HHS Public Access

Author manuscript

Ageing Res Rev. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

Ageing Res Rev. 2020 December ; 64: 101189. doi:10.1016/j.arr.2020.101189.

Time-restricted feeding (TRF) for prevention of age-related vascular cognitive impairment and dementia

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Abstract

Aging is the most significant risk factor for vascular cognitive impairment (VCI), and the number of individuals affected by VCI is expected to exponentially increase in the upcoming decades. Yet, there are no current preventative or therapeutic treatments available against the development and progression of VCI. Therefore, there is a pressing need to better understand the pathophysiology underlying these conditions, for the development of novel tools and interventions to improve cerebrovascular health and delay the onset of VCI. There is strong epidemiological and experimental evidence that lifestyle factors, including nutrition and dietary habits, significantly affect cerebrovascular health and thereby influence the pathogenesis of VCI. Here, recent evidence is presented discussing the effects of lifestyle interventions against age-related diseases which in turn, inspired novel research aimed at investigating the possible beneficial effects of dietary interventions for the prevention of cognitive decline in older adults.

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Disclosures

None.

Keywords

Time restricted feeding; Aging; Neurovascular coupling; Neurodegeneration Geroscience; Dementia; Cognitive function

1. Introduction

Declining cerebrovascular health is quickly becoming recognized as a major hallmark of age-related cognitive decline[1–7]. To account for this fact, the term "vascular cognitive impairment" (VCI) was coined to describe all forms of cognitive disorders associated with cerebrovascular pathologies[3, 4]. There is an increasing realization that the pathogenesis of Alzheimer's disease (AD) also involves microvascular pathologies[2] and as such, it may represent a special form of VCI associated with old age[4].

The study of age-related VCI is a growing global health priority. The number of individuals living over the age of 60 is projected to increase from 901 million today to nearly 2.1 billion by 2050[8]. As advanced age is the most significant risk factor for VCI, the number of individuals affected by VCI is expected to exponentially increase in the upcoming decades[3, 4]. Yet, there are no current preventative or therapeutic treatments available against the development and progression of VCI. There is a pressing need to better understand the pathophysiology underlying these conditions, for the development of novel tools and interventions to improve cerebrovascular health and delay the onset of VCI.

There is strong epidemiological and experimental evidence that lifestyle factors, including nutrition and dietary habits, significantly affect cerebrovascular health and thereby influence the pathogenesis of VCI[3, 4]. In recent years, growing interest in the effects of lifestyle interventions against age-related diseases has inspired novel research aimed at investigating the possible beneficial effects of dietary interventions for the prevention of cognitive decline in older adults.

2. Dietary interventions to promote healthy vascular aging: from calorie restriction to time-restricted feeding

Calorie restriction (CR) is a dietary regimen that reduces the daily food intake of an individual relative to its normal energy consumption, without causing malnutrition. CR exerts clear beneficial effects on healthspan and lifespan in short-lived species[17–19], positively impacts health of long-lived non-human primates (*Macaca mulatta*)[9–11], and recently was also shown to increase maximum lifespan in the gray mouse lemur (*Microcebus murinus*) by more than 22 percent[9].

Experimental evidence suggests that CR is an effective nutritional lifestyle intervention that can improve cardiovascular health[12–15] and cognitive function[16–20]. A published study suggests that even when implemented over a short period, CR can confer cardiovascular health benefits[12]. CR studies performed in the last two decades have been critical in improving our understanding of the physiological mechanisms by which CR prevents vascular aging[21] and extends lifespan in many animal models[10, 22–24]. CR has been

documented to exert multifaceted cardiovascular protective effects, including reduced oxidative damage[13, 25], improved insulin sensitivity[26], improved endothelial function[27–31] and nitric oxide (NO) bioavailability[27, 32–36], and reduced risk of atherosclerosis[15]. Besides the observed beneficial effects of CR on the large conduit vasculature, CR was also shown to confer persistent anti-oxidative, pro-angiogenic, and anti-inflammatory effects, and promote an anti-aging gene expression profile in cerebromicrovascular endothelial cells of aged rats[37]. Recent evidence from non-human primate studies suggests that circulating factors induced by CR also promote endothelial protective effects, up-regulating endothelial angiogenic processes[38]. This is

