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Review

The effects of time-restricted eating on sleep, cognitive decline, and Alzheimer's disease

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ABSTRACT

According to the United Nations, by 2050, one in six individuals will be over age 65 globally, and one in four people would be aged 65 and older in western countries. The unprecedented growth of the aging population is associated with increased age-related disorders like Alzheimer's disease (AD) and Mild cognitive impairment (MCI). To date, no cure is known for AD, thus lifestyle interventions including calorie restriction (CR) and time-restricted eating (TRE) are proposed as potential approach to delay the onset and progression of the disease. Sleep disturbances are common in people with MCI and AD. Moreover, accumulating data indicates that pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), IL-6, IL-8 and IL-10 increase in individuals with AD and MCI versus healthy subjects. Thus, the purpose of the present review is to describe the potential effects of TRE on sleep, cognition decline, and neuroinflammatory markers in humans. Preliminary evidence suggests that TRE may produce neuroprotective effects on cognition and reduce neuro-inflammatory markers related to AD in humans. To date, no studies investigated the effects of TRE on sleep disturbances and patients with AD. Thereby, the impact of TRE on cognition in individuals with cognitive decline and AD needs to be investigated further in randomized controlled trials (RCTs).

1. Introduction

The percentage of older adults is increasing rapidly worldwide, and it is expected that the number of older people globally will double by 2050 (United Nations Department of Economic and Social Affairs, Population Division, 2020). The unprecedented growth of the aging population has increased the incidence of age-related neurodegenerative diseases like dementia (GBD Neurology Collaborators, 2019). AD is the most prevalent neurodegenerative disease affecting over 50 million aging people worldwide (Blaikie et al., 2022). MCI is a pre-stage for dementia that is reversible (Shimada et al., 2019).

The incurable nature of dementia has thus led to an urgent need for lifestyle interventions that can delay the onset and progression of the disease. Accumulating data from clinical and animal studies indicate that intermittent fasting (IF)—an approach in which individuals fast periodically—may be useful for the prevention and treatment of neurodegenerative diseases (Hadem et al., 2019; Fontana et al., 2021). Recently, time-restricted eating (TRE)—a form of IF—has gained much attention as it does not involve calorie counting. TRE involves limiting the eating window to 8- to 12-h with fasting—drinking only water and calorie-free coffee/tea—for 12 to 16 h within a 24-h cycle (Anton et al., 2021). Yet, the impact of TRE on human brain, specifically in people with neurological disorder is still unclear. The potential benefits of TRE on age-related cerebromicrovascular dysfunction—which has a pivotal role in vascular cognitive impairment—has already been investigated (Balasubramanian et al., 2020). TRE is suggested to restore endothelial function and neurovascular coupling response through attenuation of oxidative stress and inflammation (Hatori et al., 2012; Chaix et al., 2014). In addition, TRE may improve blood-brain barrier disruption which has a role in cognitive function improvement (Balasubramanian et al., 2020).

In this review, we examine the possible underlying mechanisms of potential neuroprotective effects of TRE and relevant existing human research on the effects of TRE on markers of mild cognitive impairment (MCI) and AD.

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2. The mechanisms underlying the potential neuroprotective benefits of TRE

The mechanism underlying the potential health benefits of TRE remains to be fully understood (see Fig. 1). One possible mechanism through which TRE may induce cognitive improvement arose from findings that suggests TRE regulates circadian rhythm and autophagy through aligning food intake with circadian rhythm (Hatori et al., 2012; Jamshed et al., 2019; Ulgherait et al., 2021; Zeb et al., 2021). The circadian clock coordinates metabolism and physiological functions including glucose, insulin sensitivity, lipid levels, energy expenditure, inflammation, sleep and cognitive function (Wyatt et al., 1999; Poggiogalle et al., 2018; Stenvers et al., 2019; Wang and Li, 2021); thereby circadian rhythm dysregulation is common in sleep disorders and Alzheimer's disease (Wu et al., 2006; Coogan et al., 2013; Hoyt and Obrietan, 2022).

