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Intermitten Fasting and Caloric Restriction in Adults: Differential Effect on Cognitive Function and Neurobiological Outcomes: A Systematic Review

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Abstract: Intermittent fasting (IF) and caloric restriction (CR) represent dietary strategies based on energy intake limitation that have been widely investigated for their potential benefits on metabolic processes and brain performance. This systematic review aims to evaluate the relationship and effects of IF and CR on cognitive function and neurobiological outcomes related to brain inflammation in adult populations. Literature retrieval was carried out through the PubMed and ScienceDirect databases using inclusion criteria structured by the PICOS framework, resulting in 10 eligible studies. The analysis showed that several studies reported improvements in cognitive function following IF/CR interventions, which were thought to be associated with enhanced neurogenesis and reduced inflammatory markers. However, several other studies found no significant differences compared with the control groups, which may have been influenced by the relatively short duration of the interventions, limitations in cognitive assessment methods, and the relatively healthy characteristics of the study populations. Therefore, the neurobiological mechanisms underlying the effects of these dietary interventions cannot be fully explained. In summary, IF and CR show promise as nutritional interventions to promote cognitive function in adults; however, the current body of evidence is still heterogeneous, highlighting the need for future studies employing more rigorous methodologies and extended intervention durations.

Keywords: Caloric restriction; Cognitive function; Inflammation Markers; Intermittent fasting; Neurobiological outcomes.

Introduction

Intermittent fasting (IF) and caloric restriction (CR) are two nutritional intervention paradigms that have gained increasing attention in modern health and neuroscience research. IF refers to a dietary pattern that regulates the timing of food intake through alternating periods of eating and fasting. IF interventions can take several forms, including time-restricted feeding, alternate-day fasting, and the Ramadan fasting model (daily fasting for one month), which naturally imposes a rhythm of fasting and feeding (Alkurd *et al*., 2024). Other forms of IF commonly applied in humans include 5:2 diet and time-restricted feeding (TRF), in which daily food intake is limited to 8-12 hours (Wilhelmi de Toledo *et al*., 2020). Meanwhile, CR is defined as a consistent reduction in daily energy intake without causing chronic malnutrition, with the aim of extending lifespan and reducing the risk of chronic diseases (Colman *et al*., 2009).

Intermittent fasting (IF) is considered to confer health benefits by enhancing physiological function through metabolic adaptations triggered by reduced energy intake. This dietary pattern can generate mild metabolic stress and facilitate periodic metabolic switching from glucose-based energy utilization

to ketone metabolism, a process that has been associated with improved brain function and increased neural resilience (Mattson *et al.,* 2018).

Intermittent fasting (IF) has become increasingly popular among the general population as an alternative approach for weight management and metabolic health improvement, both in individuals without underlying conditions and those with metabolic disorders (Anton *et al*., 2013; Barnosky *et al*., 2014; Harvie *et al*., 2013; Varady, 2011; Mattson *et al*., 2016). Several fasting regimens have been introduced, such as alternate-day fasting (ADF) (Varady, 2011) and modified alternate-day fasting (ADMF) (Varady *et al*., 2013). In contrast, caloric restriction (CR) has historically been more widely investigated in animal studies; however, its implementation in human populations has received growing interest, particularly in relation to health maintenance and aging-related interventions. Despite this, the outcomes of both IF and CR are not consistently observed and may depend on multiple factors, including the type of dietary protocol applied, individual health conditions, habitual dietary intake, and the length of the intervention period (Alkurd *et al*., 2024).

Accumulating evidence indicates that intermittent fasting (IF) and caloric restriction (CR) may affect neurobiological processes as well as cognitive outcomes. A recent systematic review has documented inconsistent findings regarding the impact of these dietary approaches on brain-derived neurotrophic factor (BDNF) levels and cognitive performance in humans. While certain studies reported elevations in BDNF accompanied by improvements in cognitive function, others found no significant effects or even reductions in BDNF following particular interventions. Such inconsistencies underscore the complex interplay between dietary patterns and brain health, both in healthy individuals and in populations with metabolic disorders (Alkurd *et al*., 2024). These differences in response suggest that IF and CR may not exert uniform effects on brain health and cognitive outcomes, and that certain cognitive domains may be more sensitive to specific dietary interventions.