In the late 1980s two parallel studies[10, 39] were initiated to determine the effect of CR in rhesus monkeys. While the impact on lifespan differed between these two studies, both groups observed a substantial improvement in healthspan, indicating that CR-derived benefits are conserved in monkeys[40]. This evidence suggests that the ability of CR to convey health benefits may also be translatable to humans[40, 41]. To better understand the feasibility and translatability of CR in humans, the National Institute on Aging (NIA) supported an innovative 2-year long clinical trial named Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE)[42] where over 200 healthy young and middle-aged individuals in were assigned to a 25% CR regimen or to continue their regular diet. Amongst the results, individuals assigned to 25% CR were able to reduce their calorie intake by only 11.9%. Despite the scant adherence, CR administration in healthy individuals resulted in weight loss[43], reduced whole body oxidative stress[44], decreased systolic and diastolic blood pressure[43], and a modest improvement in working memory[45]. Another study showed that long-term calorie restriction may reduce the risk for atherosclerosis in humans[15].

Despite these advances, CR in humans has also shown adverse effects in some studies, which limit its clinical usefulness. These adverse effects include cold sensitivity, menstrual irregularities, and hormonal changes. CR regimens also resulted in reduced bone mineral density at clinically relevant sites of osteoporotic fractures[46], diminished aerobic capacity, and episodic anemia in some participants[43]. Recent evidence obtained in rodents suggest that the declining body weight, and potential impaired immune functionality[42] associated with strict dietary restriction may not be suitable for frail older adults at risk of malnutrition, hypothermia, and bacterial/viral infection[42, 47–49]. Lastly, adherence to CR regimens remains a challenge and a translational barrier as most humans are not able or willing to reduce their calorie intake by 30% over extensive periods of time. Thus, alternative nutritional strategies tailored to the needs of older adults must be developed to obtain health benefits similar to those offered by CR, while limiting the risk of undesired adverse effects. Recent excitement in favor of strategies that could recapitulate the benefits of CR has driven growing interest in a set of lifestyle interventions collectively referred to as intermittent fasting (IF) (Figure 1). Any dietary regimen that includes periods of voluntary abstinence from food falls within the definition of intermittent fasting[50]. Time restricted feeding (TRF) is considered to be one of the best ways to approach intermittent fasting for elderly individuals. Two other widely used paradigms are the 5:2 diet, which allows for 5 days of *ad libitum* feeding and 2 days of complete fasting, and alternate day feeding, which involves alternation between fast days and *ad libitum* feeding days. Unlike other IF approaches, TRF does not limit one's daily calorie intake (Figure 1). In fact, some of the observed beneficial

effects of CR may at least in part be attributed to the inadvertent administration of a TRF regimen. Laboratory rodents undergoing CR tend to consume the entirety of their daily food allowance in a few hours. After the food is finished they have no choice but fast for the remainder of the day (up to 20 hours) until the next feeding takes place[51]. This observation has generated a lot of enthusiasm and motivated a series of studies investigating the mechanistic inner workings of TRF. Indeed, recent work has indicated that the differential effects on lifespan observed in non-human primate CR studies may be largely due to the duration of fasting that occurred in the different experimental regimens[52].

TRF is not designed as a calorie-deficit method, but instead as a pattern of eating (Figure 1) which recent work suggests may be more effective in promoting fat loss and regulating the impairment of glucose metabolism in humans, as compared with other CR regimens[53]. TRF is potentially the most practical strategy for normal weight older adults as it allows consumption of all required daily calories within a condensed daily feeding window (4, 6, or 8 hours), resulting in a prolonged fasting period without a net reduction in calorie intake[54, 55]. The potential effects of TRF against age-related VCI are currently under investigation, and based on recent evidence, TRF could be a viable and easily attainable therapeutic lifestyle-intervention for slowing the development of age-related cerebromicrovascular pathology and ameliorating age-related cognitive decline. The present review focuses on potential mechanisms of TRF-induced cerebromicrovascular protection and its possible use to prevent VCI.

