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# Systematic Review Article: Effects of Long-Term Fasting and Caloric Restriction on Physiological and Metabolic Functions.

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## Abstract

Long-term fasting (LTF) and caloric restriction (CR) have garnered increasing interest as interventions that may confer numerous health benefits, including improved metabolic health, enhanced cardiovascular function, neuroprotection, and extended longevity. The potential to influence physiological processes such as insulin sensitivity, lipid metabolism, inflammation, oxidative stress, and cellular repair mechanisms makes these interventions promising avenues for both disease prevention and health optimization. This systematic review examines the body of research surrounding LTF and CR, their physiological impacts, the molecular mechanisms driving these changes, and the challenges and risks associated with their long-term application. We also explore future research directions and possible therapeutic applications in the context of aging and age-related diseases.

**Key Words**: Long-Term Fasting, Caloric Restrictions, Physiological Functions, Metabolic Functions, Disease Prevention.

## Introduction

The pursuit of longevity and improved health-span—defined as the period during which an individual maintains optimal health—has been a central focus of medical and scientific research for decades. Among various lifestyle interventions that have been studied, two dietary strategies, long-term fasting (LTF) and caloric restriction (CR), stand out for their potential to mitigate the effects of aging and improve overall health. While caloric restriction, the reduction of caloric intake without malnutrition, has been studied extensively in animal models, its translation into human health has been more recent. Long-term fasting, including intermittent fasting and periodic fasting over days or weeks, has emerged as a comparable intervention that may offer similar benefits.[1,2]

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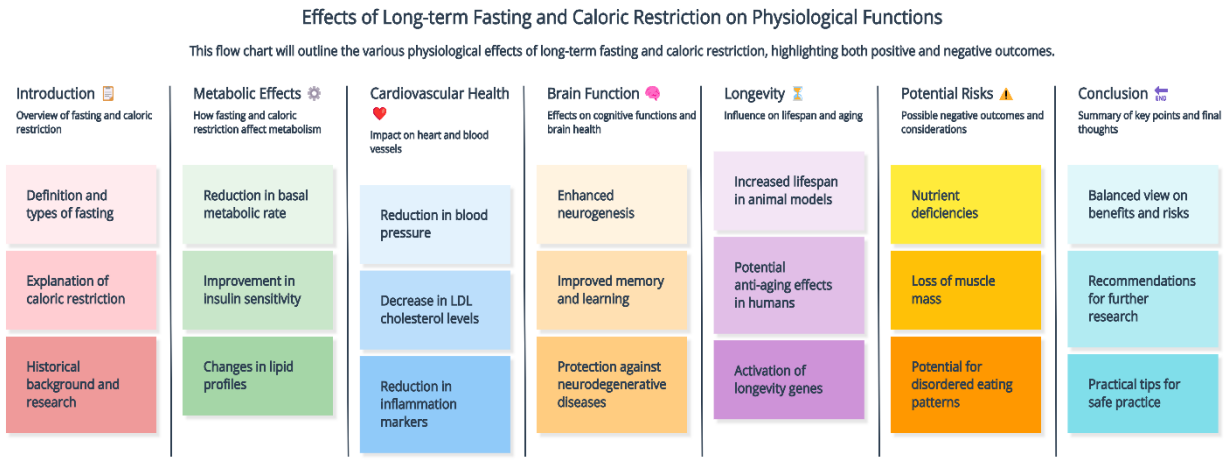
This review aims to summarize and synthesize current research on LTF and CR, focusing on their effects on physiological functions such as metabolism, cardiovascular health, brain function, and aging. Furthermore, we discuss the mechanisms through which these dietary interventions exert their effects, the practical challenges involved in their long-term application, and the future directions of research in this field.




## Material and Methods

### Search Strategy

A comprehensive literature search was conducted across multiple databases, including PubMed, Scopus, and Web of Science, covering publications from 1990 to 2023. The search terms included "long-term fasting," "caloric restriction," "metabolism," "cardiovascular function," "neuroprotection," "aging," "longevity," and "physiological functions." Studies were selected based on relevance to the topic, with a focus on those that provided data on human or animal models of LTF or CR and their impact on metabolic health, cardiovascular function, neuroprotection, and aging processes.

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### Inclusion and Exclusion Criteria

Inclusion criteria:

- Studies evaluating the physiological effects of LTF or CR on metabolic, cardiovascular, neurological, or aging-related functions.
- Both human clinical trials and well-constructed animal model studies.
- Reviews and meta-analyses that provide synthesis or data relevant to the discussed physiological functions.