Although preliminary evidence regarding the relationship between intermittent fasting (IF), caloric restriction (CR), cognitive function, and neurobiological biomarkers is increasing, studies that comprehensively compare these dietary interventions in adult human populations remain limited, and the findings are often heterogeneous. Differences in research methodologies, participant age ranges, intervention durations, and variability in the cognitive domains assessed present significant challenges in establishing consistent scientific evidence. In light of the rising prevalence of metabolic disorders alongside the increasing global burden of neurodegenerative diseases, understanding the effects of time-restricted eating and energy limitation on brain function has become increasingly important. These dietary approaches should not be viewed solely as trends, but rather as promising non-pharmacological strategies for both prevention and therapeutic purposes. Accordingly, this systematic literature review was undertaken to compare the effects of intermittent fasting and caloric restriction on cognitive performance and associated neurobiological outcomes in adult populations.

Materials and Methods

The systematic literature review (SLR) was carried out following the PRISMA framework to ensure a structured and transparent reporting process (Page *et al*., 2021; Liberati *et al.*, 2009). PRISMA offers a standardized and reproducible approach for identifying relevant literature, as well as guiding the processes of study selection, screening, and critical appraisal (Razgan *et al*., 2021). The stages of the PRISMA procedure applied in this review are presented in Figure 1.

Data sources and search strategy

Relevant articles were searched using the PubMed and ScienceDirect online databases. To obtain recent and comprehensive evidence, the literature search was limited to studies published within the last 10 years (2016–2026). The keywords used in the search included “intermittent fasting,” “caloric restriction,” “cognitive function,” and “brain inflammation.” The search strategy applied Boolean operators to identify relevant and accurate articles. The Boolean search string used was (“intermittent

fasting" OR "caloric restriction") AND ("cognitive function" OR "brain inflammation"). The data collection procedure was adapted from previous systematic literature review studies conducted by Alsayed *et al.* (2023) and Aini *et al.* (2023), with several modifications.

