aging, University of Wisconsin, and University of Maryland), and the longest study has been running since 1987 (see review [8]). Two of the groups are focusing on CR's impact on health and life span and one is investigating the effects of CR on obesity and diabetes (see review [8]). A fourth group from Wake Forest University performed a 4 year CR study on *Cynomolgus* monkeys specifically focusing on atherosclerosis [14]. The majority of the animals in these studies are rhesus

monkeys, with a median life span of 26 years and a maximal life span of 40 years in captivity (see review [15]). When the studies were started, the animals' age range was 1–17 years [4,16,17]. The CR in the monkeys at University of Wisconsin, National Institute on Aging, and Wake Forest University was a 30% reduction in calories from baseline and at the University of Maryland was a change in diet to achieve a pre-specified weight in the normal-lean range [4,14,16,17].

### 3.1. CR and longevity in non-human primates (NHP)

The studies are ongoing and the jury is still out on whether CR extends the life span in NHP. However, the group from University of Wisconsin recently published their 20 year data showing a significantly increased chance of survival in the CR monkeys, 80%, versus the control monkeys, 50% [4]. The group at University of Maryland found similar results, though theirs did not reach statistical significance [16]. At the University of Wisconsin, 37% of the control monkeys that have died succumbed to an age-related disease whereas only 13% of the CR monkeys died secondary to an age-related disease [4].

### 3.2. Change in body composition

Although the studies regarding the effect of CR on life span are ongoing, there is abundant data on the impact of CR on health in NHP. CR is consistently noted to cause a decrease in both body weight and body composition, with a decrease in body fat [4,14,16,17]. Specifically, CR reduces total abdominal and intra-abdominal fat mass as evaluated by CT scan [14] and reduces trunk to leg fat ratio [18], both established risk factors for cardiovascular disease. There are other changes in body composition associated with CR. The typical loss of muscle mass with age is significantly less in the CR monkeys [4]. There are also some differences in bone density. Male CR rhesus monkeys are noted to have lower bone mineral density versus controls, likely secondary to differences in body mass [19]. There are no observed differences in bone mineral density or markers of bone turnover in the female CR rhesus monkeys versus controls [20]. It is, however, important to note that the females have been on the CR diet 5 years less than the males. Importantly, despite the lower bone mineral density seen in the male monkeys, there was no observed increase in fractures [17].

### 3.3. Glucose regulation

Another finding seen in all 4 studies reported to date is significant improvement in glucose regulation. CR monkeys have significantly lower fasting glucose and improved insulin sensitivity versus control monkeys [14,21,22]. At the University of Wisconsin, after 20 years of adult-onset CR, 16 out of 38 control monkeys had progressed to diabetes or pre-diabetes whereas none of the 38 CR monkeys had [4]. Thus, while reduced energy expenditure associated with CR could represent a potential mechanism of life prolongation, the impact of improved insulin sensitivity in and of itself has to be considered.

### 3.4. Cardiovascular effects

CR also seems to improve cardiovascular disease in the nonhuman primates, though this finding has not been uniform across the studies. The Wake Forest University group fed both the control and CR monkeys an atherogenic diet with 30% of calories from fat [23] whereas the groups at the National Institute on Aging and University of Wisconsin fed the control and CR monkeys a diet much lower in fat (5% and 10% respectively) [24,25]. The CR monkeys in the Wake Forest University study had no improvement in cholesterol,

- Prolonged caloric restriction improves longevity in yeast, nematodes, rodents and other lower animals
- Calorie restriction in non-human primates has been shown to prevent age-related disease including diabetes, cancer, cardiovascular disease and brain atrophy
- In rhesus monkeys, a younger outward appearance has been observed after 20 years of decreased calorie intake
- Studies of caloric restriction and longevity in humans are still ongoing, however the impact of prolonged caloric restriction appears to be beneficial and has some possible anti-aging effects

**Fig. 1.** Key points.

blood pressure, or coronary artery atherosclerosis [14]. In contrast, the CR monkeys who were fed lower fat diets at the other institutions had lower triglyceride levels and higher HDL sub-fractions compared to the control monkeys [8,24]. Additionally, the female CR monkeys had lower blood pressures versus controls [17]. The CR monkeys at the University of Wisconsin had a 50% reduction in cardiovascular disease versus controls [4].

### 3.5. Other effects

In rhesus monkeys, CR was also found to reduce the incidence of neoplasia by 50%, reduce brain atrophy associated with aging, and result in a younger outward appearance [4]. Although final data regarding CR and life span is not yet available for all the NHP currently being studied, the initial results appear promising. Not only does there appear to be a prolongation of life, this prolongation appears to be a healthy one with a decreased risk of diabetes, cardiovascular disease, and cancer.

