Food for Thought

Cognitive effects of intermittent fasting

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Objectives:

1

DISCUSS NUTRITION AND COGNITIVE DECLINE: HIGH RISK AND PROTECTIVE DIETS

2

REVIEW INTERMITTENT FASTING: PROTOCOLS, COGNITIVE EFFECTS IN PRECLINICAL AND CLINICAL STUDIES AND NEUROPSYCHOLOGICAL MECHANISMS

3

SUMMARIZE CLINICAL APPLICATION: SAFETY CONSIDERATIONS, IMPLEMENTATION, AND MONITORING

Nutrition: modifiable risk factor for Cognitive decline

• Undernutrition is independently associated with both cognitive decline (HR 1.20) and incident dementia (HR 1.57) shown in a pooled cohort study of over 9,000 older adults over approximately 8 years of follow-up.

• Food insecurity has also been linked to faster memory decline in middle-to-older-aged adults.

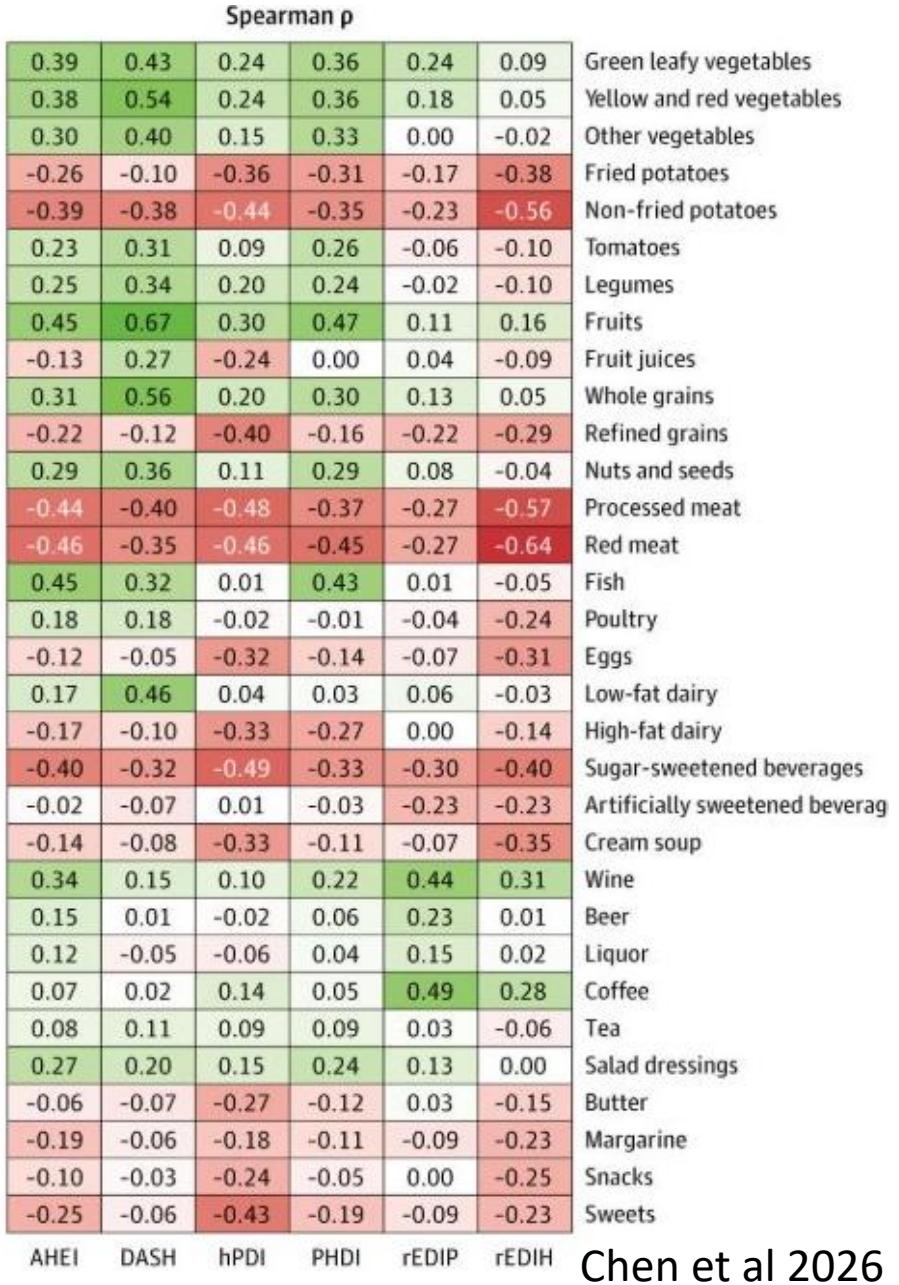
• Malnutrition is an independent predictor of cognitive decline seen in a prospective Chinese longitudinal study found a dose-response relationship: mild malnutrition (score of GNRI 92–98) was associated with a 0.95-point lower MMSE score, and moderate-to-severe malnutrition (score of GNRI<92) with a 1.39-point lower MMSE score

