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REVIEW

# Effects of Caloric Restriction and Intermittent Fasting and Their Combined Exercise on Cognitive Functioning: A Review

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## Abstract

**Purpose of Review** The impact of dietary habits on cognitive function is increasingly gaining attention. The review is to discuss how caloric restriction (CR) and intermittent fasting (IF) can enhance cognitive function in healthy states through multiple pathways that interact with one another. Secondly, to explore the effects of CR and IF on cognitive function in conditions of neurodegenerative diseases, obesity diabetes and aging, as well as potential synergistic effects in combination with exercise to prevent cognitively related neurodegenerative diseases.

**Recent Findings** With age, the human brain ages and develops corresponding neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and epilepsy, which in turn trigger cognitive impairment. Recent research indicates that the impact of diet and exercise on cognitive function is increasingly gaining attention.

**Summary** The benefits of exercise for cognitive function and brain plasticity are numerous, and future research can examine the efficacy of particular dietary regimens during physical activity when combined with diet which can prevent cognitive decline.

**Keywords** Caloric restriction · Intermittent fasting · Cognitive · Neurodegenerative diseases · Exercise

## Introduction

There is a close connection between cognitive function and normal work and life. Research suggests cognitive decline may begin between 20 and 30 years of age [1], and it gets worse with age for people in this category. Among older adults, the prevalence of neurodegenerative diseases has increased significantly in recent years, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, epilepsy, and stroke can all impact brain function, resulting in cognitive decline [2, 3]. It is also important to note that chronic diseases such as obesity and diabetes are risk factors for cognitive decline. Globally, the population is aging, which exacerbates cognitive impairments. Hence, maintaining normal cognitive function and preventing and mitigating cognitive decline are important scientific issues today.

Despite the fact that drugs can be used clinically to improve cognitive performance, the development of this class of drugs is time-consuming and expensive, and long-term use can also have adverse effects on humans. Neurodegenerative diseases, such as Alzheimer's and Parkinson's, are commonly managed through the oral administration of pharmacological agents, including but not limited to donepezil, memantine, levodopa, and entacapone, and the central nervous system contains many protective barriers, so most drugs do not reach the brain fully, but are metabolized by the liver instead. Because the drugs are not utilized efficiently, they need to be administered at higher concentrations for the treatment to be effective, which leads to toxic effects on the heart, liver, and other organs [4]. For example, donepezil, a drug used in the treatment of AD, which has shown cognitive improvements at increased dosages in clinical studies. However, the drug may also cause gastrointestinal side effects, leading to severe side effects like anorexia, vomiting, and diarrhea [5]. While Levodopa remains the top treatment for PD's associated bradykinesia and rigidity, prolonged use of the medication has shown that symptoms like depression,

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anxiety, and cognitive impairments linked to PD don't get better, but might actually worsen these symptoms [6]. Consequently, in the field of cognitive function, non-pharmacological treatments like dietary pattern changes, physical activity, and good routines are attracting considerable attention [7]. A diet intervention is considered an effective way to prevent cognitive decline. Increasing research is being conducted on caloric restriction (CR) and intermittent fasting (IF), noted for their ease of execution, superior adherence, and potential future benefits in safeguarding cognitive function.

A systematic evaluation of the mechanisms by which CR and IF may improve cognitive function in healthy and non-healthy states is presented in this paper, and suggests that exercise may have the potential to enhance the cognitive improvement of CR or IF, providing new insights for future research on dietary prevention of cognitive decline.