3. Biological effects of time restricted feeding

Initial findings indicate that TRF could provide many of the benefits of CR, while minimizing the risks and drawbacks associated with forced calorie deficit, such as excessive weight loss, decreased bone mineral density, and poor adherence to food deprivation. Condensing food consumption within a contained time window while fasting the rest of the day recapitulates health benefits of CR, such as reduced oxidative stress and adiposity[56–58]. TRF has also been shown to elicit adaptive, evolutionarily conserved, systemic cellular responses across organs, resulting in decreased inflammation, increased stress resistance, improved glucose regulation[59], neuroprotective effects, improved redox status, increased production of neurotrophic factors that promote neurogenesis, and improvement in mitochondrial function[60] (Figure 2). Alternation between prolonged fasting and a brief feeding state, promotes an intermittent metabolic switch, as adipose–derived ketone utilization becomes preferred over liver-derived glucose as the source of fuel for the body, especially the brain[61]. During TRF metabolic switching is repeated every day, eliciting prolonged systemic and cellular responses that are sustained into the fed state to improve cognitive function and disease resistance[62, 63]. Metabolic switching may be one of the most critical factors driving the beneficial effects of CR, and even more pronounced metabolic fluctuations can be achieved using intermittent fasting regimens like TRF. Some recent evidence even suggests that in some regards the beneficial effects exerted by metabolic switching may go beyond those obtainable from CR alone[64–67]. The metabolic switch from glucose to ketone body utilization was found to positively affect metabolic flexibility and improve energy production efficiency[57]. The rationale behind the concept of TRF arose within the framework of the circadian rhythm, an adaptation evolved in humans and other

animals in response to narrow windows of food availability and long fasts between meals. It is hypothesized that daytime feeding periods result in activation of mechanisms that increase cell growth (mTOR activation) and differentiation, while during night-time, fasting pathways conserving energy and activating cellular repair are preferentially activated (e.g. AMPK, SIRT-1 and autophagy)[68]. Reinforcing a time-restricted feeding protocol is presumed to modulate the circadian cycle and improve regulation of hypothalamic function, which controls feelings of hunger and satiety, energy metabolism, and inflammatory response[69].

4. Potential effects of TRF on cerebromicrovascular pathophysiological alterations relevant for the genesis of VCI

Age-related structural and functional cerebrovascular alterations thought to contribute to the pathogenesis of VCI are illustrated in Figure 3[70]. While available data on the direct effects of TRF on cerebromicrovascular mechanisms contributing to the development of VCI are scarce, potential beneficial cerebromicrovascular effects of TRF can be predicted based on its effects on the peripheral vasculature and/or circulating biomarkers in preclinical and clinical studies. By expanding on those findings that drive vasculo-protection in the peripheral circulation, novel studies may be performed to identify potential understudied mechanisms that may be protective of the cerebral microcirculation as this could be beneficial against age-related vascular cognitive impairment and related dementias.

4.1 Endothelial dysfunction

Aging-induced cerebromicrovascular dysfunction plays a central role in impaired blood supply of the aging brain[71–76]. Age-related increases in the production of reactive oxygen species (ROS) by NADPH oxidases[75, 77–79] and mitochondria[7, 37, 71, 72, 76, 80–82] are believed to contribute to the development of endothelial dysfunction in both pre-clinical[83] and clinical studies[84]. Excess production of superoxide reacts with endothelium-derived nitric oxide (NO) to produce the highly reactive oxidant peroxynitrite ($ONOO^-$)[85], which mediates many of the detrimental effects of vascular oxidative stress. This includes cytotoxic effects, mitochondria dysfunction, and upregulation of pro-inflammatory pathways. Excess free radical production exacerbates vascular inflammation and contributes to the pathogenesis of age-related cognitive impairment[86, 87]. CR[31, 37] and fasting[88] were shown to attenuate endothelial oxidative stress and restore endothelial function. Interestingly, administration of TRF was also reported to diminish ROS production and improve endothelial function[89], which may be predictive of a cerebrovascular protective role against the age-related dysregulation of cerebral blood flow and genesis of VCI. This possibility should be investigated in clinical and experimental studies.

In this regard, observational studies performed on individuals practicing TRF for a month during Ramadan, when eating is not allowed during hours of daylight, creating ~12 hour fasting window[90, 91], are particularly interesting. After the Ramadan fasting period, participants exhibit lower circulating markers of oxidative stress and inflammation[92, 93]. TRF practiced during Ramadan also improves plasma cholesterol and lipid profiles, and lowers blood pressure in older adults with at least one risk factor for CVD[94]. Although, the calorie intake and exact fasting time in studies on Ramadan practitioners is difficult to

estimate, the aforementioned data warrant further studies to assess relevant cerebromicrovascular and cognitive endpoints.