•Malnutrition is thought to worsen cognitive decline through impairing neurotransmitter synthesis, insufficient cerebral energy supply, chronic inflammation, oxidative stress, blood-brain barrier dysfunction, gut-brain axis dysregulation.

Noale et al 2024, Lu et al 2023 , Sun et al 2021

Nutrition and Cognitive decline: Risks

- **Potentially harmful**: Saturated fat, red and processed meats, fried foods, sugar-sweetened beverages, and heavy alcohol consumption found to worsen cognitive function in patients with Subjective Cognitive Decline (SCD)



Chen et al 2026

Nutrition and Cognitive decline: Protective Diets

•**Protective food groups**: Fish and seafood, green leafy vegetables, berries, nuts, and moderate coffee and wine consumption found to improve cognition in SCD

- **Protective micronutrients**: Omega-3 fatty acids, (especially from fish), B vitamins, (particularly folate), vitamin D, polyphenols/flavonoids, vitamin E, and β-carotene found to improve cognition in SCD

Additionally benefits were most pronounced when the diet was followed during mid adulthood (ages 45–54).

This protective food groups are incorporated in the in the DASH and Mediterranean diet.

Spearman ρ

AHEI	DASH	hPDI	PHDI	rEDIP	rEDIH	
0.39	0.43	0.24	0.36	0.24	0.09	Green leafy vegetables
0.38	0.54	0.24	0.36	0.18	0.05	Yellow and red vegetables
0.30	0.40	0.15	0.33	0.00	-0.02	Other vegetables
-0.26	-0.10	-0.36	-0.31	-0.17	-0.38	Fried potatoes
-0.39	-0.38	-0.44	-0.35	-0.23	-0.56	Non-fried potatoes
0.23	0.31	0.09	0.26	-0.06	-0.10	Tomatoes
0.25	0.34	0.20	0.24	-0.02	-0.10	Legumes
0.45	0.67	0.30	0.47	0.11	0.16	Fruits
-0.13	0.27	-0.24	0.00	0.04	-0.09	Fruit juices
0.31	0.56	0.20	0.30	0.13	0.05	Whole grains
-0.22	-0.12	-0.40	-0.16	-0.22	-0.29	Refined grains
0.29	0.36	0.11	0.29	0.08	-0.04	Nuts and seeds
-0.44	-0.40	-0.48	-0.37	-0.27	-0.57	Processed meat
-0.46	-0.35	-0.46	-0.45	-0.27	-0.64	Red meat
0.45	0.32	0.01	0.43	0.01	-0.05	Fish
0.18	0.18	-0.02	-0.01	-0.04	-0.24	Poultry
-0.12	-0.05	-0.32	-0.14	-0.07	-0.31	Eggs
0.17	0.46	0.04	0.03	0.06	-0.03	Low-fat dairy
-0.17	-0.10	-0.33	-0.27	0.00	-0.14	High-fat dairy
-0.40	-0.32	-0.49	-0.33	-0.30	-0.40	Sugar-sweetened beverages
-0.02	-0.07	0.01	-0.03	-0.23	-0.23	Artificially sweetened beverages
-0.14	-0.08	-0.33	-0.11	-0.07	-0.35	Cream soup
0.34	0.15	0.10	0.22	0.44	0.31	Wine
0.15	0.01	-0.02	0.06	0.23	0.01	Beer
0.12	-0.05	-0.06	0.04	0.15	0.02	Liquor
0.07	0.02	0.14	0.05	0.49	0.28	Coffee
0.08	0.11	0.09	0.09	0.03	-0.06	Tea
0.27	0.20	0.15	0.24	0.13	0.00	Salad dressings
-0.06	-0.07	-0.27	-0.12	0.03	-0.15	Butter
-0.19	-0.06	-0.18	-0.11	-0.09	-0.23	Margarine
-0.10	-0.03	-0.24	-0.05	0.00	-0.25	Snacks
-0.25	-0.06	-0.43	-0.19	-0.09	-0.23	Sweets