## Effect of CR and IF on Cognitive Function Under Healthy Condition

### CR and Cognitive Function

CR, also known as dietary restriction (DR), refers to the restriction of the total daily calorie intake (usually 20–40%) while providing the organism with sufficient nutrients such as essential amino acids and vitamins, to ensure that the organism does not suffer from malnutrition [7, 8]. Currently, researchers have studied the role of CR in human and non-human lifespans to determine the regulatory mechanisms following CR intervention. Among them, the activation of anti-inflammatory response is one of the mechanisms by which CR is associated with cognitive function. Inflammatory-triggered neuroinflammation may result in deficits in learning and memory, exemplified by interleukin-6 (IL-6) and tumor necrosis factor (TNFα), potentially disrupting cognitive processes via neurogenesis and neuroplasticity pathways, certain animal studies indicate that CR elevates IL-10, an anti-inflammatory agent, while reducing IL-6 and TNFα levels to safeguard neuron survival and growth [9]. CR is considered to be one of the most effective ways to improve cognitive performance in rodents, especially protective against cognitive deficits caused by aging or chronic diseases. Research indicates that the physiological mechanisms in CR-fed older rodents mirror those in younger ones, for instance, CR doesn't alter serum cholesterol in adult rats, yet it markedly diminishes age-related increases in serum cholesterol [7, 10]. Appropriate CR not only improves the performance of rats in behavioral tests of learning and memory, but also enhances their brain function and synaptic plasticity, and increases the generation of new neurons. As an illustration, CR could elevate the hippocampus's brain-derived trophic factor (BDNF) levels by activating the gene expression of heat shock proteins, BDNF is widely present in the brain, plays a pivotal role in neuronal survival, growth, and operation, and is essential for cognitive functions like memory acquisition and emotional control [9, 11, 12]. Based on the optimization of nutrients, feeding strategy and other considerations, the researchers have designed the appropriate CR protocol under these conditions and proved after six months of experiments that CR could enhance the cognitive function of KM mice [13].

In human research, CR can not only analyze changes in the brain and explain the mechanisms associated with cognitive performance, but also prevent the onset of a variety of diseases associated with aging [9]. Oxidative stress is another potential mechanism through which CR is associated with cognitive function. Often, oxidative stress produces oxidative damage, which many consider to be the primary basis of aging. Dysregulation of the antioxidant capacity of reactive oxygen species and other free radicals also affects the health of the organism [10]. Growing research suggests that CR plays a significant role in stimulating the production of reactive oxygen species, contributing to neuroprotection and decelerating aging. This might also stem from CR's antioxidant properties, influenced by various factors like species, gender, CR duration, and the type of reactive oxygen species [7]. In the Okinawa region of Japan, the dietary and phenotypic data of 70-somethings and centenarians are consistent with CR, which provides evidence for the long-term application of CR in humans, and that they exhibit higher levels of dehydroepiandrosterone to slow aging, as well as lower mortality rates to minimize the incidence of age-related diseases, compared with other counterparts who don't receive CR [14]. Similarly, a two-year study in healthy elderly volunteers has found that long-term CR did not adversely affect cognition and was effective in improving memory, which might be related to lower protein intake, as protein restriction reduced protein oxidation in the brain and improved memory [15]. A three-month CR has also been shown to improve memory in healthy older adults, where increased insulin sensitivity and decreased inflammatory activity may be mediators for increased synaptic plasticity in the brain and stimulation of neuroprotective pathways to maintain the cognitive health of older adults [16].

### IF and Cognitive Function

IF consists of several types, the common ones being: periodic fasting (PF) or 5:2 diet, time-restricted feeding (TRF), alternate day fasting (ADF) and modified alternate day fasting. PF is fasting for two days in a week and free-feeding for the remaining five days; TRF is to limit eating to 6–8 h a day; ADF alternates between fasting days and free-feeding days, while improved alternate-day fasting allows for low-calorie intake (15–25% of calorie needs) during the fasting period [17]; There is also the

Ramadan Intermittent Fasting (RIF), which consists mainly of abstaining from all food and liquids between dawn and dusk, and lasts for about 30 days, but the duration of daytime fasting is strongly influenced by geographic location and the season, with a general fasting period of 10 h, and in some areas, such as the high latitudes, it can be as much as 18 h/day in the summer months [9, 18].

