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NUTRITION AND THE BRAIN (J NASSER, SECTION EDITOR)

# Comparison of the Impact of the Mediterranean Diet, Anti-Inflammatory Diet, Seventh-Day Adventist Diet, and Ketogenic Diet Relative to Cognition and Cognitive Decline

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## Abstract

*Purpose of Review* Increasing evidence points toward the importance of diet and its impact on cognitive decline. This review seeks to clarify the impact of four diets on cognition: the Mediterranean diet, the anti-inflammatory diet, the Seventh Day Adventist diet, and the Ketogenic diet.

*Recent Findings* Of the diets reviewed, the Mediterranean diet provides the strongest evidence for efficacy. Studies regarding the anti-inflammatory diet and Seventh Day Adventist diet are sparse, heterogeneous in quality and outcome measurements, providing limited reliable data. There is also minimal research confirming the cognitive benefits of the Ketogenic diet.

*Summary* Increasing evidence supports the use of the Mediterranean diet to reduce cognitive decline. The MIND-diet, a combination of the Mediterranean and DASH diets, seems especially promising, likely due to its anti-inflammatory properties. The Ketogenic diet may also have potential efficacy; however, adherence in older populations may be difficult given frequent adverse effects. Future research should focus on long-term, well-controlled studies confirming the impact of various diets, as well as the combination of diets and lifestyle modification.

**Keywords** Mediterranean diet · MIND diet · Inflammation · Anti-inflammatory diet · Ketogenic diet · Ketone bodies · Medium chain triglycerides · Seventh Day Adventist diet · Adventist Health Study · Dementia · Cognitive function · Cognitive impairment

## Introduction

Cognitive impairment in later life is a pathological process which can range in severity from mild cognitive impairment to major neurocognitive disorder, also known as dementia [1]. In 2016, the estimated global prevalence of people living with dementia was 43.8 million, up from 20.2 million in 1990. There were also 2.3 million dementia-related deaths in 2016. In 2017, the cost of caregiving for American patients living with Alzheimer's disease (AD) was approximately US $232 billion, and the average lifespan cost of caring for one person suffering from dementia was US $341, 840. These costs do not consider the mental and physical toll on unpaid caregivers, and the resultant cost to the medical system [2].

In recent years, increasing evidence has emphasized the importance of diet and its impact on mental health, specifically its role in cognitive decline [3••]. Therefore, it behooves healthcare providers to examine the impact of common diets on cognition, as well as to provide recommendations to help promote cognitive well-being.

This paper aims to clarify the impact of four diets on cognition: the Mediterranean diet, the anti-inflammatory diet, the Seventh Day Adventist diet, and the Ketogenic diet.

## Search Strategy and Selection Criteria

PubMed was searched for original research and systematic review articles. Search terms including "Mediterranean diet", "'inflammation' AND 'diet'", OR "'ketogenic diet', 'ketone bodies', or 'medium chain triglyceride'", "Seventh Day

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Adventist Diet", "vegetarian", and "Adventist Health Study 2" in combination with "dementia", "cognitive function", and "cognitive impairment". The reference lists of selected articles were also reviewed for relevant literature. Initial searches were conducted for data from the past 5 years; if insufficient data was available, searches were expanded to older relevant literature.

## Mediterranean Diet: Pattern and Rationale

The Mediterranean diet (MD) is the most extensively studied dietary pattern and is primarily characterized by high consumption of plant-based products including fruits, vegetables, legumes, whole grains, and olive oil; moderate consumption of animal products comprised primarily of fish and poultry, with limited quantity of dairy products and alcohol. The main source of fat is from olive oil [4–6]. Several population-based and prospective epidemiological studies have shown that adherence to the MD has protective effects against a myriad of health issues including cardiovascular disease, stroke, obesity, hypertension, several types of cancer, and allergic diseases [7, 8••]. Of particular interest is the impact of the MD on cognition. Several systematic reviews looking at primarily observational studies demonstrated that higher adherence to the MD is associated with reduced risk of dementia, mild cognitive impairment, or progression from mild cognitive impairment to dementia [9–18]. Oxidative damage and inflammation are implicated in the pathogenesis of dementia, in particular Alzheimer's disease, and the MD is a dietary pattern rich in antioxidant and anti-inflammatory properties [19, 20].