Chen et al 2026

Nutrition and Cognitive decline: Protective Diets

Mediterranean diet: High in fruits, vegetables, legumes, fish, olive oil, and moderate wine.

The Landmark PREDIMED trial had a nested sub-studies (4–6.5 years follow-up) which showed cognitive benefits of Mediterranean diet supplemented with nuts or olive oil over a low-fat diet control.

Estruch et al 2018

Nutrition and Cognitive decline: Protective Diets

DASH (Dietary Approach to stop Hypertension) diet: Originally designed for blood pressure control

A recent cohort study of 159,347 participants found the DASH diet showed the strongest association with lower SCD risk (RR 0.59 comparing 90th vs. 10th percentile of adherence) and better objectively measured cognition

Chen et al. (2026)

Nutrition and Cognitive decline: Protective Diets

MIND diet (Mediterranean-DASH Intervention for Neurodegenerative Delay): Combines elements of Mediterranean and DASH diets with special emphasis on green leafy vegetables and berries.

A meta-analysis of 11 cohort studies (224,049 participants) found the highest tertile of MIND diet adherence was associated with a 17% lower risk of dementia.

A large cohort study (130,240 participants, up to 43 years follow-up) found adherence to the Mediterranean and MIND diets was associated with 14–21% lower dementia risk and 0.75–1.59 fewer years of cognitive aging.

Chen et al 2023 , Liu et al 2026

What about Fasting?

- **Short term fasting**

  Fasting duration of 12 hours found no meaningful difference in cognitive performance between fasted and satiated healthy adults with longer interval showing reduction in cognitive function

- **Starvation**

  severe caloric restriction (40-45%) or starvation produced neurologic deficits, irritability, depression, lethargy, and dizziness alongside anemia and muscle wasting.

- **Intermittent fasting**

  Repeated intermittent fasting (IF) and moderate caloric restriction (CR) are associated with cognitive improvement rather than decline

Bamberg and Moreau 2025, Dulloo 2021, Kapogiannis et al 2024

Intermittent Fasting Protocols

Protocol	Description	Typical Regimen
Time-Restricted Eating (TRE)	Daily eating confined to a set window; fasting the remaining hours	16:8 (most popular), 14:10, or 12:12; eating window of 4–10 hours
Alternate-Day Fasting (ADF)	Alternating between fasting days and unrestricted eating days	Fasting days: 0–600 kcal (often ~500 kcal); ad libitum on non-fasting days
5:2 (Whole-Day Fasting)	Energy restriction on 2 days per week (consecutive or non-consecutive)	500–600 kcal on 2 fasting days; unrestricted eating the other 5 days
Periodic Fasting	Less frequent but prolonged fasting periods	2–5 day water-only fast or 4–7 day fasting-mimicking diet

Semnani-Azad et al 2025

Preclinical

Multiple rodent studies show consistent cognitive benefits from IF protocols.

- In female C57BL6 mice, 3 months of every-other-day feeding improved long-term memory retention compared to both matched 10% daily caloric restriction and ad libitum feeding.
- Male Fischer-344 rats on 10 weeks of alternate-day fasting demonstrated significantly better memory performance compared to ad libitum controls ($p = 0.0186$). Revealed sex-specific effects, with IF improving memory only in male rats while having no significant cognitive effect in females.
- In Alzheimer's disease models, IF shows therapeutic potential. Studies using 3xTg-AD mice found that 3 months of alternate-day feeding promoted neuronal differentiation and maturation in the dentate gyrus and ameliorated cognitive dysfunction.
- In APP mutant mice (Alzheimer disease model), IF reduced neuronal network hyperexcitability and ameliorated deficits in hippocampal synaptic plasticity.