Globally, in certain conventional and ethnomedical frameworks, fasting is acknowledged as a remedy for both long-term and short-term diseases, and research involving animals and humans has been shown its potential link to decreased oxidative stress, weight reduction, and deceleration of aging [19, 20]. In the mouse model, 11 months of IF not only increased the thickness of the CA1 pyramidal cell layer and the expression of the dendritic protein drebrin in the hippocampus but also reduced the occurrence of oxidative stress [21]. CA1 is a key brain area for neuroplasticity and is essential for learning and memory. The increased thickness of CA1 leads to improved learning and memory skills in behavioral assessments, as well as enhanced brain function and structure in mice. Clinical research has been recorded the positive impacts of IF. To determine if fasting contributes to post-surgery neurocognitive impairments, scientists subjected mice to a brief 9-h fast [22]. This fasting led to elevated c-Fos (indicative of neuronal activation) levels in the hippocampus and several subcortical areas, while caspase-3 remained inactive in the brain, enhancing neuronal function and spatial memory recognition. Normally, c-Fos can be rapidly expressed in neurons after stimulation and reaches its peak after a few minutes, which can play an important role in the enhancement of neuroplasticity and synaptic function in the brain. That is, fasting does not cause apoptosis and cognitive impairment. Typically, the brain's intricate functions demand substantial energy, yet its energy stores are finite, making ketone bodies a viable substitute energy source for sustaining the brain's energy processing [17]. During fasting, the body undergoes a transition from glucose to ketone metabolism, and the brain and autonomic nervous system adapt to the deprivation of food, which plays a crucial role in promoting health and reducing the occurrence of diseases. As a source of energy for neurons, ketones may have the ability to enhance neuronal and cognitive function. For example, mice were fed ketogenic diets run farther and made fewer errors on behavioral tests than other groups, suggesting improvements in both physical and cognitive performance [23–25].

## Effect of CR and IF on Cognitive Functions Under Unhealthy Condition

### Neurodegenerative Diseases

As one of the most common neurodegenerative diseases, Alzheimer's disease (AD) is characterized by the pathology of β-amyloid (Aβ) plaques and neurofibrillary tangles, which lead to neuronal death and, consequently, cognitive impairment [2]. Most people have only 4–8 years of life left after their first diagnosis of AD, and the difficulty in treating AD is that its pathogenesis is not fully understood and its treatment options lack effectiveness, with two currently approved compounds providing only mild symptom management and having no impact on the long-term progression of the disease, and more than 20 compounds that have been tested and shown to have no effect in slowing cognitive decline [26]. It has long been known that diet affects human health, and following certain diets, such as reducing daily calorie intake and regular fasting, can help alleviate the occurrence of neurodegenerative diseases and prolong life. For example, studies have shown that certain diets can prevent the development of neurodegenerative diseases and have many potential characteristics that directly affect the progress of AD; that is, dietary intervention to prevent cognitive decline may be the most feasible [26, 27].

There are currently a handful of studies influencing in the AD process through diet, and one of the more promising processes is autophagy. Autophagy not only degrades aggregated proteins such as amyloid, but may also ameliorate AD-induced hypometabolism in the brain. Following a 68-week experimental period, Müller et al. [28] were discovered that a similar duration of CR enhanced the neuronal health in APPswe/PS1delta9 (tg) mice, in contrast to a 16-week period. The APPswe/PS1delta9 mouse, a recognized model for Alzheimer's Disease in mice, shows that elevated levels of APPswe (amyloid precursor protein mutation) and PS1delta9 (mutant precursor protease 1) result in a significant rise in Aβ, exacerbating cognitive deterioration. This improvement in neuronal function and stability resulted in improved cognitive performance in the Morris water maze in tg mice, subsequently boosting autophagy through elevated levels of LC3BII and p62 proteins, and a notable decrease in microglia iba-1 was observed with Aβ plaques. After prolonged IF intervention in a mouse model of brain injury, markers of autophagic activity were increased in the brain, and both apoptosis and oxidative stress associated with neurodegeneration were significantly reduced, demonstrating that IF could robustly protect neurons through autophagy and cell-specific Aβ clearance at all stages of AD-related disease progression [29]. Similarly, studies in tg mice indicated that brief IF may result in reduced mTOR activity, enhanced neuronal autophagy, and serve a neuroprotective function [30].