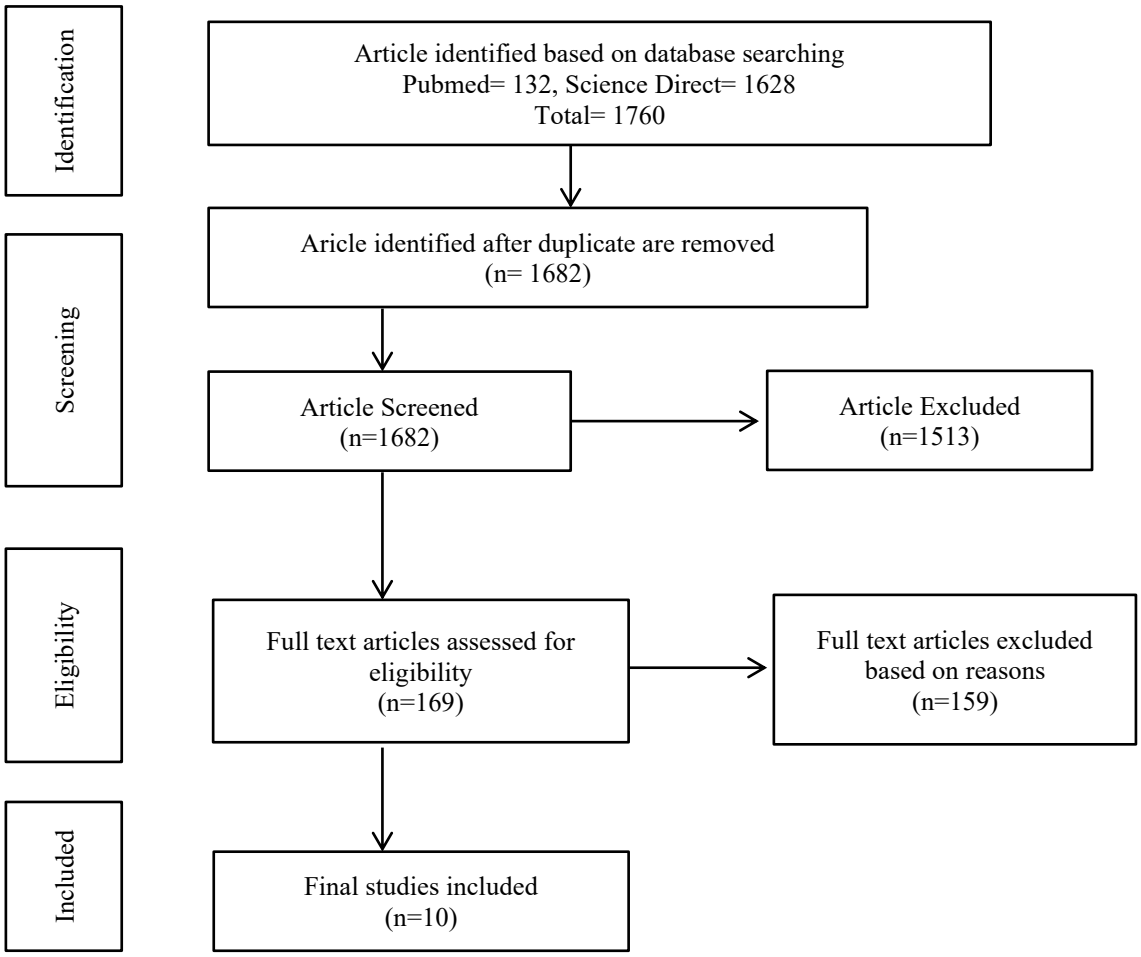

Figure 1. PRISMA diagram of article collection based on search keywords selection

Study inclusion and exclusion criteria

During the identification phase, the keyword search retrieved 132 records from PubMed and 1628 records from ScienceDirect, resulting in a total of 1,760 articles. Following the removal of duplicate entries and studies that were not relevant or did not meet the inclusion criteria, 1682 records were retained for the initial screening stage. Subsequent screening based on titles and abstracts led to the exclusion of 1513 articles. The remaining 169 studies were then subjected to full-text evaluation to determine their eligibility. After applying the predefined inclusion and exclusion criteria, a total of 10 articles were finally included in this systematic literature review.

In particular, the studies selected for inclusion in this systematic literature review were required to fulfill the following criteria: articles published between 2016 and 2026, full-text availability, relevant associated data, clinical trials or randomized controlled trials, studies conducted in adult human populations, original research articles, and open-access publications. The specific inclusion and exclusion criteria applied during the study selection process are summarized in Table 1.

Research Question

The formulation of research questions (RQs) plays a crucial role in determining the scope and guiding the intended outcomes of a study. In this systematic literature review, the research question was formulated as follows: "*In adult populations, how do intermittent fasting and caloric restriction influence cognitive function and neurobiological inflammatory markers compared with usual dietary controls?*

Table 1. PICOS table of article data inclusion and exclusion criteria

Component	Inclusion Criteria	Exclusion Criteria
P (Population)	• Adult people (≥18 years) • Individuals who are either healthy or have conditions such as obesity, prediabetes, or other metabolic disorders • Male and female	• Children or teenagers (<18 years) • Animal studies or in vitro
I (Intervention)	• Intermittent fasting regimens (including time-restricted feeding, alternate-day fasting, and the 5:2 fasting protocol) • Continuous caloric restriction (energy restriction terstruktur) • Interventions with a clear duration	• Nutritional supplementation without energy restriction • Macronutrient composition diet with calorie restriction • Calorie restriction mimetic
C (Comparison)	• Usual diet • Ad libitum diet • Non-fasting control • Standard diet control group	• Studies without control group
O (Primary Outcome)	• Cognitive Function measured by validated instruments (memory, executive function, attention, working memory)	• Studies that only measure mood, quality of life, or depression without objective cognitive tests
O (Secondary: Neurobiological Outcomes)	• Inflammatory biomarker • Oxidative Stress marker • Neuroenergetik marker • Indicators of neuronal integrity or neurogenesis	• Studies that only report weight, BMI or metabolic parameters without neurobiological outcomes
S (Study Design)	• Randomized Controlled Trial (RCT) • Clinical Trial terkontrol • Observational study designs (including cohort, case-control, and cross-sectional studies)	• Case report • Review article • Meta-analysis • Editorial, commentary