Dias et al 2021, Sudasinghe et al 2025, Li et al 2020, Liu et al 2019

Fasting protocols Studied in Geriatric Populations

5:2 Intermittent Fasting

- An 8-week RCT in **40 cognitively intact older adults** (mean age ~60s) **with insulin resistance** compared 5:2 IF (two non-consecutive days of ~500 kcal) to a healthy living diet. Both groups improved executive function and memory, but **5:2 IF showed advantages on certain cognitive measures** and produced greater weight loss.
- 5:2 IF decreased the brain-age-gap estimate on MRI (reflecting slowed biological brain aging), reduced brain glucose on MR spectroscopy, and improved neuronal insulin signaling biomarkers in neuron-derived extracellular vesicles.

Kapogiannis et al 2024

Fasting protocols Studied in Geriatric Populations

Time-Restricted Eating (TRE)

- A 2025 pilot RCT (n= 46, mean age 74 years), was first RCT to demonstrate cognitive benefit of 15:9 TRE in MCI versus ad libitum eating for 12 weeks. The TRE group showed significant improvement in **MoCA total score** (β = 1.70 at 12 weeks, p = 0.007), **attention**, and v**erbal recognition memory** (AVLT-H recognition score, β = 2.44, p = 0.008) compared with controls
- A separate ongoing trial is underway testing a 10-hour eating window over 6 months in adults aged 55–80 to assess neurovascular coupling and cognitive performance.

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Wang et al. 2025, Pinaffi-Langley et al. 2024

Fasting protocols Studied in Geriatric Populations

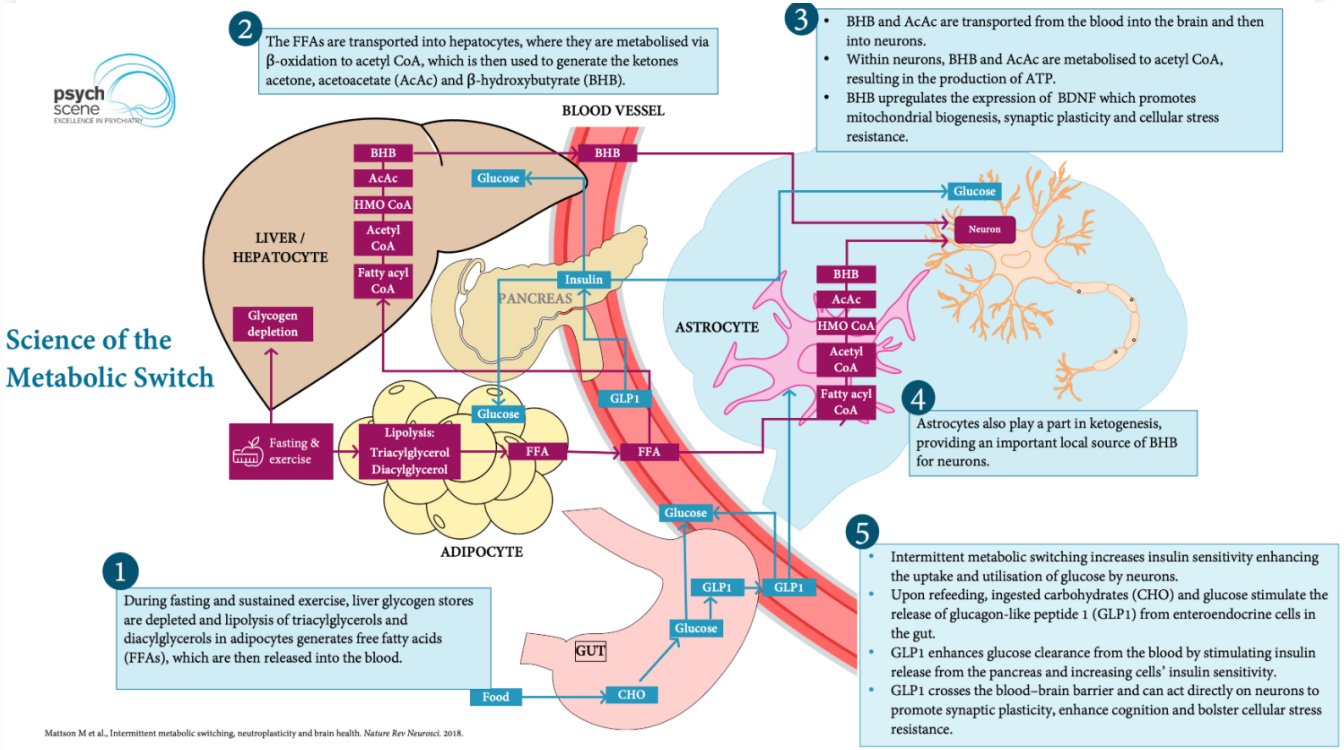
Daily Caloric Restriction (~25–30%)