Parkinson's disease (PD) is also a prevalent neurodegenerative condition among elderly individuals, distinguished by the existence of Lewy vesicles of α-synuclein in the brain and the depletion or impairment of dopamine (DA) neurons

in the substantia nigra regions, resulting in unregulated discharge of striatal neurons and subsequent cognitive decline [2, 31]. Energy restriction (CR and IF) in the PD model enhances cognitive function and promotes hippocampal neurogenesis through the safeguarding of DA neurons [32]. Following a 6-month period of CR, adult rhesus monkeys were administered Parkinson's disease through the injection of the neurotoxin 1-methyl-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The researchers observed that CR alleviated dysfunction in DA neurons and enhanced glial cell line-derived brain neurotrophic factor (GDNF), and BDNF within the monkeys' brains, indicating that CR could potentially alleviate PD and reduce the risk of humans developing PD [33]. In PD mice undergoing a CR regimen, it was discovered that 28 days of CR safeguards DA neurons against proteasome disruption-related toxicity and potentially mitigates neurodegenerative disorders [34]. Again in PD mice, IF was found to reduce MPTP-induced DA neuronal deficits and nigrostriatal astrocyte activation over a period of 2 weeks, as well as increase the expression of GDNF and BDNF, which suggests that the importance of the balance between inflammation and neurotrophic factors in the brain can influence PD [35].

## Obesity

Human epidemiological and rodent experiments have shown in the past decade that obesity caused by a long-term high-fat diet (HFD) is associated with cognitive decline. For example, regular consumption of fatty meats, baked goods, butter, and margarine can cause the body to produce large amounts of saturated and trans fats, resulting in obesity. Saturated fats potentially increase the risk of AD. HFD and a lack of vitamins and minerals in old age also aggravate cognitive decline [36]. Furthermore, genetics may also be a factor in the development of obesity; for instance, parental obesity doubles the risk of obese or non-obese children in adulthood and affects subsequent health and disease risk, with an increasing number of studies indicating that obesity can have a detrimental effect on cognitive functioning [37]. To avert the risk of obesity due to weight gain, cognitive function can be safeguarded by dietary restrictions to cut down on weight and reduce body fat percentage.

It was found that obesity-induced decline in hippocampal synaptic plasticity and cognitive impairment might be mediated by CR to regulate n-methyl-d-aspartate receptors (NMDARs)-mediated hippocampal responses to obesity-induced changes and to improve and stabilize the damaged part of the hippocampus, in which the NMDARs, a heterodimeric protein consisting of three subunits of NR1, NR2, and NR3, is associated with hippocampal dependent learning and memory, and its decline affects cognitive functions, whereas 10 weeks of CR restored homeostasis to physiological levels of NMDARs activity in obese rats [38]. Kim et al. [39] showed insulin resistance, neuroglial activation, blood–brain barrier leakage, and memory deficits in mice induced by HFD, all of which improved with 12 weeks of CR intervention, and since neural granule proteins are a major contributor to memory deficits in HFD, CR may be intervening through neural granule protein-associated calcium signaling. In addition, increased oxidative stress typically induces cognitive deficits, and in one test, researchers gave mice 11 months of HFD or IF, respectively, and found that IF mice had better cognitive performance and lower indicators of oxidative stress [21]. 6 weeks of IF was also shown to attenuate cerebellar morphological changes induced in HFD rats, reduce markers of oxidative stress, attenuate inflammation and reestablish autophagic homeostasis [40].