## Impact of the MD: Current Evidence

Many recent studies demonstrate a trend towards improvement of cognitive function in patients with the highest adherence to the MD. In summary, high MD adherence (most frequently assessed by the MDScale developed by Trichopoulou et al. [21, 22], and the alternate MDScale by Panagiotakos et al. [23]) was significantly associated with better cognitive status as indicated by higher Mini-Mental State Examination (MMSE) scores and less depressive symptomatology as indicated by lower Geriatric Depression Scale (GDS) scores [24, 25]. Additionally, Anastasiou et al. revealed that each unit increase in the MDScale was associated with a 10% decrease in the odds for dementia, as assessed by a full clinical and neuropsychological evaluation. The researchers also evaluated the relationship between adherence to the MD (determined by MDScale proposed by Panagiotakos) and cognitive performance, assessed via five cognitive domains (memory, language, attention-speed, executive functioning, visuospatial perception). It was concluded that higher MDScale adherence quartiles were positively correlated with higher cognitive performance in memory, language, visuospatial perception, and the composite cognitive score [26].

In another study evaluating the relationship between the MD and cognitive decline, 1046 participants without dementia symptoms over the age of 64 (mean age 73.1) from the Hellenic Longitudinal Investigation of Aging and Diet (HELIAD) cohort were evaluated at 3-year intervals. Results revealed that individuals in the highest MDScale adherence quartile had a 72% lower risk for developing dementia, compared to those in the lowest quartile. There was also an 8% risk reduction for dementia incidence with each additional unit of MDScale adherence [25]. Many other studies have reached similar conclusions, revealing that the MD was associated with better cognitive function in specific domains including global cognition, as assessed by the MMSE and National Health and Nutrition Examination Survey (NHANES): cognitive function questionnaire score; memory (immediate and delayed recall); language (WAIS vocabulary); executive functioning (WAIS); and verbal memory (HVLT-R, ANT) [27, 28, 30]. On the other hand, some studies have not established significant associations between adherence to the MD and cognitive decline. Olsson et al. evaluated the relationship between a Mediterranean-like diet (through a 7-day food diary and modified Mediterranean Diet Scale, the mMDS) and development of Alzheimer's disease (based on NINCDS-ADRDA and DSM-IV criteria), dementia, and cognitive impairment (MMSE). Results revealed that only the highest tertile adherence score on the mMDS was significantly associated with a lower risk of cognitive impairment ($OR = 0.32$, 95% $CI$: 0.11, 0.89), while the other tertiles on the mMDS were not associated with less AD, dementia, or cognitive impairment [31].

A relatively newer hybrid dietary pattern developed in 2015 by Dr. Martha Clare Morris is the MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) Diet, which combines the MD and the Dietary Approaches to Stop Hypertension (DASH) diet. Briefly, the DASH diet features high consumption of fruits, vegetables, whole grains, and low-fat dairy products, and reduced sodium intake [32]. In this study, participants of the Rush Memory and Aging Project (MAP) were recruited and followed the MD diet alone, DASH diet alone, or MIND diet. Diet adherence scores were computed from responses to a semi-quantitative food frequency questionnaire (FFQ). In adjusted proportional hazards models, it was found that highest tertile of MIND diet scores (score range 8.5–12.5) had a 53% decrease ($HR = 0.47$, 85% $CI$ 0.26, 0.76) in the rate of developing AD compared with participants in the lowest tertile (score range: 2.5–6.5). However, MAP participants in the second tertile also had a statistically significant 35% reduction in AD rate

compared with those in the first tertile (*HR* = 0.65, 95% *CI* 0.44, 0.98) [32, 33] Currently, a new study evaluating the association of the MIND diet and cognitive function is being developed by Liu et al. [34••]. This study is a randomized controlled intervention trial assessing 604 adults between 65 and 84 years old randomized to either the MIND diet with mild caloric restriction or their usual diet with mild caloric restriction (250 kcal/day). The primary end point is assessing change in global cognitive score measured by a battery of tests over a 3-year period. Diet adherence will be assessed by the MIND diet score ranging from 0 to 15, which higher scores indicating greater adherence [34••].

## MD: Discussion

Relevant literature supports that greater adherence to the MD is associated with better cognitive health and function. The few studies that veer away from this conclusion may have differences in study populations and assessment methodologies to assess the primary outcome of diet adherence and cognition. While the MD has been shown to have a multitude of benefits on cognition, the diet's inherent restrictions of certain food groups including refined grains and oils, red and processed meats, and dairy products may impact long-term adherence in some populations.