TRE also activates the metabolic switch which occurs 12–36 h after fasting is initiated and free fatty acids are released into the blood (Anton et al., 2021). Results of animal and human pilot studies indicate that the metabolic switch may optimize brain health by increasing the levels of ketone, brain-derived neurotrophic factor (BDNF), fibroblast growth factor-2 (FGF2), Sirtuin1&3, autophagy ad DNA damage (Mattson et al., 2018; Jamshed et al., 2019) which results in enhanced cerebrovascular and cognitive function. Moreover, it may reduce glucose, leptin, insulin, inflammatory cytokines, and the mammalian target of rapamycin (mTOR) pathway activity, which results in improving cognition and preventing dysfunction and degeneration of neurons, thus protecting the brain from neurodegenerative diseases like Alzheimer's disease. β-hydroxybutyrate (BHB)—a ketone which is the product of the metabolic switch—serves as a signaling molecule that upregulates BDNF expression in neurons and thereby improves synaptic plasticity (Hood et al., 2016; Mattson et al., 2018; Hu et al., 2018). In addition, IF upregulates autophagy in cerebral cortical and cerebellar neurons (Alirezaei et al., 2010), through inhibiting mTOR protein synthesis pathway, and activation of adaptive cellular stress response signaling pathways that promote mitochondrial health, and DNA repair (Longo and Mattson, 2014; Mattson et al., 2017). In laboratory animals, TRE induced BHB, reduced blood glucose, and improved sleep-phase in AD mice compared to the control (Whittaker et al., 2021). Similarly, TRE combined with 30–40 % calorie restriction lowered the accumulation of Aβ plaques in *App*-mutant mice (Wang et al., 2005; Patel et al., 2021), and IF improved cognitive impairment in the triple-transgenic mouse model of AD (Halagappa et al., 2007).

Additionally, TRE (with ad libitum intake) produces weight loss (1–4 % with ad libitum intake and $\geq$ 5 % when combined with CR) in adults with obesity (Gabel et al., 2018; Ezzati et al., 2022). Accumulating evidence from systematic reviews and meta-analysis suggest the association of overweight and obesity with cognitive decline and increased risk of AD and vascular dementia (Pedditizi et al., 2016; Tang et al., 2021), while weight loss improves cognitive function in adults with overweight and obesity (Veronese et al., 2017). Therefore, weight loss induced by TRE may be another pathway which may play a role in cognitive improvement.

3. The effects of TRE on sleep and cognitive decline

Sleep disorders are common in both MCI and AD (Pak et al., 2020). Similarly, insomnia and sleep apnea are associated with AD (Osorio et al., 2011; Kuo et al., 2020). Sleep disturbances are known as a major risk factor for AD and linked with inflammation (Hansson et al., 2006; Alvarez et al., 2007). We note that in examining existing studies on TRE on sleep and cognitive decline, the studies conducted have solely focused on one or the other, and not considered both together.

To the best of our knowledge, no study has yet investigated the effects of TRE on sleep disturbances in humans; however, the effects of TRE on sleep in healthy individuals have been examined in nine studies (Gill and Panda, 2015; Hutchison et al., 2019; Gabel et al., 2018; Parr et al., 2020; Kesztyüs et al., 2020; Cienfuegos, 2021; Lowe et al., 2020; Wilkinson et al., 2020; Xie et al., 2022) (see Table 1). The *Pittsburgh Sleep Quality Index* (*PSQI*) was carried out to assess sleep quality and disturbances in six trials (Gabel et al., 2018; Parr et al., 2020; Cienfuegos, 2021; Lowe et al., 2020; Wilkinson et al., 2020; Xie et al., 2022). No trial reported significant improvement in sleep quality using the PSQI survey. In the most recent trial, a 5-week randomized controlled trial (RCT) by Xie et al. (2022) showed no significant change in sleep quality between early TRE (fasting between 6 a.m.–3 p.m.), mid-day TRE (11 a.m.–8 p.m.) and control (ad lib intake) in 82 healthy subjects without obesity but the sleep quality improvement was greater in early TRE group (PSQI: $\Delta = -1.08 \pm 1.78$ vs. $\Delta = -0.22 \pm 2.19$ and $\Delta = -0.36 \pm 1.73$, respectively).