- healthy elderly adults (mean age 60.5 years) showed a **20% increase in verbal memory scores** after **3 months of 30% caloric restriction**, correlated with decreased insulin and CRP levels.
- In obese elderly patients with MCI, 12 months of caloric restriction induced weight loss, improved verbal memory, verbal fluency, executive function, and global cognition, with the strongest effects in younger seniors and APOE ε4 carriers.
- A meta-analysis of 11 RCTs confirmed dietary restriction (CR and IF combined) had a significant positive effect on cognition (SMD = 0.22), with the **greatest benefit in MCI populations** (SMD = 0.36).
- The PREDIMED-Plus Cognition sub study (n = 487)assessed neurocognitive function at baseline, 1 year, and 3 years.
  - Key findings include : Higher baseline verbal memory, vasoconstrictive praxis, and inhibition predicted successful weight loss (≥8%) at 3 years in the intervention group
  - Moderate improvements in **memory and executive function** were seen during follow-up in both groups, with greater memory improvements associated with higher diet adherence

Witte et al. (2009), Horie et al. (2016) Lü et al. (2023), Soldevila-Domenech 2021

Neuropsychological mechanisms of fasting on Cognition

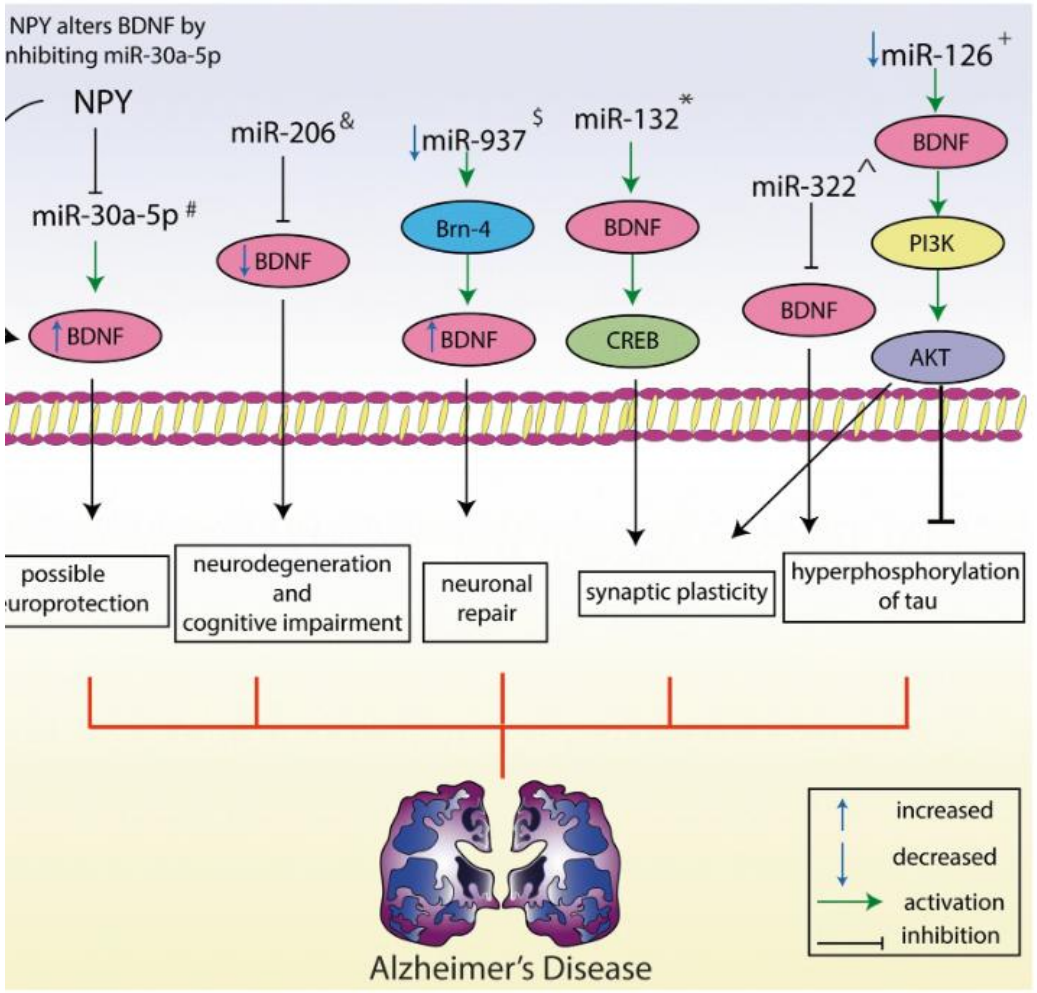
- **Metabolic switch to ketone bodies**: Occurs with fasting beyond 10–14 hours triggers hepatic ketogenesis; ketones (β-hydroxybutyrate) serve as an neuronal fuel and activates signaling cascades involving AMPK, reduced mTOR, enhanced autophagy, and mitochondrial biogenesis.