An important consideration for future research is to establish more standardized neuropsychological assessment criteria. Studies that reach conflicting conclusions regarding the efficacy of the MD in reducing cognitive decline risk may be secondary to differences in neuropsychological assessment methodology [29]. Larger, longer, controlled trials are also needed. Looking at the potential benefits of the MD when started earlier in life and continued vs starting in later life needs to be examined. The utility and factors impacting adherence to the MD in various ethnic/racial groups need to be better understood. Combining the MD with other lifestyle interventions such as exercise, control of cardiovascular risk factors such as hypertension, obesity, smoking, and diabetes, and mindfulness/spirituality needs to be explored. Lastly, research is needed to better understand the factors impacting adherence to the MD and how adherence can be improved.

## Anti-Inflammatory Diet: Pattern and Rationale

Inflammation, the body's natural defense against infection and injury, is strongly implicated in the development of many neurodegenerative diseases. Studies on AD have found that sustained activation of microglia, the macrophages of the central nervous system, can cause permanent damage itself, as well as exacerbate both amyloid beta-plaque and neurofibrillary tangle pathology [35•]. Aging is associated with increased oxidative damage, damaging cellular lipids, proteins, and both nuclear and mitochondrial DNA [36]. An imbalance between pro-inflammatory and anti-inflammatory processes can be seen in AD, including elevation of pro-inflammatory cytokines (interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)) [35•].

The anti-inflammatory diet (AID) aims at increasing anti-inflammatory foods and decreasing pro-inflammatory foods. This means incorporating seafood, fruits, vegetables, legumes, and nuts rich in Ω-3 fatty acids, polyphenols, antioxidants, and reducing items abundant in trans-fat, processed sugars, and refined carbohydrates [37]. There are no specific guidelines for an "anti-inflammatory diet"; rather, there are a variety of different diets with the same anti-inflammatory principles. At the time of this publication, there is no AID designed specifically for prevention/delay or treatment of people with dementia. There is a growing amount of literature on foods that can promote or reduce inflammation, both directly, and through the microbiome [38]. A research tool, the dietary inflammatory index (DII) was designed to measure dietary inflammatory potential [39], ranking diets on a numerical scale based on serum markers, with higher DII indicating more inflammation.

## Impact of the AID: Current Evidence

In one animal study, mice who were fed an anti-inflammatory diet for 15 months showed decreased loss of synaptic structural proteins, inhibited neuroinflammatory activity, and enhanced autophagy compared to mice on a standard diet [40].

A cross-sectional study surveyed 330 older adults, mean age 79, without dementia regarding dietary patterns from the prior year and obtained serum inflammatory markers from which an inflammatory nutrient pattern (INP) was calculated. Assuming dietary patterns were unchanged over time, participants were imagined by MRI and cognitive functions were assessed an average of 5 years after dietary survey. After adjusting for demographics, education, BMI, Apoprotein-ε4 expression, and vascular medical conditions, the study found that increased INP was associated with smaller total brain volume and visuospatial scores compared to lower INP. There was no significant difference in language, memory, speed, executive function, and mean cognition [41].

The Women's Health Initiative Memory Study surveyed 7085 women in the USA between the ages of 65 and 79. Participants' DII was calculated at baseline and patients were followed for an average of 9.7 years. Cognitive function was evaluated annually using the Modified Mini-Mental State Test (3MS). Participants in the highest inflammatory quartile performed worse overall on the 3MS. Overall hazard

ratio for developing mild cognitive impairment/dementia was highest in the inflammatory group compared to lowest inflammatory group [42].

Data was analyzed from the 2011 to 2012 and 2013 to 2014 National Health and Nutrition Survey and included 1723 adults aged 60–85, with mean age of 68, who did not have significant chronic diseases. They assessed diet using a 24-h dietary recall interview and calculated DII scores. Memory was assessed using multiple tests including the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word learning subset, animal fluency test, and the digit symbol substitution test (DSST). After adjusting for demographics, BMI, smoking, sleep, exercise, and depression screening scores, DII was not statistically associated with differences in 2 out of 3 trials of the CERAD test but did show statistical significance in animal fluency and DSST [43].