Exclusion criteria:

- Studies focusing exclusively on short-term fasting (<30 days) or caloric reduction with no assessment of physiological effects beyond weight loss.
- Non-peer-reviewed articles or studies not available in full text.
- Articles that did not evaluate specific physiological functions or lacked clarity in defining the intervention.

### Data Extraction and Synthesis

The primary focus of data extraction included study design, population or animal models used, duration of intervention, and the reported effects on specific physiological markers. These markers included changes in insulin sensitivity, glucose metabolism, lipid profiles, cardiovascular health, neuroprotection, inflammatory markers, oxidative stress, telomere length, and longevity outcomes. Data were synthesized qualitatively, with a focus on identifying consistent patterns and key differences across studies.

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## Results

The results from both animal and human studies indicate that LTF and CR exert significant and beneficial effects on several key physiological functions. The following subsections break down the major findings according to their impact on metabolic health, cardiovascular function, brain health, and longevity.

### Metabolic Effects

### Insulin Sensitivity and Glucose Metabolism

Both CR and LTF have been extensively studied for their effects on insulin sensitivity and glucose regulation, which are critical factors in metabolic health and the prevention of diseases such as type 2 diabetes. CR is associated with enhanced insulin sensitivity across a range of animal models and human populations. The mechanisms through which CR improves glucose

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metabolism involve both direct and indirect actions on cellular energy regulation pathways, including AMP-activated protein kinase (AMPK), sirtuin signaling, and insulin-like growth factor-1 (IGF-1) downregulation [3]. In rodents, CR has been shown to significantly delay the onset of diabetes by improving beta-cell function and enhancing insulin secretion [4].

Human studies similarly support these findings. Heilbronn et al. conducted a six-month study on non-obese individuals, demonstrating that CR improved insulin sensitivity and reduced fasting glucose levels, providing strong evidence that CR can play a role in preventing metabolic diseases in humans [5]. In addition, long-term fasting, including intermittent fasting, has shown comparable improvements in glucose metabolism. Studies suggest that LTF promotes better glycemic control by reducing fasting insulin levels and promoting glucose uptake by skeletal muscles and adipose tissues [6].

**Lipid Metabolism and Fat Oxidation**

LTF and CR both induce favorable changes in lipid metabolism. CR leads to reductions in total cholesterol, low-density lipoprotein (LDL), and triglycerides, while promoting increases in high-density lipoprotein (HDL). This lipid profile shift is associated with a decreased risk of cardiovascular diseases, particularly atherosclerosis [7]. Animal models demonstrate that CR promotes fatty acid oxidation by increasing the expression of enzymes involved in lipid breakdown, which reduces fat deposition and enhances overall metabolic flexibility [8].

Human studies align with these findings. Intermittent fasting, a form of LTF, has been shown to significantly improve lipid profiles, with reductions in LDL cholesterol and triglycerides observed after 12 weeks of fasting protocols [9]. These effects are largely driven by enhanced fat mobilization and oxidation, leading to improved body composition and a reduction in visceral fat.

**Mitochondrial Function and Oxidative Stress**

Mitochondrial efficiency is a crucial aspect of cellular metabolism, and both CR and LTF positively influence mitochondrial function. Sirtuin activation, particularly SIRT1, plays a pivotal role in enhancing mitochondrial biogenesis and improving cellular energy production. By upregulating the production of key mitochondrial proteins, CR promotes more efficient ATP production and reduces the generation of reactive oxygen species (ROS) [10].

Oxidative stress, a hallmark of aging and many chronic diseases, is significantly reduced under CR conditions. This reduction in oxidative stress is due to both enhanced mitochondrial efficiency and the increased expression of endogenous antioxidant enzymes such as superoxide dismutase and catalase. Animal studies show that CR reduces oxidative damage in tissues, which translates into better overall health and delayed onset of age-related diseases [11].

**Cardiovascular Health**

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## Blood Pressure and Vascular Function

One of the most well-documented effects of CR and LTF is the reduction in blood pressure, which has profound implications for cardiovascular health. CR has been shown to reduce both systolic and diastolic blood pressure in animal models and human studies. These reductions are thought to be mediated through improved vascular elasticity, decreased oxidative stress, and enhanced nitric oxide production, which improves endothelial function [12].

A long-term study by Fontana et al. demonstrated that individuals practicing CR exhibited significantly lower blood pressure and improved arterial compliance compared to those on unrestricted diets. This finding suggests that CR may reduce the risk of hypertension and other cardiovascular conditions [13]. Similar results have been observed in individuals practicing intermittent fasting, with studies reporting reduced blood pressure and improved vascular function [14].