4.2 Impaired neurovascular coupling

In humans, as well as in laboratory animals, oxygen and nutrient storage capacity in the central nervous system is limited, and even momentary interruptions in oxygen supply and nutrient delivery rapidly impair neuronal function[1, 95]. To maintain intact cognitive abilities, the actively-firing brain neurons require a constant provision of oxygen and nutrients as well as effective wash-out of metabolic waste. These are achieved through a homeostatic feed-forward mechanism present in the brain, known as neurovascular coupling, which adjusts cerebral blood flow to match neural activity and prevents neural ischemic damage, neurodegeneration and cognitive impairment[1]. Clinical and experimental studies suggest that age-related functional impairments of cerebral microcirculation compromise neurovascular coupling responses, which likely contributes to age-related cognitive decline[1, 5, 7, 71, 96–102]. Pre-clinical studies show that treatments designed to restore endothelial function and cellular energetics[71], and improve endothelium-dependent NO bioavailability[7, 71], were successful in reversing the age-related impairment in neurovascular coupling responses.

Recent pre-clinical work in rodents has shown that TRF can potentially confer vasoprotective effects through attenuation of pro-inflammatory processes[54, 65, 103, 104]. As such, it is plausible that TRF-induced improvement in endothelial function[105] may reverse the age-associated decrease in endothelial-dependent NO bioavailability, improving cerebromicrovascular function and brain perfusion. Future studies should test this possibility by assessing the effects on endothelium-dependent neurovascular coupling responses.

4.3 Cerebral microhemorrhages

Cerebral microhemorrhages or microbleeds are small chronic intracerebral hemorrhages which are caused by rupture of small arterioles or capillaries[106–108]. Aging and hypertension are major risk factors for the genesis of cerebral microhemorrhages[106]. The prevalence of cerebral microhemorrhages reaches over 50% in older adults at risk[106]. Cerebral microhemorrhages are clinically significant as they were shown to contribute to cognitive impairment, geriatric psychiatric syndromes, and gait disorders[106, 108, 109]. Studies have shown that increased vascular oxidative stress is closely linked to increased matrix metalloproteinase activity in the vascular wall[108, 110], resulting in impaired structural integrity of the microvasculature and increased risk cerebral microhemorrhages.

In pre-clinical and clinical studies, administration of TRF results in attenuated risk for cardiovascular diseases[89], restores endothelial vasorelaxation[111] and substantially decreases blood pressure[94]. CR was shown to down-regulate matrix metalloproteinases and protect against pathologic remodeling of the extracellular matrix in aged arteries and prevent aneurysm formation[112, 113]. These findings, taken together with the demonstrated CR-like anti-oxidative effects of intermittent fasting[51, 114], raise the possibility that TRF might confer protection against the development of microhemorrhages. Additional experimental studies are warranted to test this hypothesis.

4.4 Blood-brain barrier disruption

Strong evidence in murine models supports the concept that age-related cerebrovascular dysfunction is associated with blood-brain barrier disruption and the resulting neuroinflammation[101, 115]. There is data showing that CR exerts protective effects on the blood brain barrier[116], which may contribute to its beneficial effects on cognitive function. Further preclinical studies are needed to investigate whether the TRF-induced reduction in oxidative stress and changes in endothelial vasodilation also lead to improved blood-brain barrier function in aging. Importantly, a recent study reported no effect of an every-other-day feeding regimen on blood-brain barrier permeability in a mouse model of Alzheimer's disease[117]. However, the study reported that this type of treatment enhanced neuronal deficits and inflammation

4.5 Age-related changes in the synthesis of paracrine mediators: cytokines, chemokines and growth factors

The microvascular endothelium is an important source of paracrine mediators, including cytokines, chemokines[37] and growth factors (e.g. brain-derived neurotrophic factor [BDNF], insulin-like growth factor-1 [IGF-1], pituitary adenylate cyclase-activating peptide [PACAP][118, 119]) that play an important role in autocrine regulation of microvascular functions as well as in regulating the function of neurons, astrocytes and glial cells. In aging the synthesis/release of these paracrine mediators is significantly altered, which contributes to age-related neuronal and glial dysfunction, increased neuroinflammation, and disruption of neurogenic niches[70].