Five thousand and eighty-three British participants from the Whitehall II cohort study were followed for an average of 10 years. The highest DII tertile was associated with greater decline in reasoning but no significant difference in memory, verbal fluency, and global cognition compared to the lowest tertile. However, there was no significant difference in mini-mental state examination (MMSE) scores between diet pattern quartiles after adjusting for demographics and health-related factors [44].

The Iowa Women's Health Study surveyed 37,525 women aged 55–69 on baseline dietary intake and calculated DII, which was then stratified into quartiles. Participants were followed up for a mean of 20.7 years. DII was not significantly associated with Alzheimer's disease and unspecified dementia, although it was found to be significantly associated with all-cause mortality (including cerebrovascular disease, coronary heart disease, cancer) [45].

A total of 2796 participants in the French Supplémentation en Vitamines et Minéraux Antioxydants study aged 45–60 were randomized to either a placebo or daily antioxidant (vitamin C, β-carotene, vitamin E, selenium, zinc) for 8 years. A 24-h dietary record was assessed every 2 months during the 8 trial years and healthy aging was assessed approximately 5–7 years after supplementation completion. The researchers defined healthy aging as the absence of major chronic diseases such as cancer, cardiovascular disease, and diabetes, and the absence of limitations in activities of daily living, while maintaining high level of cognitive and physical function. DII was then calculated based on these records. The highest DII tertile had statistically significantly less participants with good cognitive functioning compared to the lowest tertile. When stratified by treatment group, there was a significant reduction in probability of overall healthy aging, defined as low risk of disability, disease, and maintaining cognitive and physical functioning, in the placebo group based on DII tertiles, but no significant findings in the antioxidant supplement group across tertiles. This suggests a possible protective benefit on antioxidant supplementation [46].

## AID: Discussion

While there is some evidence for the cognitive benefits of an AID, there are significant limitations in this research, and the results are not as robust as the connection with the MD. For those who cannot tolerate the MD due to dietary/religious restrictions, the AID may be a beneficial alternative.

This research is also limited by the heterogeneity of AID definitions across different studies. The main studies investigating inflammatory potential in diet are observational and based on participants' self-identified dietary patterns. The inflammatory potential is calculated after participant input and not based on a set of dietary guidelines. Although the studies adjusted the results for different variables including race, sex, age education, and physical health, there still exists potential confounding bias of socioeconomic components that influence participants' dietary choices. In addition, the studies only assessed dietary patterns at the beginning of the study and did not reassess dietary changes throughout the study duration.

The AID overlaps greatly with the MD based on the nature of the foods predominant in the MD, and the beneficial effects of the MD have been at least partially attributed to its anti-inflammatory properties. Adding an anti-inflammatory modifier onto the MD may be beneficial for neurocognitive diseases. An example is the recently designed ITIS diet, a modified MD diet with anti-inflammatory adjustments for people with rheumatoid arthritis [47•]. However, available studies have shown low adherence to the AID, which may hinder adherence to a mixed MD-AID. A potential future direction could be development of this type of modified diet and comparing its efficacy to the AID and MD alone.

## Seventh Day Adventist Diet: Pattern and Rationale

The Seventh Day Adventist Church (SDAC), a Protestant Christian Denomination established in 1863, is distinguished both by its emphasis on health and a holistic approach to the person [48]. Specifically, the SDAC promotes vegetarianism and consumption of meats deemed "clean" by the book of Leviticus and prohibits smoking and drinking alcohol [49]. Vegetarianism in the SDAC is broad and encompasses subcategories including semi-vegetarian, pesco-vegetarian, lacto-ovo-vegetarian, and vegan [50]. Meats deemed clean by the SDAC include poultry, fish, non-pork red meats, and

Kosher meats. Those who follow the SDAC display some variation in their diet choices, namely, some Adventists are vegan or vegetarians while others consume meat and other animal derived products regularly [51, 52]. Studies conducted on the Seventh Day Adventist diet (SDAD) suggest the diet may provide health benefits, including a reduction in morbidity and mortality, although data regarding its effects on neurocognitive functions is limited.