In addition to the PSQI survey, Wilkinson et al. (2020) assessed sleep quality with the myCircadianClock app and reported significant

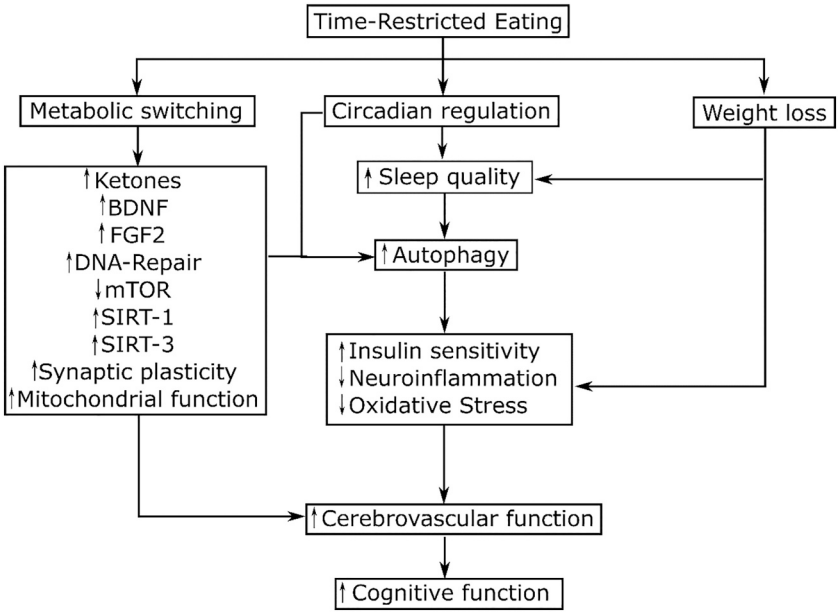

Fig. 1. The proposed mechanisms through which time-restricted eating may induce neuroprotective benefits.

Table 1
Summary of human studies on the effects of time-restricted eating on sleep, cognitive decline, and neuroinflammation.