Mayor 2023, De Cabo and Mattson 2019

Neuropsychological mechanisms of fasting on Cognition

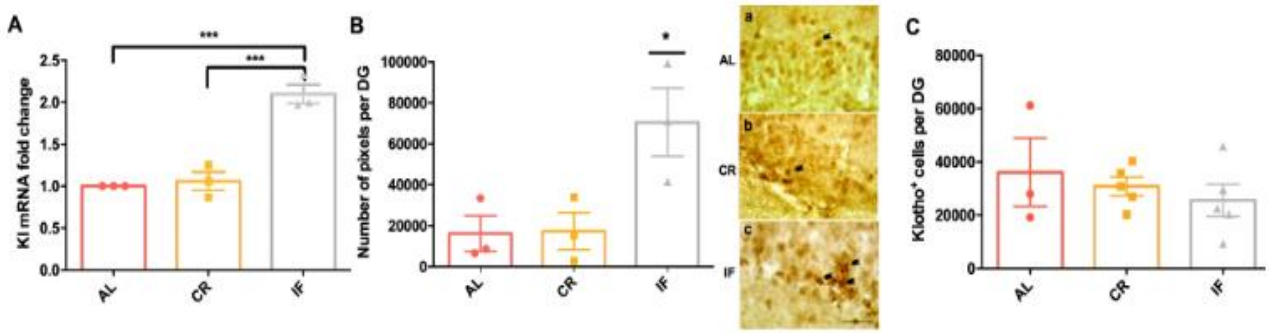
- **BDNF upregulation** — Intermittent Fasting consistently increases brain-derived neurotrophic factor in animal models, enhancing synaptic plasticity, learning, and memory. Age-related BDNF decline is associated with cognitive impairment and Alzheimer's disease risk.



Seidler K, and Barrow 2022. .

Neuropsychological mechanisms of fasting on Cognition

- **Hippocampal neurogenesis** — IF promotes adult hippocampal neurogenesis and neuronal differentiation, with IF upregulating the longevity gene Klotho. Upregulation of Klotho promotes oligodendrogenesis, increased neuroblasts and myelination.