CR was shown to 'rejuvenate' the trophic function of cerebromicrovascular endothelial cells[37]. Additionally, chronic intermittent fasting has been shown to up-regulate microvascular BDNF and VEGF signaling[120]. Recent evidence suggests that β-hydroxybutyrate, a ketone generated in response to fasting, can upregulate the expression of BDNF, which confers mitochondrial protection, and promotes synaptic plasticity and cellular stress resistance[59]. Further pre-clinical studies should be conducted to investigate the effect of TRF on the modulation on vascular trophic factors that could affect cognitive outcomes.

4.6 Cerebromicrovascular rarefaction

Cerebromicrovascular density typically declines with advanced age[73, 121–123], which contributes to decreased cerebral blood flow and promotes cognitive decline[124]. The mechanisms underlying age-related cerebromicrovascular rarefaction include increased endothelial apoptosis and impaired angiogenic processes[37, 118, 122, 124–126]. Important in that regard is that CR confers significant anti-apoptotic and pro-angiogenic endothelial effects and results in increased capillarization in the aged rodent brain[37, 38, 127]. It would be of interest to explore if TRF also exerts anti-apoptotic and pro-angiogenic endothelial effects, reversing age-related cerebromicrovascular rarefaction. Age-related decline in circulating IGF-1 has been causally linked to capillary rarefaction[128–130] as well as other functional aspects of cerebromicrovascular aging (e.g, neurovascular dysfunction[131, 132], impaired autoregulation[133], pathological remodeling and increased microvascular fragility[134, 135]). In rodents CR decreases serum IGF- 1 concentration by 20–40%, whereas 2 year of CR in the

CALERIE study had no effect on circulating IGF-1 in humans[136]. Previous studies have reported mixed results concerning the effect of TRF on circulating IGF- 1. No changes in circulating IGF-1 were observed during Ramadan intermittent fasting[137]. In contrast, eight weeks of a TRF regimen (16/8) was shown to result in a significant decline in IGF-1 levels in study participants[138]. Because of the significant cerebromicrovascular protective effects of IGF-1 future studies should compare the effects of different TRF regimens and explore the impact of TRF-induced changes in IGF-1 on cerebromicrovascular physiology.

5. Conclusions

The pre-clinical and clinical studies discussed in this review provide prima facie evidence for the potential vasoprotective effects of metabolic lifestyle interventions such as CR, intermittent fasting and TRF. TRF interventions are an innovative approach, despite it is possible that CR and TRF may share some commons mechanisms, there may be other mechanisms involved that could exert CR-independent beneficial effects[139]. Future studies should address the effects of TRF on cerebromicrovascular health in both experimental studies on pre-clinical models of aging, and clinical investigations. In particular, investigating the effects of TRF on endothelial-dependent vasodilation and neurovascular coupling response would be of critical importance to understand the translational implications of TRF and other similar nutritional lifestyle interventions. Assessment of cognitive outcomes in response to administration of TRF, both in pre-clinical and clinical studies, will establish its usefulness for prevention of VCI. New TRF regimens combined with dietary advice tailored to the needs of older adults should be developed to reap the full cerebrovascular and cognitive health benefits while limiting the risk of undesired adverse effects. Although TRF seems to be protective against different unhealthy diets in mice[54, 55], in older adults a combination of a healthy diets and an effective modified eating pattern is desirable. Ideally, effective TRF regimens should be adapted to different lifestyles. The cerebrovascular effects of the occasional deviation from TRF (e.g. a change in eating pattern between weekdays and weekends) should be elucidated. Future studies should also determine the legacy effect on cerebrovascular and cognitive endpoint after cessation of TRF. Finally, the therapeutic effect of TRF on vascular/cerebrovascular impairment associated with pre-existing diet-induced obesity[88, 126, 140–145] has to be explored. Addressing these questions both in preclinical studies and the clinical setting will be critical to elucidate the effectiveness and limitations of TRF for prevention of VCI.

Acknowledgement

This work was supported by grants from the American Heart Association (to ST), the NIA-supported Geroscience Training Program in Oklahoma (T32AG052363), the NIA-supported Oklahoma Nathan Shock Center, and the NIGMS supported Center of Biomedical Research Excellence (CoBRE) (1P20GM125528-01A1).