## 4. Caloric restriction in humans

Several studies evaluating CR (accidental and intentional) in humans have been published. These include observational studies of religious fasts [26], Okinawans [27], and Biosphere 2 [28] as well as a randomized controlled trial, CALERIE (Comprehensive Assessment of the Long Term Effects of Reducing Intake of Energy) [29,30]. While there is no definitive data that CR prolongs life in humans (because of the long life span), data on the health effects of CR are convincing and will be discussed here.

### 4.1. Religious fasts

The religious fasts that have been studied include Muslims fasting from sunrise to sunset during the month of Ramadan, Greek Orthodox who eat a restricted and nearly vegetarian diet for 180–200 days per year, and Christians following the Daniel Fast (a vegan diet) for 21–40 days (see review [26]). Studies of BMI, lipids, and glucose and insulin parameters in Muslims during Ramadan reveal no consistent results [26]. In Greek Orthodox, BMI, total cholesterol, and LDL are decreased post-fast as compared to pre-fast [31]. A study that enrolled people into a 21 day Daniel Fast found improvements in total cholesterol, LDL, blood pressure, insulin, and C-reactive protein with only a minimal decrease in body weight [32]. People do these fasts for religious reasons rather than long term health but these observational studies provide some data to support the use of even short term caloric and dietary restriction.

Additionally, potential impact of compensatory over eating or binge eating following the fasts should be investigated.

### 4.2. Okinawa, Japan

People from the Japanese island of Okinawa have a life expectancy among the highest in the world and one of the highest rates of centenarians [33]. The eternal nature versus nurture question has been repeatedly posed in studies on Okinawans and it is intriguing that they have a lower caloric intake and a longer life span than the mainland Japanese population. An epidemiologic study was performed to further evaluate this information [27]. The study found that in the elderly Okinawans, there had been a lower caloric intake and negative energy balance in earlier life with a resultant life-long low BMI, decreased risk for age-related disease, and an extended life span versus mainland Japanese and Americans [27].

### 4.3. Biosphere 2

The Biosphere 2 study included 4 men and 4 women inside a sealed environment for 2 years. During that time, they consumed a low calorie, nutrient dense, mostly vegetarian diet (approximately 1800–2000 kcal/day) while expending significant energy [28]. During the study period, the subjects had significant weight loss and improvements in blood pressure, glucose, insulin, cholesterol, LDL, and triglycerides [28]. The participants were followed for several months after the study and all returned to their pre-study weight and had return of the above variables to their pre-study levels suggesting the difficulty of maintaining a long term CR lifestyle [28].

### 4.4. CALERIE

The ongoing randomized, controlled, clinical trial of CR in humans is called CALERIE (Comprehensive Assessment of the Long Term Effects of Reducing Intake of Energy) [7]. This is a 2 year multicenter trial of 225 normal weight subjects randomized to a 25% CR diet or a weight maintenance diet [7]. The results of the trial are not yet published but this study was based on several smaller, single center, randomized controlled trials. The preliminary studies each had approximately 50 subjects that were randomized to a 20–25% CR diet or weight maintenance diet for 6 months to 1 year [30,34]. The studies found that the CR subjects attained a lower body weight [30,34], decreased whole body and visceral fat [34], improved fasting insulin levels [30], improvements in cardiovascular disease markers (LDL, total cholesterol to HDL ratio, and C-reactive protein) [35], and had no changes in bone density [36].

#### 4.5. Compliance with caloric restriction

The observational and randomized controlled trial data seem to support the use of CR in humans for preventing age-related diseases although data on prolonging the life span are lacking. The primary concern for long term CR in humans is the ability to maintain CR. There are several sources suggesting that maintenance of CR is difficult. In one of the preliminary CALERIE trials, study subjects were assigned to a 20% CR diet for 1 year [34]. Even in the setting of a clinical trial, participants only maintained a 10% CR over the study period [34]. Another study of 10 overweight and obese subjects placed on a very low calorie diet for a month prior to undergoing in vitro fertilization had only 6 subjects that completed the trial [37].

#### 4.6. Psychological issues associated with CR

There is also concern, especially in the popular media, that CR is really just anorexia nervosa. This was studied as part of a preliminary CALERIE study and the results showed that following a CR diet under study conditions for one year did not increase eating disorder symptoms in the subjects [38]. Although subjects in a clinical trial are different than those practicing CR independently, followers of CR strive for CR without malnutrition and aim to eat a nutrient dense but low calorie diet [5]. Despite the difficulty with compliance in the clinical trials above, some people do maintain a CR diet over the long term. There is an ongoing study at the University of California San Francisco investigating the differences between those who are able and those who are not able to maintain this behavior modification over the long term [39].