In addition, two days of CR enhanced spatial processing and visuospatial working memory in obese or overweight women, and another two-day diet nearing CR also exhibited no impact on cognitive function, potentially attributed to the brain's ability to convert from glucose to ketone bodies for energy metabolism and cognitive function preservation on a low-calorie diet, while an elevation in corticosterone stimulates glucose reserves and impacts cognitive function [41, 42]. The results of a recent study also indicated that an eight-week CR or IF intervention had no negative impact on cognitive function, quality of life, or eating habits of overweight or obese women [43]. However, given the challenges of CR, which might not be applicable among obese older adults, and the fact that aging could worsen cognitive deterioration in the long run, the researchers conducted a four-week IF intervention with overweight and inactive seniors, and discovered that IF had no negative effect on cognitive functioning, and that these seniors were able to improve their weight [44]. Numerous past studies have demonstrated that CR and IF similarly impact weight loss and lowering body mass index, with evidence indicating a more significant reduction in body fat mass through IF intervention, and also diminishes pro-inflammatory and oxidative stress elements, potentially preventing cognitive deterioration in obese groups [45].

## Diabetes

The presence of diabetes is of utmost significance for the well-being and cognitive function of individuals, and its manifestation could potentially be directly associated with Alzheimer's disease and vascular dementia [46]. In the case of type II diabetes mellitus (T2DM), which is a risk factor for cognitive impairment, and in particular insulin resistance, one of his characteristics, which usually leads to the development of neurodegenerative disorders, which in turn cause cognitive deficits [47, 48]. Once thought of as an insulin-insensitive organ, the brain is actually insulin-sensitive;

insulin receptors are widely found in brain cells, and areas of the brain with high IR expression are associated with cognitive and dietary behavior [49].

On the one hand, the temporal dimension of food intake was found to play a critically important role in regulating the gut microbiota and in the bidirectional channel of action between the brain and the gut, a channel that seems to have a clear impact on the interaction between diabetes and brain dysfunction [50, 51]. A 28-day IF intervention in a diabetic mouse model showed that IF could improve diabetes-induced cognitive deficits from the gut-metabolism-brain axis pathway, which focuses on improving brain energy metabolism and cognitive function by reorganizing the gut microbiota and metabolism, and that the effect of IF on cognitive function began to decrease after the gut microbiota was removed with antibiotics [52]. On the other hand, the researchers found that 12 weeks of IF improved insulin resistance induced by T2DM rats, while the increase in insulin sensitivity stimulated the upregulation of BDNF to produce a neuroprotective effect, and similarly to IF the effect of CR on cognitive function may also be due to the increase in insulin sensitivity and BDNF activity in T2DM patients [7, 53]. In addition, 9 weeks of CR attenuated oxidative stress and inflammation levels in T2DM rats, and in addition to oxidative damage, elevated inflammatory factors in the brain contribute to the development of cognitive impairment [7, 54].

In order to determine the viability of IF for individuals with diabetes, scientists carried out a 4-week TRE intervention in individuals with T2DM and discovered that TRE had no adverse impact on their cognitive function, both clinically and statistically [55]. Additionally, a 5-week TRF intervention was observed to enhance insulin sensitivity and oxidative stress in individuals with diabetes, and adherence to a TRF regimen may be feasible and achievable in diabetics given the relationship between dietary intake, diabetes and cognitive function [56]. Furthermore, while glycated hemoglobin is linked to cognitive decline, it remains uncertain if peak postprandial glucose is linked to cognitive function. Therefore, the researchers conducted CR on 44 patients with T2DM for a duration of 8 weeks and discovered that CR had no impact on the correlation between fasting glucose, peak postprandial glucose, and 24-h glucose descent curves and cognitive function. Additionally, the study proposes that if the individual is transitioned to a patient with hypoglycemic T2DM, the enhancement in glucose levels might be more pronounced with the intervention of CR, potentially resulting in protecting cognitive function [57].

### Ageing

As we age, brain function begins to decline, and neurodegenerative disorders due to aging can lead to cognitive impairment. This is exacerbated by excessive energy expenditure and sedentary lifestyles, but interventions with bioenergetic challenges such as CR and IF cannot only promote brain health, but also improve brain performance and prevent cognitive decline [58]. Currently, research advances during old age alone may be limited in improving cognitive deficits, with evidence suggesting that cognitive decline begins relatively early in adulthood and that these changes accumulate with age until they reach insurmountable proportions in old age [1, 2].