Results and Discussion

Total number of articles identified was 1760, then 78 articles were excluded after duplication screening, leaving 1682 articles. These were then screened again based on exclusion criteria, resulting in 169 articles. Ultimately, a total of 10 articles that satisfied the inclusion criteria were included in this review. A summary of these selected studies is presented in Table 2.

Table 2. Summary of inclusion articles

Author	Year	Study Focus	Summary
Ooi *et al.,*	2022	Effect of Islamic Sunnah intermittent fasting on cognitive function and metabolic biomarkers in older adults with mild cognitive impairment	This study examines the association between Islamic Sunnah intermittent fasting (IF) and cognitive performance in older adults with mild cognitive impairment (MCI), suggesting that factors such as oxidative stress, DNA damage, inflammation, and metabolic biomarkers play a mediating role in this relationship. The findings indicate that IF may contribute to improvements in cognitive function.
Mindikoglu *et al.,*	2020	Impact of 30-day dawn-to-sunset fasting on serum proteomics and metabolic regulation in healthy individuals	The study investigates the effects of 30-day intermittent fasting from dawn to sunset on serum proteomics in 14 healthy subjects. Results indicate significant changes in serum biomarkers associated with cancer protection and metabolic health, without calorie restriction or weight loss
Harder-Lauridsen *et al.,*	2017	Effect of Ramadan intermittent fasting on metabolic parameters and cognitive function in healthy lean men	This study evaluates the impact of Ramadan intermittent fasting (RIF) on mood and glucose variability in healthy, lean male participants. The findings revealed no significant alterations in glucose metabolism, body composition, or cognitive performance among individuals who observed Ramadan fasting.
Giles *et al.,*	2019	Short-term caloric deprivation and its effect on cognitive performance and mood during physical activity	The study investigates how calorie deprivation affects cognitive function during physical exertion in military personnel. It finds that calorie restriction impairs cognitive control and mood while increasing perceived exertion, particularly during sustained exercise, highlighting the impact of combined stressors on mental performance
Kim *et al.,*	2022	Relationship between meal frequency and Alzheimer's-related pathology in older adults	This study examines the association between low meal frequency (LMF) and decreased amyloid-beta (Aβ) accumulation in older adults without dementia, indicating that LMF may contribute to a reduced risk of Alzheimer's disease. Furthermore, increased serum ghrelin levels appear to act as a mediating factor in this relationship, underscoring the potential role of dietary patterns in influencing brain health.
Ritz *et al.,*	2026	Neurocognitive characteristics associated with food and alcohol-related behavioral disturbances	The paper investigates the relationship between Food and Alcohol Disturbance (FAD) and cognitive functioning in university students, revealing that different FAD behaviors are linked to distinct cognitive profiles. It emphasizes the need for tailored therapeutic strategies to address these cognitive vulnerabilities and improve emotional regulation and eating behaviors
Tussing-Humphreys *et al.,*	2022	Effect of Mediterranean diet with and without caloric restriction on cognition and cardiometabolic health	The study evaluated the impact of a Mediterranean dietary pattern, with and without caloric restriction, on cognition, lifestyle, and cardiometabolic parameters in obese older women. Despite notable improvements in dietary adherence, no significant differences in cognitive function were observed relative to the control group.