Study	Intervention	Participants	Sleep measurement	Cognitive measurement	Markers (plasma/CSF)	Results
Cienfuegos (2021)	**8-week RCT** 4-h TRE (3–7 p.m.) vs. 6-h TRE (1–7 p.m.) and control	49 obese adults	–	–	Plasma 8-Isoprostane, TNF-α, IL-6	↓8-Isoprostane levels in both intervention groups (4-h and 6 h-TRE) No significant changes in TNF-α, and IL-6 levels
Cienfuegos (2021)	**8-week RCT** Delayed TRE: 4-h TRE (3–7 p.m.) vs. 6-h TRE (1–7 p.m.) and control	58 obese adults	PSQI; Sleep quality, duration, insomnia severity and obstructive sleep apnea	–	–	No significant changes in sleep quality, duration, insomnia severity, or the risk of obstructive sleep apnea.
Currenti et al. (2021)	**Cross-sectional** TRE (<10 h eating window) vs >10 h eating period	883 older adults	–	Short Portable Mental Status Questionnaire (SPMSQ)	–	Those practicing TRF were less likely to have cognitive impairment vs non-TRE; Similarly, breakfast consumption was associated with lower cognitive impairment prevalence
Gabel et al. (2018)	**12-week single arm** 8-h TRE (10 a.m.–6 p.m.)	23 obese adults	PSQI; Sleep quality, duration	–	–	No significant changes in sleep quality, and duration
Gill and Panda (2015)	**16-week Single-arm:** 10-h TRE (self-selected eating window)	8 overweight and obese	Sleep duration Using self-assessment survey	–	–	↑sleep duration
Hutchison et al. (2019)	**1-week RT-Crossover** 9-h TRE (8 a.m.–5 p.m.) vs. 9-h TRE (12–9 p.m.)	15 overweight and obese males	Sleep duration was assessed by accelerometry	–	–	No significant change in sleep duration
Jamshed et al. (2019)	**4-day RT-Crossover** e-TRE (8 a.m. and 2 p.m. vs control (8 a.m. and 8 p.m.)	11 overweight adults	–	–	Ketones, BDNF, and gene expression in whole blood cells	↑ Ketones, and the expression of the stress response and aging gene *SIRT1* and the autophagy gene *LC3A* (all $p < 0.04$), in e-TRE in the morning ↑ BNDF ($p = 0.10$) and the expression of *MTOR* ($p = 0.007$) in the evening in e-TRE
Kesztyüs et al. (2020)	**12-week Single-arm** 8–9-h TRE (self-selected eating window)	99 overweight and obese adults	Sleep quality was assessed by VAS Sleep duration self-reported survey	–	–	↑sleep quality (↑10 points) No change in sleep duration
Martens et al., 2020	**6-week RCT:** TRE (16/8) without weight loss vs control	22 healthy non-obese older adults	–	NIH Toolbox Cognition Battery	Plasma IL-6, oxidized-LDL or the oxidized-to-total LDL ratio, acetoacetate and β-hydroxybutyrate	No significant changes in IL-6, oxidized-LDL or the oxidized-to-total LDL ratio, acetoacetate and β-hydroxybutyrate No improvement in cognitive performance
Moro et al. (2021)	**12-month RCT** TRE (3 meals;1 p.m.,4 p.m. and 8 p.m.) vs ND (8 a.m-8 p.m.)	20 healthy athletic males	–	–	Plasma TNF-α, IL-1β, IL-6 and 8-Isoprostane	↓TNF-α, IL-1β, IL-6 and 8-Isoprostane vs baseline and control
Lowe et al. (2020)	**12-week RCT** 8-h delayed TRE (12–8 p.m.) vs. Control	116 overweight and obese adults	Sleep quality was assessed by PSQI Sleep duration was assessed by Oura ring	–	–	No significant changes in sleep quality, and duration
Ooi et al. (2020)	**36-month longitudinal study** regularly practicing down to sunset TRE 2-d/w (r-IF), vs irregularly practicing TRE (i-IF), and non-fasters (n-IF)	99 older adults with MCI	–	Five types of cognitive tests: the Malay version of the Mini Mental Examination State (MMSE), Malay version of Montreal Cognitive Assessment (MoCA), Rey Auditory Verbal Learning Test (RAVLT), Digit Span Test, and Digit Symbol.	superoxide dismutase activity, malondialdehyde, DNA damage, plasma CRP	↑ cognitive improvements in older people with MCI in r-IF group vs i-IF and n-IF ↓superoxide dismutase activity, malondialdehyde, DNA damage, and CRP levels in r-IF vs i-IF and n-IF
Parr et al. (2020)	**4-week single-arm** 9-h TRE (10 a.m.–7 p.m.)	19 overweight and obese adults With type 2 diabetes	Sleep quality and duration was assessed by PSQI	–	–	No significant change in sleep quality/duration
Sutton et al. (2018)	**5-week RCT** early-TRE (6-h, last		–	–	Plasma 8-Isoprostane, and IL-6	↓8-Isoprostane vs control No significant changes in IL-6

(*continued on next page*)

Table 1 (*continued*)

Study	Intervention	Participants	Sleep measurement	Cognitive measurement	Markers (plasma/CSF)	Results
	meal before 3 pm) vs control (12-h. eating window)	12 prediabetic men				
Xie et al. (2022)	**5-week RCT** e-TRE (6 a.m.–3 p.m.) vs mid-day TRE (11 a.m.–8 p.m.) vs control	82 healthy adults	Sleep quality was assessed by PSQI	–	Plasma TNF-α, IL-8	↓TNF-α, IL-8 in e-TRE group vs control ↑ sleep quality in early TRE vs mid-day TRE and control
Zouhal et al. (2020)	**30-day RCT** Ramadan TRE (down to sunset) vs control	28 obese men	–	–	Plasma TNF-α, IL-6	↓TNF-α, and IL-6 in Ramadan-TRE vs control ↓TNF-α in control vs baseline

Abbreviations: RCT: Randomized controlled/comparative trial; TRE: Time restricted eating; TNF-α: Tumor necrosis factor α; IL-6: Interleukin-6; PSQI; Pittsburgh Sleep Quality Index; e-TRE: Early-time-restricted eating; BDNF: brain-derived neurotrophic factor; MTOR: Mammalian target of rapamycin; LDL: Low-density lipoprotein; IL-1β: Interleukin-1β; CRP: C-reactive protein; IL-8: Interleukin-8.

improvement in sleep quality (23 %) following a 12-week single arm intervention of 10-h TRE (Wilkinson et al., 2020). Following a 16-week TRE intervention, Gill and Panda (2015) reported improved sleep duration and weight loss of 4 % in eight overweight and obese subjects; however, the study used a self-assessment survey which is not considered a validated tool for measuring sleep duration.