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Highlights

- Caloric restriction has powerful pro-longevity and cognitive protective effects
- Evidence suggests TRF may be more easily attainable diet
- TRF may mimic the cerebrovascular protective effects elicited by CR
- Potential role of TRF against age-related vascular cognitive impairment

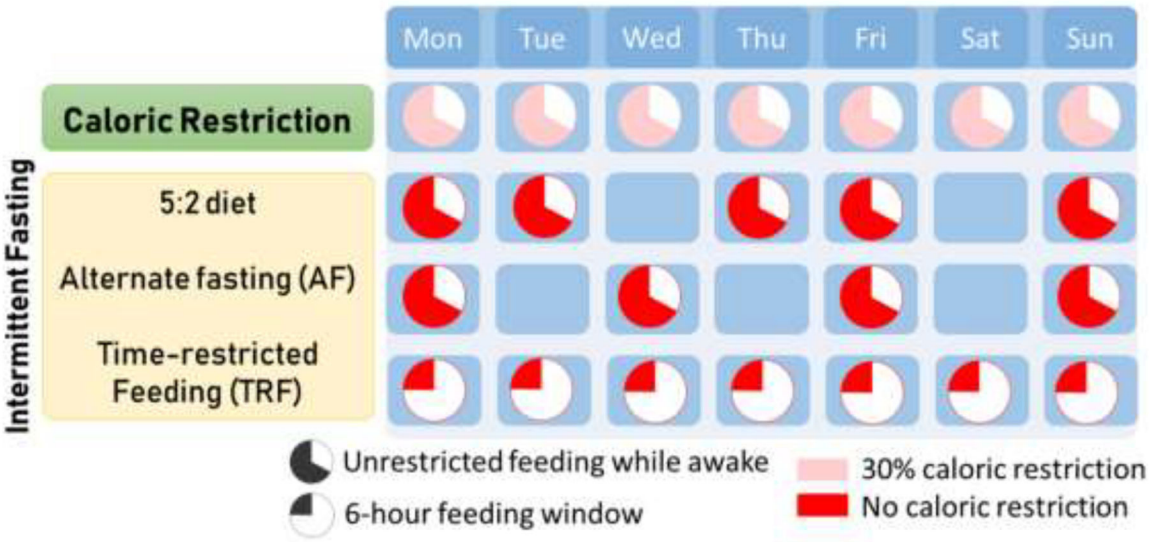

Figure 1. Comparison of CR-mimicking lifestyle nutritional interventions.

Intermittent fasting is any diet that includes regular periods of not eating or fasting. The 5:2 diet allows for ad-libitum feeding during 5 days of the week, with 2 days of complete fasting. Alternate fasting (AF) involves unrestricted eating every other day, while time-restricted feeding (TRF) consists of ad-libitum feeding every day within a specific time window that may vary from 4–8 hours.