Author	Year	Study Focus	Summary
Harder-Lauridsen *et al.,*	2017	Alternate-day caloric restriction during physical inactivity and its metabolic effects	The study evaluates the impact of alternate-day caloric restriction (ADCR) over 8 days of bed rest in healthy men. It finds that ADCR does not mitigate, and may worsen, insulin resistance and other metabolic impairments caused by inactivity, highlighting the challenges of dietary interventions in sedentary conditions
Silver *et al.,*	2023	Long-term caloric restriction and dietary patterns on spatial working memory	The study found that calorie restriction and dietary quality did not significantly impact spatial working memory in healthy adults over a two-year period. Despite improvements in dietary indices, no association with cognitive function was observed, suggesting limited effects of these nutritional strategies on working memory
Kim *et al.,*	2020	Intermittent vs continuous energy restriction on hippocampal-related cognitive function in obese adults	This study examines the effects of intermittent and continuous energy restriction on cognitive functions associated with adult hippocampal neurogenesis in individuals with central obesity. Both interventions were found to enhance pattern separation ability; however, only intermittent energy restriction was associated with a reduction in recognition memory performance, suggesting differential cognitive effects of these dietary strategies.

A key finding of this review is that the impact of IF and CR on cognitive outcomes varies across different populations and appears to be strongly influenced by baseline health status. Overall, improvements in cognitive performance and reductions in inflammatory markers are more consistently reported in individuals with metabolic impairments or mild cognitive impairment (MCI). In contrast, among metabolically healthy individuals, such as lean and metabolically adaptable adults, the effects of IF and CR are generally limited or not statistically significant. This trend can be observed when comparing the results of Ooi *et al*. (2022) and Mindikoglu *et al.* (2020) with those reported by Harder-Lauridsen *et al.* (2016), Tussing-Humphreys *et al*. (2022), and Silver *et al*. (2023).

In older adults with MCI, as reported by Ooi *et al*. (2022), IF interventions produced significant improvements in cognitive performance, including MMSE, MoCA, Digit Span, and RAVLT scores. These improvements were associated with increased antioxidant activity, reductions in inflammatory biomarkers, decreased DNA damage, and changes in metabolic markers. Individuals adhering to IF were also found to have reduced levels of C-reactive protein (CRP), a well-established acute-phase biomarker released in response to inflammatory stimuli or infection (Sproston *et al*., 2018). Previous studies have similarly reported that IF interventions may reduce CRP levels through decreased energy intake and weight loss (Wang *et al*., 2020). Increased levels of C-reactive protein (CRP) have been linked to various cognitive impairments, including endothelial dysfunction, white matter abnormalities, vascular dementia, and Alzheimer's disease (Hoth *et al*., 2007; Vicenzini *et al*., 2007).

These observations are further reinforced by a meta-analysis conducted by Lü *et al*. (2023), which demonstrated that dietary restriction provides notable cognitive benefits in individuals with mild cognitive impairment and overweight conditions. Taken together, these findings indicate that in populations with MCI, IF and CR may modulate cognitive performance and neurobiological parameters through mechanisms related to metabolic improvement, such as enhanced insulin sensitivity and decreased systemic inflammation both of which are commonly elevated in individuals with metabolic dysfunction.

The study conducted by Mindikoglu *et al.* (2020) offers a more comprehensive perspective by employing a proteomic approach to examine healthy individuals undergoing IF. The study reported increased expression of HOMER1 and decreased expression of APP and ARPP-21, suggesting a potential modulation of pathways associated with neurodegeneration. HOMER1 is a synaptic scaffolding protein involved in

glutamatergic signaling and synaptic plasticity, which are essential for memory function and overall brain performance. In contrast, APP (amyloid precursor protein) is a precursor molecule that can be cleaved to form β-amyloid peptides implicated in neurodegenerative diseases.