## Lipid Profiles and Inflammation

CR and LTF positively affect cardiovascular health by improving lipid profiles and reducing inflammation. Numerous studies have reported that CR lowers LDL cholesterol and triglycerides while maintaining or increasing HDL levels, thus reducing the risk of atherosclerosis and coronary artery disease [15]. Furthermore, CR significantly reduces inflammatory markers such as CRP and IL-6, both of which are implicated in the development of cardiovascular diseases [16].

Animal studies have confirmed these findings, showing that CR reduces the development of atherosclerotic plaques and improves endothelial function. These benefits are attributed to a reduction in systemic inflammation, improved lipid metabolism, and enhanced antioxidant defences.

## Heart Rate and Cardiovascular Autonomic Function

LTF and CR also positively affect the autonomic nervous system, as evidenced by reductions in resting heart rate and improvements in heart rate variability (HRV). HRV is a key indicator of autonomic balance, with higher HRV reflecting better cardiovascular health and lower risk of adverse events such as heart failure or arrhythmias.

Animal studies indicate that CR improves HRV by enhancing parasympathetic nervous system activity, which promotes relaxation and reduces cardiovascular stress. Human studies similarly show that CR and intermittent fasting protocols reduce heart rate and improve HRV, indicating that these interventions may offer cardioprotective benefits beyond traditional risk factors such as blood pressure and cholesterol.

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## Neuroprotective Effects

### Brain-Derived Neurotrophic Factor (BDNF) and Cognitive Function

BDNF is a critical protein involved in neuronal growth, survival, and synaptic plasticity. Both CR and LTF have been shown to increase BDNF levels, particularly in regions of the brain associated with learning and memory, such as the hippocampus. Animal models demonstrate that CR and intermittent fasting enhance neurogenesis, improve synaptic plasticity, and promote cognitive function.

In humans, intermittent fasting has been associated with improvements in mood, cognitive performance, and memory, particularly in older adults. While long-term human data are still limited, early evidence suggests that LTF and CR may play a role in preventing cognitive decline and promoting brain health.

### Prevention of Neurodegenerative Diseases

The potential neuroprotective effects of CR and LTF extend to the prevention of neurodegenerative diseases such as Alzheimer's and Parkinson's. Animal models have shown that CR reduces the accumulation of beta-amyloid plaques and tau protein aggregates, which are hallmarks of Alzheimer's disease pathology. These effects are thought to be mediated through enhanced autophagy, a process by which cells clear out damaged proteins and organelles, thus reducing the toxic burden on neurons.

In Parkinson's disease models, CR has been shown to improve mitochondrial function and reduce oxidative damage, thereby protecting dopaminergic neurons from degeneration. Although human trials are limited, observational studies suggest that individuals who practice CR may experience a slower rate of cognitive decline and a reduced risk of developing neurodegenerative diseases later in life.

### Oxidative Stress and Autophagy

Oxidative stress plays a central role in the development of neurodegenerative diseases, and both CR and LTF have been shown to reduce oxidative damage in the brain. This reduction is achieved through enhanced mitochondrial function, increased production of endogenous antioxidants, and the activation of autophagy.

Autophagy, a key cellular process for maintaining homeostasis, is upregulated during periods of fasting and caloric restriction. This process enables the brain to clear out damaged organelles and proteins, which helps protect against oxidative stress and reduce the risk of neurodegeneration. In animal models, CR-induced autophagy has been shown to improve cognitive function and protect neurons from injury.

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## Aging and Longevity

### Longevity in Animal Models

CR is one of the most well-established interventions for extending lifespan in animal models. Studies across multiple species, including yeast, flies, worms, rodents, and primates, have consistently shown that CR can extend lifespan by up to 40%. The mechanisms underlying these effects include reduced metabolic rate, enhanced DNA repair, improved mitochondrial function, and decreased oxidative damage.

In primates, long-term CR has been shown to delay the onset of age-related diseases such as cancer, diabetes, and cardiovascular disease, suggesting that CR may improve both lifespan and health span. The benefits of CR in animal models are attributed to its ability to promote cellular repair processes, reduce oxidative stress, and modulate key signaling pathways involved in aging, such as the mTOR pathway and insulin/IGF-1 signaling.