## Impact of the SDAD: Current Evidence

As with any diet, long-term outcomes are dependent on long-term diet adherence. The dietary patterns among those who adhere to the SDAD displays reduced consumption of animal products in favor of vegetarian diets [49]. Hence, the benefits of the SDAD may closely follow those of the vegetarian diet. Martins et al. demonstrated lifetime dietary patterns among the Adventist-Health-Study-2 (AHS-2) cohort through a lifetime dietary habits questionnaire that asked participants to recall intake of red meat, poultry, fish, eggs, and dairy. The study showed that Seventh Day Adventists' diet trends toward reduced consumption of animal products in favor of vegetarian patterns. Furthermore, dietary patterns among Seventh Day Adventists tend to remain stable over decades and that the highest rate of change in dietary patterns is in the first three–four decades of life [49].

Although some evidence regarding morbidity and mortality among those who follow the SDAD is present, evidence regarding the cognitive benefits of the SDAD remains limited. In a large North American cohort, the Adventist Health Study-2 (AHS-2), Orlich et al. assessed diet at baseline by quantitative food questionnaire including 5 diets (non-vegetarian, semi-vegetarian, pesco-vegetarian, lacto-ovo-vegetarian, and vegan), as in the SDAD. Specifically, the study recruited a total of 96,469 AHS-2 men and women between 2002 and 2007, of which 73,308 were analyzed; participants were US residents older than 25 years of age without history of prior cancer diagnoses (excluding nonmelanoma skin cancer) or cardiovascular disease [50]. The study identified deaths through 2009 through the National Death Index and found an overall association with lower mortality in vegetarian dietary patterns in the AHS-2 cohort [50]. Regarding cognitive benefits, specifically, Fraser et al. administered the MMSE to an elderly SDAC population to see how different variables (including diet) affected cognitive function. In 1976, the study selected 99 individuals older than 75 from a cohort of white, non-Hispanic California SDAC followers, assessed their dietary habits, education, and other variables (including current medical problems and drug therapy) and subsequently administered the MMSE in these subjects in 1991 [48]. The study, which spanned 15 years, found participants with high caloric consumption in 1976 had lower cognitive function per MMSE in 1991; however it did not confirm whether the SDAD specifically reduces the rate of cognitive decline [48].

## SDAD: Discussion

Although more research is needed relative to the cognitive effects of the SDAD, as a predominantly vegetarian diet, its mechanisms of benefit likely overlap with those of other vegetarian diets. Vegetarian diets are low in saturated fat and high in fiber content, making them low in energy density and helpful in long-term weight loss and weight maintenance [52]. Primarily, vegetarian diets may lower CVD risks by lowering the total:HDL cholesterol ratio and therefore coronary heart disease risks. Vegetarian diets may also promote anti-inflammatory pathways through increased density of poly-unsaturated fatty acids [53, 54]. Studies have shown increased cardiovascular burden may be related to increased risk of cognitive decline [52, 55]. Conversely, hypotheses surrounding the drawbacks of primarily red-meat diets point to increased sources of saturated fat and iron, which have both been associated with carcinogenesis and cardiovascular risks [52]. Specifically, Song et al. conducted a community-based prospective study that selected 1588 participants without dementia, mean age: 79.5 years, through the Rush Memory and Aging project, and followed them for up to 21 years. Participants were assessed at baseline for Framingham General Cardiovascular Risk Score (FGCRS), placed into tertiles (lowest, middle, highest) and assessed annually for composite scores [55]. The study found increased cardiovascular risk burden per FGCRS was associated with increased cognitive decline, smaller hippocampal volume, gray matter, total brain, and increased volume of white matter at 20-year follow-up [55].

Although there is evidence that the SDAD reduces morbidity and mortality in long-term adherers, data regarding cognitive benefits specifically are extremely limited. Further studies need to be conducted to explore the connection between the SDAD and memory and neurocognitive functions. Additional limitations of current studies include categorization of the SDAD and associated neurocognitive benefits, i.e., while the diet promotes vegetarianism, many followers of the SDAD continue to consume meat. As such, further studies must distinguish and establish the differences between following a specific subset of the SDAD.