A review by Raefsky and Mattson (2017) suggests that lifestyle interventions, including fasting and physical exercise, may confer neuroprotective effects by reducing the risk of neuronal dysfunction and neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. These protective effects are proposed to occur through mechanisms involving the enhancement of antioxidant defenses, activation of autophagy, and promotion of DNA repair processes. In particular, autophagy an intracellular degradation pathway induced by caloric restriction plays a key role in removing accumulated protein aggregates, including amyloid deposits. This process may reduce β-amyloid (Aβ) neuropathology, improve glucose utilization in the brain, and alleviate cerebral hypometabolism (Müller *et al.,* 2021).

Nevertheless, these findings are not consistently observed across studies. A systematic review by Harder-Lauridsen *et al*. (2016) reported that 28 days of Ramadan intermittent fasting (RIF) in healthy, lean men did not result in significant changes in memory performance, executive function, or inflammatory biomarkers such as IL-6 and TNF-α. Likewise, Silver *et al*. (2023), based on a secondary analysis of the CALERIE clinical trial, found no significant improvements in spatial memory following two years of CR in healthy adults without obesity. These findings support the hypothesis that individuals with low baseline inflammatory status and good insulin sensitivity may have limited capacity for further biological improvement. This interpretation is consistent with the review by Prabowo (2024), which suggests that IF primarily exerts metabolic benefits in individuals with metabolic dysregulation, particularly by lowering circulating insulin levels and improving insulin sensitivity in overweight or obese populations. Furthermore, a meta-analysis by Zhou *et al*. (2021) demonstrated that IF and CR can significantly reduce the expression of inflammatory cytokine and chemokine mRNA. Consequently, individuals who already exhibit low inflammatory profiles and favorable metabolic status may experience minimal additional physiological benefits from IF or CR interventions.

Research conducted by Giles *et al.* (2019) provides important insights into the short-term effects of acute energy deficit. In this study, two days of caloric restriction combined with physical activity resulted in decreased cognitive control accuracy and worsening mood states. Energy restriction during exercise negatively affected multiple mood dimensions, including anxiety, depression, confusion, and overall mood disturbance. Notably, most of these negative mood effects were observed on the second day of CR, suggesting cumulative physiological and central nervous system responses to sustained energy deficit. One possible explanation is that acute reductions in energy availability may disrupt prefrontal cortex function, a brain region highly sensitive to fluctuations in glucose supply. These findings are consistent with previous studies demonstrating that fasting combined with physical activity can influence mood states and physical performance (Aloui *et al*., 2013; Chtourou *et al*., 2011; Chtourou *et al*., 2012).

The study by Kim *et al*. (2022) adds a neuropathological perspective to the relationship between meal frequency and β-amyloid (Aβ) deposition, highlighting the potential mediating role of ghrelin. Ghrelin is a hormone associated with hunger that acts as an orexigenic signal through its interaction with the growth hormone secretagogue receptor (GHS-R), thereby influencing food intake regulation (Jeon *et al*., 2019). In the present study, extended fasting periods linked to low meal frequency (LMF) defined as consuming fewer than three meals per day were significantly correlated with reduced global amyloid-beta (Aβ) accumulation compared with high meal frequency (HMF). The authors proposed that ghrelin may serve as a partial mediator of this relationship. These observations are in line with findings from preclinical studies using Alzheimer's disease animal models, which demonstrated that dietary patterns characterized by longer intervals between meals were associated with decreased Aβ pathology and improved cognitive

performance (Singh *et al*., 2012; Shin *et al.,* 2018). Furthermore, Jeon *et al*. (2019) reported that increased ghrelin signaling may exert neuroprotective effects against Aβ accumulation and Alzheimer's disease pathology. Collectively, these findings suggest that longer fasting intervals may activate hormonal pathways that support brain health. However, causal relationships in humans remain to be established.