### Human Aging Studies

While direct evidence of lifespan extension in humans is still lacking, CR has been shown to improve biomarkers of aging and delay the onset of age-related diseases. Human populations that practice CR, such as the Okinawan elders, exhibit longer healthspans, lower levels of inflammatory cytokines, and reduced risk factors for cardiovascular disease and cancer.

The CALERIE (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) study, one of the most comprehensive human trials of CR, demonstrated that two years of CR improved metabolic markers, reduced oxidative stress, and enhanced cardiovascular function in non-obese adults. These findings suggest that CR may slow the biological aging process, even in humans who are not overweight.

### Telomere Length and Cellular Senescence

Telomeres, the protective caps at the ends of chromosomes, shorten with each cell division and are considered a marker of biological aging. CR has been shown to slow the rate of telomere shortening in both animal and human studies, potentially delaying cellular senescence and extending lifespan. Animal models show that CR reduces the activity of telomere-shortening enzymes and promotes the maintenance of telomere length, which is associated with better cellular health and longevity.

Human studies also support these findings. A study of individuals practicing CR for extended periods showed that they had longer telomeres compared to age-matched controls, suggesting that CR may preserve telomere length and slow the aging process at the cellular level. However, more research is needed to confirm these effects and determine whether they translate into increased longevity in humans.

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## Discussion

### Mechanisms of Action

The physiological benefits of CR and LTF are driven by several molecular and cellular pathways that enhance metabolic efficiency, reduce oxidative stress, and promote cellular repair processes. One of the central mechanisms involved is the activation of AMPK, a key energy sensor that regulates glucose uptake, lipid metabolism, and mitochondrial function. By activating AMPK, CR and LTF help improve insulin sensitivity, enhance fat oxidation, and reduce fat storage.

Another key pathway involved in the effects of CR and LTF is the sirtuin family of proteins, particularly SIRT1. Sirtuins regulate several processes related to aging, including DNA repair, mitochondrial biogenesis, and oxidative stress responses. CR increases the activity of SIRT1, which enhances mitochondrial function, reduces oxidative damage, and promotes cellular longevity. Additionally, reduced insulin/IGF-1 signaling, which is associated with both CR and LTF, has been shown to extend lifespan in animal models by reducing the risk of cancer and other age-related diseases.

### Challenges of Long-Term Adherence

Despite the well-documented benefits of CR and LTF, long-term adherence to these dietary interventions poses significant challenges. Many individuals struggle with the hunger, fatigue, and social limitations associated with sustained caloric reduction or intermittent fasting. In addition, the psychological impact of restrictive eating patterns may lead to difficulties in maintaining these interventions over the long term.

Intermittent fasting protocols, such as time-restricted feeding or alternate-day fasting, may offer a more sustainable approach for individuals who find continuous CR difficult to follow. These protocols allow for periodic fasting while still providing the metabolic benefits of extended fasting periods.

### Individual Variability in Response

One of the key challenges in applying CR and LTF as therapeutic interventions is the significant variability in individual responses. Factors such as genetics, baseline metabolic health, and lifestyle play a critical role in determining how an individual responds to these dietary interventions. While some individuals experience significant improvements in metabolic health and reductions in age-related diseases, others may not experience the same level of benefit.

In some cases, CR may have adverse effects, such as muscle loss, bone density reduction, or immune suppression, particularly in older adults or those with underlying health conditions.

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Personalized approaches to CR and LTF, which take into account individual variability, are necessary to ensure that these interventions are both effective and safe for all populations.

**Future Research Directions**

While the evidence supporting the benefits of CR and LTF is robust in animal models, more human studies are needed to confirm these findings and explore the long-term effects of these interventions. Large-scale, randomized controlled trials with diverse populations are essential to determine the safety and efficacy of CR and LTF in promoting longevity and reducing the risk of age-related diseases.

Additionally, research should focus on identifying biomarkers that predict individual responses to CR and LTF. This would allow for more personalized dietary strategies that maximize the benefits of these interventions while minimizing the risks. Finally, future studies should explore the potential therapeutic applications of CR and LTF in specific populations, such as individuals with metabolic syndrome, cardiovascular disease, or neurodegenerative conditions.

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## Conclusion

Long-term fasting and caloric restriction have demonstrated significant potential for improving metabolic health, cardiovascular function, neuroprotection, and possibly extending lifespan, particularly in animal models. The translation of these findings to humans is promising, but more research is needed to determine the long-term safety and efficacy of these interventions. Individual variability in response and the challenges of adherence must be considered when recommending these dietary strategies. With personalized approaches, CR and LTF could offer significant potential in promoting health and delaying aging, paving the way for new therapeutic applications.

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