Evidence suggests that >5 % weight loss can improve sleep quality in obese individuals (Verhoef et al., 2013; Martin et al., 2016). Conversely, achieving 10 % weight loss can be detrimental and increases the risk of obstructive sleep apnea (Peppard et al., 2000). None of the aforementioned studies reported >5 % weight loss versus baseline; however, TRE is believed to be associated with sleep quality independent of weight loss (Kesztyüs et al., 2020). Furthermore, in a cross-sectional study of 1226 older adults (≥64 years), a longer fasting period in TRE approach (≥12 h fasting) was associated with significantly higher sleep duration which was measured with questionnaires (Estrada-deLeón et al., 2021).

To date, no trial has tested the effects of TRE on cognitive decline in human AD subjects. However, the potential neurocognitive benefits of TRE in people with AD have been investigated in preliminary observations studies (Ooi et al., 2020; Currenti et al., 2021) (see Table 1). Ooi et al., 2020 tested the effects of a unique form of TRE in which fasters practiced fasting from down to sunset only two days per week (Monday and Thursday; no food or drink) on cognitive function among elderly people (>60 years old) with MCI in a cohort study of 3-year duration. Elderly people with MCI who regularly practice IF (2-d TRE/week) for 12 months demonstrated a significant improvement in cognitive scores (using five types of cognitive tests) as compared to irregular and non-fasters. Moreover, a significant improvement in the antioxidant superoxide dismutase levels, inflammatory markers, and DNA damage was reported in regular faster groups versus baseline following 36 months period follow up. In a recent cross-sectional study conducted by Currenti et al. (2021), the association between TRE and cognitive status in a cohort of elderly Italian adults above 50 years old (n = 916) was investigated. Elderly individuals who practiced TRE (<10 h eating window) had lower rates of cognitive impairment versus individuals with ad libitum intake [odds ratio (OR) = 0.28; 95 % confidence intervals (CI): 0.07–0.90]. Similarly, breakfast eaters demonstrated lower risk of cognitive impairments (OR = 0.37, 95 % CI: 0.16–0.89). In contrast, those having dinner did not show such association. These results indicate the importance of timing of eating in TRE interventions and its relationship with cognition in humans.

4. The effects of TRE on neuroinflammation & oxidative stress

Plasma interleukins and TRE have been explored in six RCTs in those with age ranges between 44 and 67 years (see Table 1) (Sutton et al., 2018; Martens et al., 2020; Cienfuegos, 2021; Zouhal et al., 2020; Moro et al., 2021; Xie et al., 2022). Only one study (Moro et al., 2021) tested IL-1β levels and plasma IL-6 levels were measured in five TRE interventions (Sutton et al., 2018; Martens et al., 2020; Cienfuegos, 2021; Zouhal et al., 2020; Moro et al., 2021); Of which two trials showed meaningful changes in IL-6 levels following TRE interventions (Zouhal et al., 2020; Moro et al., 2021). Significant improvements in IL-1β and IL-6 levels were shown in the TRE group (3 meals;1 p.m.,4 p.m. and 8 p.m.) compared to normal diet control (3 meals; 8 a.m., 1 p.m., and 8 p.m.) in 20 healthy subjects after 12 months (Moro et al., 2021). Similarly, Zouhal et al. (2020) carried out a one-month RCT of Ramadan TRE (from down to sunset; no drinking) in 28 obese men. The study reported a significant reduction in IL-6 levels in Ramadan TRE group vs Control. Following a 5-week intervention, IL-8 reduced significantly in early TRE group who fasted after 3 pm until 6 am compared to control (Xie et al., 2022). TNF-α was tested in four RCTs which reported inconsistent results (Cienfuegos, 2021; Zouhal et al., 2020; Moro et al., 2021; Xie et al., 2022). While TNF-α levels remained unchanged in the study by Cienfuegos (2021), it reduced significantly in studies by Moro et al. (2021), Zouhal et al. (2020) and Xie et al. (2022). The latter study reported significant improvement in only early TRE arm compared to control and no meaningful change in mid-day TRE vs control (Xie et al., 2022).