Aging in humans and experimental animals is associated with cognitive decline, especially with learning memory [59]. In animals, Singh and colleagues found that IF improved or slowed age-related cognitive decline in aged rats, with beneficial effects on brain mitochondrial complex activity and synaptic plasticity, using a comparison of adult and aged rat studies [11]. In another subsequent study, Singh et al. [60] replaced aged rats with middle-aged rats and continued the study with the rest of the conditions unchanged. They found that the implementation of IF in the middle-aged stage attenuated age-related damage to synaptic and synaptic growth-regulating proteins, effectively delaying brain aging. In humans, an Italian study showed that TRF was positively associated with improved cognitive function in older adults, but in two other studies, TRF did not appear to have a significant effect on cognitive performance in adults [61].

On the other hand, Yang et al. [62] found that CR may ameliorate aging-related cognitive deficits by activating hippocampal autophagy. Interestingly, mTOR signaling as an inhibitor of autophagy was more active in young mice, and instead declined in older mice, meaning that mTOR was not over-activated, leading to the abnormalization of normal brain aging after CR intervention during aging, but rather, it was efficiently sustaining the hippocampal autophagy degradation. Metabolic reserves were thought to have the ability to support neuronal circuits and prevent cognitive decline, and Lin et al. [63] found that aged CR rats had similar circuits in metabolism and neuronal function to young rats, namely that CR successfully prevented age-related declines in neuronal activity, with beneficial effects on brain aging. For normal adults, CR does not negatively affect their cognitive function, and even has a slight positive effect on generating [15]. In contrast, in older adults, CR can provide a more significant improvement in their cognitive performance, the mechanism of which may be related to higher synaptic plasticity and stimulation of neural facilitatory pathways in the brain [16].

## Synergistic Effects of CR and IF and Exercise on Cognitive Functions

A growing body of research suggests that both exercise and dietary interventions can prevent cognitive decline, and when implemented in combination, they can influence both

energy metabolism management and the bases and processes of synaptic plasticity, especially the latter, which is crucial to cognitive function [9, 64]. In a randomized controlled trial, researchers randomly assigned healthy men and women aged 57–78 years to six groups: control, resistance exercise, aerobic exercise, dietary intervention, resistance exercise and dietary intervention, and aerobic exercise and dietary intervention, and found that a combination of at least moderate-intensity aerobic exercise and dietary intervention was needed for improving cognitive performance in older adults, while the rest of the groups did not find significant effects on cognitive performance [65]. Notably, the combination of CR or IF with exercise may also improve cognitive functioning (Fig. 1).

Several studies have demonstrated that the combination of IF and exercise can enhance cognitive functioning [66]. A recent study showed that the combination of 20 h of IF and exercise increased BDNF concentrations more than normal eating or exercise, especially as the release of free BDNF from the body's circulation was not affected and continued to increase as the duration and intensity of exercise increased, a finding that also opens up the possibility of non-pharmacological BDNF-mediated prevention of cognitive decline, a discovery that is known to play an important role in neuroplasticity, learning, and memory [67]. Additionally, it was demonstrated that the integration of IF and exercise resulted in an augmentation of spatial memory and protein levels of BDNF in the hippocampus of Wistar rats, while IF led to a significant increase of approximately 2- to fourfold in voluntary locomotor activity in rats [68]. The augmentation of BDNF triggered the generation of mitochondrial matter in neurons and enhanced the levels of PGC-1α, thereby assuming a crucial role in the functioning of hippocampal dendritic spines and synaptic plasticity within the brain [69]. What's more, the combination of IF and exercise could reduce insulin resistance, increase hippocampal neurons, reduce inflammation and oxidative stress, optimize brain function and prevent the development of neurodegenerative diseases [32, 70].