## Ketogenic Diet: Pattern and Rationale

Since its use in refractory epilepsy in the 1920s, the ketogenic diet (KD) has gained interest as a potential therapy in neurodegenerative diseases [56]. It is defined as a very high-fat, low-carbohydrate diet which mimics the metabolism during prolonged fasting without caloric

deprivation to sustain growth and development. Essentially, the body shifts from the metabolism of glucose to that of fatty acids, inducing nutritional ketosis in which the liver produces ketone bodies (KB), such as acetoacetate (AcAc) and β-hydroxybutyrate (β-OHB) [57, 58]. Neuroprotective effects have been observed at the cellular level through various mechanisms: reduction of excitatory neurotransmitters (e.g., glutamate) [59] and oxidative stress; increased adenosine triphosphate availability; and anti-apoptotic properties which help to stabilize synaptic function [60•, 61]. KB also enhances central and peripheral neuron energy metabolism by stimulating mitochondrial biogenesis and upregulating oxidative phosphorylation [60•, 62].

In Alzheimer's disease (AD), emerging evidence has demonstrated specific protective effects of KB against cerebral Aβ toxicity and cell damage in hippocampal neurons [63]. KB can reduce Aβ levels and promote the action of the endogenous anti-inflammatory molecules (e.g., PPAR-γ) [64, 65]. By providing ketones to the brain as alternative fuel, the KD can alleviate the effects of impaired glucose metabolism; a prominent feature of AD [66, 67]. In fact, KB uptake across the blood–brain barrier remains the same in persons with AD and mild cognitive impairment (MCI) as in cognitively healthy, age-matched controls. Increasing ketone availability to compensate for the brain energy deficit is the core feature of "keto-neurotherapeutic" interventions [68].

The classic KD is composed of a macronutrient ratio of fat to protein and carbohydrate combined equal to 3–4:1, reducing carbohydrates to ≤ 10% of consumed energy [57, 58, 69]. The KD contains mainly long-chain fatty acids found in foods such as avocados, fatty fish, olives, nuts, seeds, and vegetable oils. The decrease in carbohydrate intake may require a significant change in eating habits, and therefore, adherence is often poor [60•]. As this diet is difficult to maintain, an alternative KD has been proposed based on medium-chain triglycerides (MCT) provided in coconut and palm kernel oil [57, 60•, 69]. Research has demonstrated that ketonemia can be achieved with these variants of KD, via ingestion of MCT supplements and exogenous ketone esters even with carbohydrate consumption [68–70]. In 2009, the US FDA approved an MCT product, caprylidene (Axona), as a medical food for the supplemental treatment of Alzheimer's disease [71].

## Impact of the KD: Current Evidence

Ketogenic interventions including a high-fat KD and a regular diet with MCT or ketone esters have shown to have beneficial effects on cognitive function by compensating for hypoglycemia in mild-moderate AD [72, 73], severe AD [74], and type 1 diabetes [75]. More recent studies have predominantly utilized MCT supplementation to achieve ketonemia, as they may be more feasible than dietary interventions [76].

Abe et al. [77] tested the cognitive effects of a prolonged intervention of MCT in a 3-month randomized, controlled, parallel group trial. A total of 38 elderly nursing home residents (mean age 86.6 ± 4.8 years) were allocated to 3 groups: the first received a L-leucine and cholecalciferol supplement with 6 g of MCT (LD + MCT); the second group received the same supplement with 6 g of long-chain triglycerides (LD + LCT); while the control group received no supplements. Cognition was assessed at baseline and after the 3-month intervention, using the Mini-Mental State Examination (MMSE) and Nishimura geriatric rating scale for mental state (NM scale). After 3 months, participants in the LD + MCT group had increases in MMSE score by 10.6% (from 16.6 to 18.4 points, $p < 0.05$). Additionally, their NM scale score increased by 30.6% (from 24.6 to 32.2 points, $p < 0.001$), whereas participants in the LD + LCT and control groups decreased by 11.2% and 26.1%, respectively.

In 2020, the same authors randomized 64 elderly nursing home residents (mean age 85.5 ± 6.8 years; *BMI* 18.6 ± 2.5 kg/m$^2$) to 3 groups: the MCT group (6 g/day MCT), the positive control group (L-leucine and cholecalciferol plus MCT), and the negative control group (6 g/day LCT) [78]. Ten participants withdrew from the study as they moved to other nursing homes for economic reasons, 5 dropped out due to loss of appetite, and 1 dropped out at the request of a family member. The remaining 48 participants who completed the study reported no side effects, including diarrhea. Following the 3-month intervention, MCT supplementation increased the MMSE score by 3.5 points from a mean baseline of 17.5, whereas LCT supplementation decreased MMSE score by − 0.7 points from a mean baseline of 17. In contrast, O'Neill et al. [79] assessed the impact of a 14-day trial of an MCT called GSK2981710 in a double-blind, randomized, placebo-controlled crossover study with 80 healthy older adults. Although 30 g/day resulted in peak β-OHB concentrations, there were no significant improvements in cognitive function or memory-related neuronal activity. The lack of effect could be related to MCT composition, insufficient trial duration, or study population. Moreover, 75% of participants reported diarrhea, and 11% participants were withdrawn due to one or more adverse events.