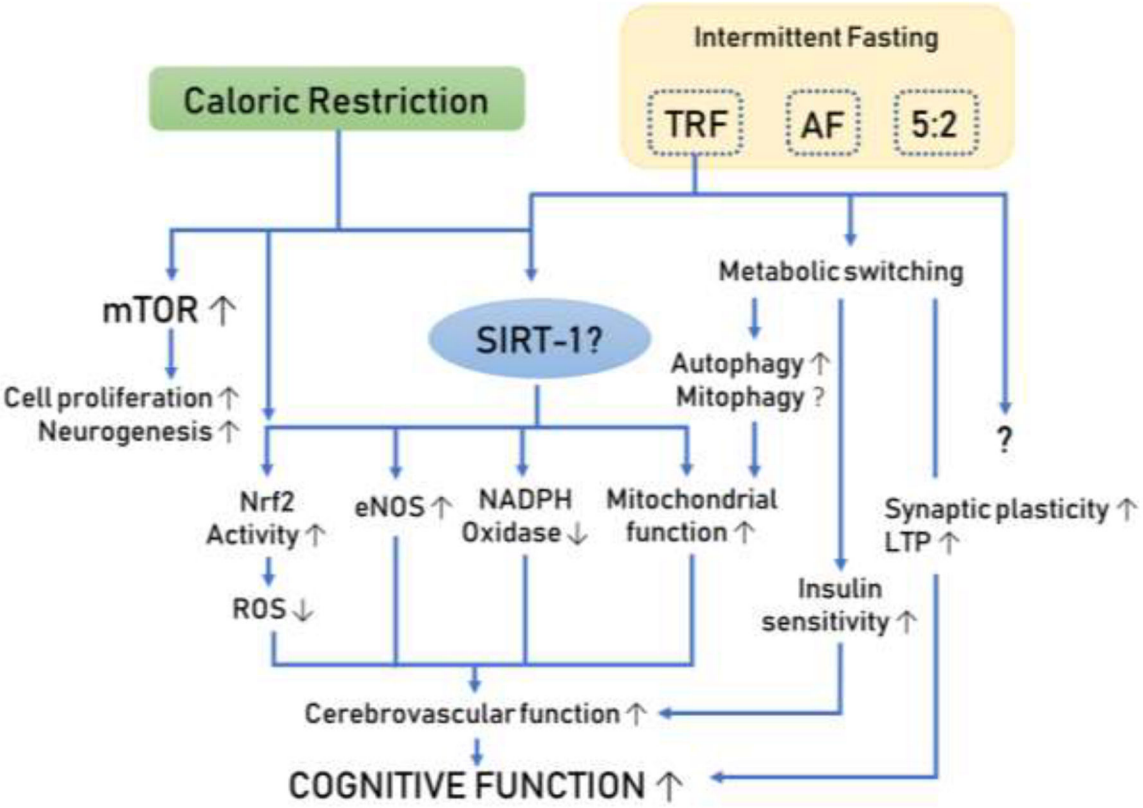

Figure 2. Schematic diagram illustrating the potential shared mechanisms between caloric restriction and intermittent fasting.

Extensive investigations of CR have demonstrated its powerful pro-longevity action and cognitive protective effects. New evidence suggests that more attainable diets (such as TRF) may confer similar beneficial effects mimicking the cerebrovascular protective effects elicited by CR.

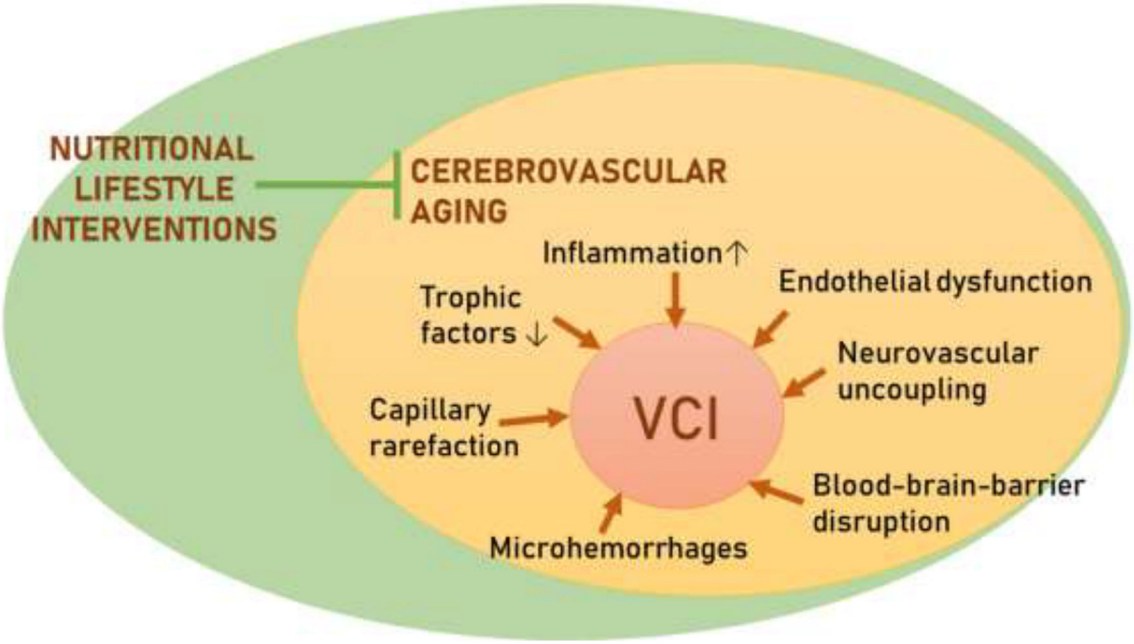

Figure 3. Scheme of cerebromicrovascular mechanisms contributing to the pathogenesis of age-related vascular cognitive impairment.

Nutritional lifestyle interventions, such as CR, have proved to be efficacious in preventing and, at least partially, reversing the downstream consequence of vascular aging. In humans, adherence to CR regimen remains a challenge and a translational barrier. Alternative nutritional strategies tailored to the needs of older adults must be developed to reap health benefits similar to that offered by CR while limiting the risk of undesired adverse effects.