Studies by Ritz *et al*. (2026) and Tussing-Humphreys *et al*. (2022) indicate that caloric restriction implemented within extreme dietary patterns or medium-term interventions such as an eight-month Mediterranean diet combined with caloric restriction does not necessarily lead to significant cognitive improvement. This variability may be influenced by several factors, including psychological responses to dietary restriction, overall diet quality, and adherence to the intervention protocol. Similarly, Harder-Lauridsen *et al.* (2017) reported that increases in cognitive scores observed after a period of bed rest combined with fasting and/or physical activity were likely influenced by practice effects associated with repeated administration of the CANTAB test battery, despite the instrument being designed to minimize such effects. The absence of changes in hippocampal volume further supports the interpretation that these short-term cognitive improvements may not reflect structural neurobiological adaptations. Evidence from previous research also suggests that measurable changes in memory function and hippocampal structure require prolonged interventions. For instance, Erickson *et al*. (2011) reported that lifestyle interventions, particularly regular physical activity, were associated with an approximately 2% increase in hippocampal volume following one year of consistent engagement.

The study conducted by Kim et al. (2020) introduces additional complexity to the existing evidence through a randomized controlled trial (RCT) involving individuals with central obesity. The results showed no significant difference between intermittent energy restriction (IER) and continuous energy restriction (CER) in enhancing hippocampus-dependent cognitive function. Moreover, an unexpected decrease in recognition memory was observed in the IER group. These findings appear to challenge the hypothesis that IF exerts consistent neuroprotective effects on cognitive function. One possible explanation is the so-called "obesity paradox," in which weight loss in certain populations particularly in older adults has been associated with an increased risk of cognitive decline (Oreopoulos *et al*., 2009; Sellbom *et al*., 2012). Another potential explanation is the relatively short duration of the intervention. The four-week intervention period may have been insufficient to induce biological adaptations such as activation of autophagy pathways, modulation of inflammatory responses, or measurable increases in neurogenesis in humans.

Conceptually, these findings can be interpreted through the "metabolic inflammatory threshold hypothesis." According to this framework, IF and CR may exert beneficial effects on cognitive function primarily in individuals with elevated systemic inflammation, insulin resistance, or early neuropathological accumulation that can be improved through energy restriction. In contrast, individuals who already exhibit optimal metabolic and inflammatory homeostasis may experience minimal measurable cognitive changes following these interventions. In addition to baseline metabolic status, the duration of the intervention also appears to play an important role in determining cognitive and neurobiological outcomes. One possible mechanism may involve brain-derived neurotrophic factor (BDNF), a neurotrophin abundantly expressed in the hippocampus and cerebral cortex that plays a central role in regulating synaptic plasticity and memory function.. Evidence suggests that IF and CR can increase BDNF expression; however, these effects are often dependent on sustained intervention periods before significant changes become detectable (Alkurd *et al*., 2024).

Thus, the available evidence does not support the assumption that IF and CR universally improves cognitive function across all adult populations. Instead, the observed effects appear to be context dependent and are influenced by several factors, including baseline metabolic status, duration of the intervention, cognitive assessment methods, and underlying inflammatory profiles. Future research should aim to standardize IF and CR intervention

protocols, incorporate a comprehensive panel of inflammatory and neurotrophic biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and brain-derived neurotrophic factor (BDNF) and employ domain-specific cognitive test batteries to minimize practice effects associated with repeated cognitive assessments

Conclusion

Based on the findings of this systematic review of ten studies that met the inclusion criteria, IF and CR appear to have potential roles in modulating cognitive function and neurobiological mechanisms associated with brain health in adult populations. Several studies reported improvements in memory performance and cognitive outcomes, which may be mediated by mechanisms such as enhanced neuroplasticity, increased neurogenesis, and reduced inflammatory activity. However, the evidence remains inconsistent. A number of studies reported no significant differences between intervention and control groups, which may be attributable to methodological factors, including short intervention durations, small sample sizes, and limitations in cognitive assessment tools. In addition, several studies did not directly measure brain-related inflammatory biomarkers, limiting the ability to fully elucidate the relationship between energy restriction and neuroinflammatory processes. Therefore, future research should employ more comprehensive clinical trial designs with longer intervention periods and integrate both cognitive assessments and neurobiological biomarkers. Such approaches are essential to better understand the mechanisms and long-term effects of IF and CR on brain health.

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