CR was no exception, as researchers divided high-fat diet-induced rats into two groups before performing sham surgery (HFS) and ovariectomy (HFO), respectively, followed by a 7-week combination of CR and exercise intervention and found that brain function and cognition were better restored in both groups, whereas a single CR or exercise intervention, while both attenuating metabolic and hippocampal dysfunction, nevertheless, did not attenuate the cognitive decline in the former for both HFS and HFO rats, and the latter improved cognition only in the HFS rats [71]. Kishi et al. [72] also demonstrated that 28 days of CR and exercise improved cognitive performance and increased BDNF in the hippocampus of hypertensive rats more than either exercise or CR alone, suggesting that the combination of the two could have a synergistic protective effect against cognitive decline. In addition, insulin resistance induced by diabetes, which in turn leads to cognitive decline in mice, was ameliorated by a combination of CR and exercise intervention, and increased BDNF levels and hippocampal dendritic spine density [73]. The results of 52 weeks of combined CR and exercise in overweight or obese T2DM patients demonstrated an improvement in cognitive function, as well as a positive correlation between cognitive improvement and weight loss, indicating that a combination of diet and exercise may be advantageous for those with T2DM [74].

In the AD or PD model, starting a regular exercise program early or midlife may not only improve quality of life, but may also reduce the onset of cognitive deficits and slow

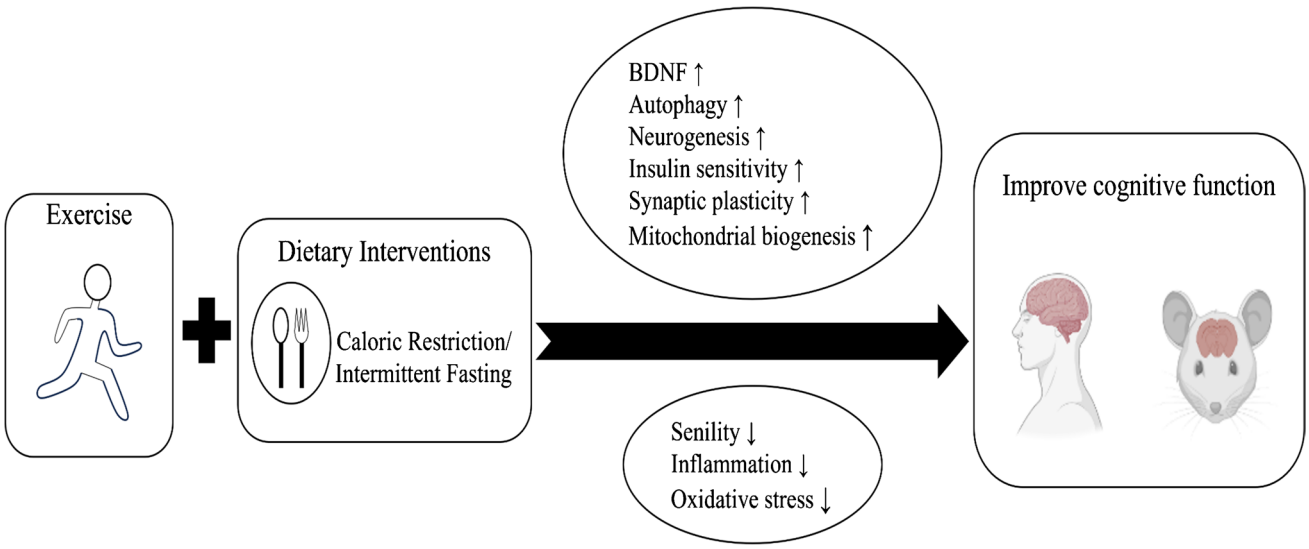


**Fig. 1** CR or IF combined with exercise may improve cognitive function through these pathways

the progression of the disease, while those who are normally healthy expect to optimize their brain performance through a combination of different dietary modalities and exercise, which can easily be incorporated into a work or home program that not only improves brain health, but also may have implications for the prevention of obesity, diabetes, and related neurodegenerative disorders, including AD and PD [75].