Ohnuma et al. conducted a 3-month trial of the MCT caprylidene (Axona) (40 g of powder containing 20 g of caprylic triglycerides) and found no significant improvement in cognitive function measured by the MMSE and ADAS-Cog (Japanese version). This open-label, observational prospective study included 22 Japanese participants with sporadic mild-to-moderate AD, whose mean age was 63.9 (± 8.5) years [80]. Of note, they implemented a dose-titration method from

10 to 40 g of MCT 7 days prior, which successfully decreased GI adverse effects. In fact, only one participant had diarrhea at month 3. Serum total KB at month 3 did not significantly correlate with ΔMMSE and ΔADAS for any of 22 participants, even the 15 participants without the ApoE4 allele. Some ApoE4-negative participants with baseline MMSE ≥ 14 showed improvement in their cognitive functions. However, this study was unable to demonstrate clear cognitive benefits of caprylidene in a trial with small sample size and without a placebo control. These factors may contribute to the discrepancy of results with a previous report by Henderson et al. in 2009, which also studied caprylidene (also known as AC-1202) in 152 participants with mild-to-moderate AD [81]. Statistically significant differences in ADAS-Cog scores were seen in participants receiving AC-1202 compared to placebo, most notably in ApoE4 non-carriers. In 2020, Henderson et al. conducted a large, placebo-controlled trial in 413 participants with mild-to-moderate AD receiving either a new ketogenic formula (AC-1204) or placebo for 26 weeks. No effect was found on the ADAS-Cog for participants who were either ApoE4 carriers or non-carriers. Moreover, ketone levels were only modestly elevated, less than half of the increase seen with AC-1202 [81].

In 2021, Phillips et al. [82] conducted the first randomized crossover trial of a ketogenic diet in participants with uniform diagnoses of AD. 26 participants were randomly assigned to the modified KD or usual diet supplemented with low-fat healthy eating guidelines over 12 weeks, separated by a 10-week washout period. Primary outcomes were mean within-individual changes in the Addenbrookes Cognitive Examination-III scale, AD Cooperative Study-Activities of Daily Living (ADCS-ADL) inventory, and Quality of Life in AD questionnaire. Although the KD did not significantly improve cognition, participants on the KD achieved sustained physiological ketosis (mean β-OHB level: 0.95 ± 0.34 mmol/L) and significantly improved in daily function and quality of life. Twenty one out of 26 participants (81%) completed the KD treatment. Only one withdrawal was attributed to diarrhea due to increased coconut oil intake beyond the recommended amount. Four participants declined to alter their usual diet (e.g., removing daily sugar, beer), resulting in withdrawal from participation. The most common adverse effect on both diets was irritability. On the KD, no serious adverse events occurred. Cardiovascular risk factors were favorably impacted. Compared with usual diet, patients on the KD showed decreases in weight (2.62 ± 3.29 kg), body mass index, HbA1C, no changes in triglycerides, and increases in HDL, LDL, and total cholesterol from baseline to week 12. Despite these secondary outcomes, the benefits of the KD on cardiovascular risk factors remain controversial.