Oxidative stress has been thought to play a role in neurodegenerative diseases (Jensen et al., 2021). Levels of oxidative damage correlate significantly with the neurodegenerative impairment in various populations (Jensen et al., 2021). 8-Isoprostane is a marker of oxidative stress that may be a surrogate biomarker of the mitochondrial health in AD. To date, only two trials examined plasma levels of 8-Isoprostane in relation to TRE (Sutton et al., 2018; Cienfuegos, 2021) and 8-Isoprostane significant declined in both studies. Sutton et al. (2018) examined early TRE (e-TRE) intervention (6-h eating window, last meal before 3 pm) in 12 prediabetic men for 5 weeks and reported significant reduction (14 %) in 8-Isoprostane in e-TRE arm as compared to the control. In consistent with these findings, another TRE trial compared the effects of two forms of TRE [4-h TRE (3–7 p.m.) vs 6-h TRE (1–7 p.m.)] vs control and demonstrated significant reductions in both interventions group vs control [37 % and 34 %, respectively] (Cienfuegos, 2021).

5. Perspectives and future studies

Neuroinflammation plays a critical role in the pathogenesis of AD (Heneka et al., 2015). Evidence indicates that inflammation promotes pathological processes that lead to AD (McCaulley and Grush, 2015; Tarkowski et al., 2003). Accumulating data suggest that pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, IL-8 and IL-10 increase in individuals with AD and MCI versus healthy subjects (Bettcher et al., 2018; Guzman-Martinez et al., 2019; Angiulli et al., 2021; Ogunmokun et al., 2021). Interleukins contribute with complex intercellular interactions in neurons, microglia, astrocytes, and intracellular signal transduction events (Stamouli and Politis, 2016). Elevated levels of pro-inflammatory markers including TNF-α, IL-1β, and IL-6, is linked with amyloid beta (Aβ) in brains of people with AD (Wang et al., 2015). Thus, the abnormal accumulation of Aβ induces excessive release of inflammatory cytokines resulting in neuronal and synaptic dysfunction

and cognitive decline. Oxidative stress which occurs in the brain with aging is also associated with inflammation and believed to have a key role in MCI and AD (Nunomura and Perry, 2020).

Previous studies in both animal and humans suggest that CR and TRE reduces DNA damage by attenuating telomere erosion through regulating nuclear factor kappa B and the production of proinflammatory markers like C-reactive protein (Fann et al., 2014; Ooi et al., 2020). TRE has been reported to improve cognitive decline by downregulating inflammatory responses (Ooi et al., 2020). Although one of the limitations of included studies is that some TRE trials did not indicate the time that fasting initiated, preliminary evidence from short-term trials suggest that early- TRE can improve TNF-α, oxidative stress, BDNF and sleep quality which are the markers of MCI and AD (Jamshed et al., 2019; Sutton et al., 2018; Xie et al., 2022). Another limitation is that most trials have been conducted in healthy young people which limits the generalizability of their findings to other age groups. Given that TRE was reported to improve cognition in animal models (Hernandez et al., 2022), the impact of TRE on cognition in humans, specifically in people with cognitive decline needs to be investigated further. Future clinical studies are needed to investigate the role TRE can play in relation to sleep disturbances and cognition decline in AD.

6. Conclusion

TRE appears to be promising for its potential to reduce the markers of aging and neurodegenerative disease. Nevertheless, the mechanisms for these benefits are poorly understood. Moreover, the optimal time to initiate fasting needs to be elucidated in future trials. The potential benefits of TRE in neurodegenerative diseases like MCI and AD in the context of sleep should be further investigated.

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CRediT authorship contribution statement

Armin Ezzati conducted the search, analyzed the data, and wrote the manuscript. Victoria M. Pak conceived the presented idea, contributed to the writing, and critically revised the manuscript.

Declaration of competing interest

The authors have no reported conflicts of interests.

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