#### 4.7. Studies of potential heritability of longevity in humans

Although there is no definitive data that CR promotes longevity in humans, there are studies looking at people with exceptional longevity from the Longevity Study at Albert Einstein College of Medicine (see review [40]). One hundred forty-five centenarians were studied and found to have a strong family history of longevity and a low prevalence of age-related disease [41]. Although the subjects had longevity and protection from age related disease, 20% were obese, 90% smoked, and none followed a vegetarian diet or avidly exercised [42]. Importantly, the centenarians' offspring were found to be healthier than age matched controls (see review [40]). This information suggests that exceptional longevity in humans may be more related to genetics than lifestyle (see review [40]).

### 5. Caloric restriction and fertility/reproductive senescence

As mentioned above, CR impacts multiple physiologic processes. We will now focus more on CR's effects on fertility and reproductive senescence. A long held theory exists that in CR states, animals allocate resources away from reproduction and towards longevity [43]. That hypothesis is challenged, however, by the increased reproduction in CR yeast [9]. Additionally, there are some studies in higher animals that challenge this theory.

#### 5.1. Fertility effects in male rhesus monkeys

The NHP undergoing CR were prevented from mating but there is evidence from surrogate markers that CR does not significantly impact male fertility. Male rhesus monkeys were studied after 7 years of a 30% CR diet and found to have no difference in LH or testosterone levels when compared to control monkeys [44]. In the same cohort of monkeys, there were no differences in semen parameters between CR and control monkeys after 8 years [45].

#### 5.2. Reproductive senescence in rodents

In rodents, there is intriguing evidence that suggests short CR interventions followed by normal diet re-feeding improves both reproductive senescence and post-re-feeding fertility. In female rats placed on a 4 month CR diet in adulthood, ovarian follicular reserve and fertility were maintained well past the control group upon return to an ad libitum diet (23 months versus 15.5 months) [46]. However, fertility and survival of offspring were extremely poor during the period of CR [46].

Another study of female mice used CR for only 30 days when the mice were 6 weeks of age and found that the CR mice had higher fecundity than controls when returned to an ad libitum diet [43]. These findings are quite interesting given the fact that infertility in humans is increasing secondary to a delay in childbearing and diminished ovarian reserve [47].

#### 5.3. CR and fertility in humans

In humans, there is little data on CR and fertility or reproductive senescence. In overweight and obese women, weight loss is known to improve metabolic abnormalities and lead to the resumption of spontaneous ovulation [48]. However, there are no randomized controlled trials of long term CR and fertility in humans. Additionally, there are no reports regarding fertility from the clinical trials of CRs in humans.

There was a pilot study of 10 overweight and obese women who were placed on a very low calorie diet immediately prior to in vitro fertilization (IVF) [37]. The study had a 40% drop-out rate and does not report on pregnancy rates or pregnancy outcomes so it is difficult to draw any conclusions from the data presented [37]. There is evidence from the Dutch famine that those conceived during this period of malnutrition had an increase in health problems over the course of their life [49]. This information is likely not applicable to CR because a famine is a time of malnutrition whereas those practicing CR should have adequate nutrition but low caloric intake.

### 6. Conclusions

Caloric restriction has been shown to prolong life in a variety of species and to prevent age-related disease in non-human primates. Evidence that CR could prevent age-related disease in humans is emerging. Recent data regarding improved reproductive senescence with CR in rodents needs to be investigated in humans. The mechanisms by which CR is effective in prolonging life appear to be similar across species. Further research needs to be done to identify the specific nutrient-sensing pathways implicated in anti-aging effects of CR as well their downstream effects, especially in humans. Behavioral research is warranted to investigate why some individuals are able to comply with this strict behavior change in the long term whereas most are not. Although CR was shown to prolong life nearly 80 years ago, there is much left to learn about it. Most importantly, perhaps, the jury is still out on whether caloric restriction truly has the ability to prolong a healthy and productive life in humans.

#### Contributors

Lauren Roth is the first author. She and the senior author made an outline for the manuscript together. Dr. Roth did most of the literature search and wrote the first draft of the paper. She also did the final editing to the paper.

Alex Polotsky is the senior author. He and the first author did the outline for the paper together. He assisted with the literature

search and edited the draft of the manuscript. He also approved the final draft of the paper.

### Competing interests

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