## Limitations and Future Perspectives

Up until now, the applicability of CR and IF's positive impacts on cognitive function, as seen in animal studies, in clinical environments, particularly for treating neurodegenerative disorders, remains unconfirmed. The majority of human research is still observational, indicating that CR and IF's influence on cognitive function is primarily preventative [17]. As an illustration, after IF intervention, the reduction of amyloid precursor protein levels and mTOR pathway activity in healthy populations enhances hippocampal neurogenesis, which may potentially guarding against the onset of AD [2]. Likewise, the number of clinical studies on CR and IF impacting cognitive function in obese groups is constrained, and the absence of prolonged trials addressing specific benefits or detrimental impacts in obese groups remains unclear. Diabetic individuals may face a risk of ketoacidosis and hypoglycemia because IF, when combined with TRF therapy, could be effective and prevent negative side effects. Starting off at 12 h for eating, patients can soon adjust to this eating schedule for more flexibility in their eating timing. Hence, it's advisable for those with diabetes to receive proper nutritional guidance before undergoing IF intervention [76]. In other aspects, the clinical application of CR and IF still faces some potential challenges and barriers, including the identification of possible targets of physiological processes occurring during dietary restriction that have beneficial effects on cognitive function that are not yet comprehensive, such as neuroglia and astrocytes may play unexplored roles [17]; a randomized clinical trial revealed IF's greater dropout rate than CR, inconsistent adherence to the intervention, and challenges for early intervention participants in limiting calories to around 500 kcal bi-daily [77]; dietary restriction may leave people in a state of hunger, irritability and reduced concentration and lead to changes in quality of life and mood with negative consequences, among others [78]. Consequently, the significance of long-term research becomes evident; such studies offer not just a thorough tracking of participants but also more dependable experimental results to overcome these obstacles and hurdles. Furthermore, the impact of physical activity on memory improvement might hinge on alterations in circadian patterns. Research indicates that daytime and nocturnal mice exhibit a higher increase in BDNF and p-CREB levels in their hippocampus compared to their pre-dawn counterparts, and given their nocturnal activity, there's a possibility that humans, on the other hand, can improve their memory during morning exercise [79]. Finally, the diversity among individuals leads to an absence of specific dietary recommendations for each subject, duration of adherence and methods of exercising [80].

Future research ought to focus on the elderly, establishing prolonged and extensive trials to gather insights into how dietary habits impact human quality of life, emotional state, and cognitive actions. Research might explore how combining CR or IF with physical activity influences brain health and cognitive function, the duration of compliance required to affect cognitive function, and its greater efficacy in averting neurodegenerative disorders that hinder cognitive decline.

## Conclusions

Incorporating CR and IF into one's routine not only improves cognitive function in healthy individuals, but also inhibits the emergence of cognitive impairments in unhealthy conditions like neurodegenerative diseases, obesity, diabetes, and aging. Proper dietary interventions can enhance cognitive function through CR and IF, whether used over an extended or brief period. Aside from that, exercise can significantly amplify or harmonize the safeguarding of cognitive function by CR and IF. All of the above still require further and more robust research to validate the safety and effectiveness of CR and IF.

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  This article outlines the effects of IF on brain metabolism, which induces molecular and cellular adaptations in neurons thereby enhancing synaptic plasticity and neurogenesis. IF is highly adherent and more suitable for assessing beneficial effects on cognitive function in a clinical setting. It depicts the key molecular pathways modified during IF and involved in beneficial central actions.

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  This study examined the independent and combined effects of diet and exercise on cognitive function in a middle-aged and older population through a long-term randomized controlled trials. The study analyzed the four years of data using intention-to-treat principles and linear mixed-effects modeling. Results indicate that the combination of a healthy diet and moderate-intensity aerobic exercise can improve cognitive function in older individuals.

**Author contributions** CRediT authorship contribution statement: Junming Wang: Conceptualization, Methodology, Software, Data curation, Writing-Original draft preparation. Yifeng Rang: Visualization, Investigation, Writing-Reviewing and Editing. Chunhong Liu: Supervision, Validation, Writing- Reviewing and Editing.

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**Data Availability** No datasets were generated or analysed during the current study.

## Declarations

**Conflicts of Interest** The authors declare no competing interests.

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