A combined approach of a ketogenic supplement and the MD has recently been proposed as an alternative therapy. A MD enriched with coconut oil (which contains MCTs) demonstrated a positive effect in temporal orientation, visuospatial ability, and semantic and episodic memory (measured by the 7 Minute Screen), in 44 participants with mild-to-moderate AD [83]. The positive effect was most prominent in females, though improvements were also seen in males and severe states of AD. Neth et al. [84] investigated a modified Mediterranean-ketogenic diet (MMKD) vs the American Heart Association Diet (AHAD) in 20 participants with subjective memory complaints diagnosed using Alzheimer's Disease Neuroimaging Initiative criteria ($n = 11$, mean age 64.3 ± 6.3 years) or mild cognitive impairment ($n = 9$, mean age 63.4 ± 4.0 years). Target macronutrient composition was 60–65% fat, 30% protein, and 5–10% carbohydrate for MMKD; and 15–20% fat, 20–30% protein, and 55–65% carbohydrate for AHAD. The MMKD emphasized protein sources low in saturated fat (fish, lean meats), healthy fats, fruits and vegetables, and whole grains within limits. Those on the MMKD were also supplied with 1L of extra virgin olive oil to use as a source of fat in their diet. Participants on the AHAD were encouraged to eat fruits, vegetables, and carbohydrates containing adequate fiber, while limiting fat intake to < 40 g/day. They did not receive supplementary olive oil. Mean adherence rates assessed by dietician assessment of daily food records were 90% for the MMKD and 95% for the AHAD. Cognitive tests included the Free and Cued Selective Reminding Test (FCSRT), story recall (Wechsler Memory Scale-Revised), and the ADAS-Cog12. Memory performance assessed by the FCSRT improved after both diets, but not story recall or ADAS-Cog12 scores. MMKD correlated with increased cerebrospinal fluid Aβ42 and decreased tau, increased cerebral perfusion and KB uptake on PET imaging. These results support the hypothesis that a ketogenic diet promotes cerebral ketosis and contributes to enhanced perfusion.

## KD: Discussion

Overall, limited current research indicates that there may be cognitive benefits of a keto-neurotherapeutic strategy in persons with MCI and mild-to-moderate AD. For persons with moderate to severe AD, it may not be effective or feasible due to caregiver burden to promote adherence [85]. Recommending the KD to older adults is concerning due to possible consequences such as reduced appetite, caloric intake reduction, and malnutrition. Often referred to as the "keto flu," short-term adverse effects of the KD include nausea, vomiting, headache, fatigue, dizziness, insomnia, and poor exercise tolerance. Chronic adverse effects include hepatic steatosis, elevated liver enzymes, hypoproteinemia,

and vitamin and mineral deficiencies [86]. Phillip et al. have demonstrated that high rates of retention, adherence, and safety can be achieved on a modified KD [82], but long-term health implications of the KD remain uncertain. Ketone supplementation may be preferred to increase adherence. Recent studies on KD and MCT most commonly reported gastrointestinal-related adverse events (e.g., diarrhea and flatulence), which often contributed to poor adherence and withdrawal from participation. Implementing a dose-titration method of MCT can ease side effects [80], thus potentially increasing adherence and reducing the risk of dehydration in this frail population. Primary outcomes and cognitive measures have varied in the studies included in this review. When a larger sample was used [68, 72], MCT had no cognitive effect. This was likely due to insufficient ketonemia and possible interaction with participants' comorbidities. A genotype-specific effect of ketogenic treatment is also evident as individuals who are ApoE4 negative seem to respond more positively. Theories for this effect are related to differences in mitochondrial function and ketone utilization, but the exact mechanism has not been identified [87]. Further investigation is warranted to establish a dose threshold at which KB has the most efficacy in larger samples for greater external validity. Additionally, future studies should include the use of CSF Aβ or tau levels or other biomarkers in order to increase the diagnostic accuracy of participants [88].

## Conclusion

At present, there are multiple dietary interventions which claim to prevent or slow cognitive decline in older adults with or without cognitive impairment; however, there is a lack of large, long-term, randomized, placebo-controlled studies relative to efficacy and adherence/tolerability/safety. There is a growing amount of evidence for the KD, but its adverse side-effects lead to poor adherence, thus making the KD a potentially unsustainable long-term diet for many. Using a dose titration for the KD and/or MCT component of the KD could help resolve this issue. As for the SDAD and the AID, evidence of benefit is difficult to determine given the heterogeneity of study designs and outcome measures. Currently, the most empirically supported diet to improve cognitive function is the MIND diet, which is a hybrid of the Mediterranean and DASH diets. The benefits of this dietary approach may be secondary to its anti-inflammatory properties. Further research via large, long-term, randomized, placebo-controlled trials is warranted in order to confirm the impact of these promising dietary approaches in improving cognition in older adults with or at-risk for dementia. Studies which combine dietary approaches with other healthy lifestyle interventions are needed but appear promising.

## Compliance with Ethical Standards

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

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance


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