Dias et al 2021

Summary

Protocol	Eating Pattern	Key Geriatric Cognitive Evidence	Best Candidate Population
5:2 IF	5 days normal + 2 days ~500 kcal	Improved executive function, memory; reduced brain-age-gap on MRI	Overweight older adults with insulin resistance
TRE (15:9 or 14:10)	9–14 h fast daily	Improved MoCA, attention, verbal recognition in elderly MCI (pilot RCT)	Elderly with MCI; wider windows (10–15 h eating) preferred for safety
Daily CR (25–30%)	Continuous caloric reduction	20% verbal memory improvement; benefits in MCI across multiple domains	Obese elderly, especially APOE ε4 carriers
Alternate-day fasting	Alternating fast/feed days	Strong preclinical data; limited human geriatric cognitive data	Research setting only in elderly

Kapogiannis et al 2024 , Wang et al. 2025, Pinaffi-Langley et al. 2024 , Horie et al. (2016) Lü et al. (2023),

Canadian Guidelines

- The **5:2 intermittent fasting** and **time-restricted eating (TRE)** protocols have the most direct clinical trial evidence for cognitive benefit, while **daily caloric restriction (~25–30%)** has the longest track record. **All protocols are still supported by small, short-duration studies, and no protocol has been confirmed in large-scale, long-term geriatric trials specifically for cognition.**

- **WHO Risk Reduction of Cognitive Decline and Dementia Guidelines** (2019) and the **AmericanHeart Association Scientific Statement on Brain Health** (2021) recommend the Mediterranean, DASH, and MIND diets — based primarily on observational evidence. Neither body addresses intermittent fasting

Safety Consideration

Safety Considerations in Geriatric Patients

- Fasting protocols carry specific risks in older adults that should be weighed against cognitive benefits:
- **Sarcopenia and lean mass loss**: TRE with narrow eating windows (6–8 hours) may impact recommended dietary practices for optimizing skeletal muscle anabolism in older adults, potentially worsening sarcopenia. Adequate protein intake and resistance training should accompany any weight-loss regimen to mitigate lean mass loss.
- **Malnutrition risk**: CR remains controversial for **non-obese older adults** due to insufficient evidence and malnutrition concerns. Potential adverse effects include hypoglycemia, dehydration, fatigue, dizziness, and syncope.

De Cabo and Mattson 2019

Safety Consideration

- **Frailty**: Clinical studies have focused mainly on overweight young and middle-aged adults, and benefits and safety cannot be generalized to other age groups. Animal data suggest late-life every-other-day fasting can reduce frailty indices, but this effect showed benefit primarily in males.

- **Patient selection**: The strongest cognitive benefits have been observed in patients who are **overweight/obese and/or have insulin resistance or MCI**

De Cabo and Mattson 2019

Implementation

Time-Restricted Eating (TRE):	Should be gradual over several months with slow reduction the daily eating window with a goal of fasting 12-18 hours per day
	A 12-hour fasting window combined with Mediterranean diet showed benefits in adults over 60, with reductions in BMI, waist circumference, and blood pressure
	Short-term TRE (<8 hours eating window for 6 weeks) was safe and well-tolerated in healthy non-obese midlife and older adults, with no adverse effects on lean mass or bone density

Martens et al 2020, Dote-Montero et al 2025 , Domaszewski et al 2023

Implementation

5:2 Intermittent Fasting:	Gradual caloric reduction on fasting days over 4 months: Month 1: 900-1000 calories, 1 day per week Month 2: 900-1000 calories, 2 days per week Month 3: 750 calories, 2 days per week Month 4: 500 calories, 2 days per week
	Evidence suggests 5:2 fasting produces more clinically meaningful weight loss than TRE in older adults. Would not be recommended in individuals with difficulty maintaining healthy weight.

De Cabo and Mattson 2019

Implementation

Essential Safeguards	**Adequate protein intake and resistance training must be part of any weight-loss regimen** to reduce lean mass loss and avoid worsening frailty
	Nutritional Monitoring: Consultation with a dietitian or nutritionist is essential to ensure nutritional needs are met and provide ongoing counseling
	Potential Adverse Effects: Dehydration, hypoglycemia, fatigue, weakness, dizziness, hypotension, insomnia, nausea, headache, presyncope/syncope, dyspepsia, and excessive hunger
	Initial side effects: hunger, irritability, reduced concentration. Typically resolve within 1 month of initiating intermittent fasting

Ashtary-Larky et al 2021, Garegnani et al 2026

Questions?

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