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NUTRITION AND THE BRAIN (J NASSER, SECTION EDITOR)

Effect of Dietary Intake Through Whole Foods on Cognitive Function: Review of Randomized Controlled Trials

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Abstract

Purpose of Review This review evaluated recent randomized controlled trials (RCTs) examining the chronic intake of whole foods associated with the Mediterranean, Dietary Approaches to Stop Hypertension (DASH), Mediterranean-DASH Intervention for Neurogenerative Delay (MIND), and ketogenic (KETO) diets on cognitive function.

Recent Findings We identified RCTs related to olive oil ($N=3$), nuts ($N=7$), fatty fish ($N=1$), lean meats ($N=4$), fruits and vegetables ($N=9$), legumes ($N=1$), and low-fat dairy ($N=4$), with 26/29 reporting positive results on at least one measure of cognition. We also identified 6 RCTs related to whole food–induced KETO diets, with half reporting positive effects on cognition.

Summary Variations in study design (i.e., generally the studies are < 6 months and include middle-aged and older, cognitively intact participants) and small sample sizes make it difficult to draw conclusions across studies; however, the current evidence from RCTs generally supports individual component intakes of these dietary patterns as an effective, nonpharmacological approach to improve cognitive health in adults.

Keywords Whole foods · Cognitive function · Mediterranean diet · DASH diet · MIND diet · Ketogenic diet

Introduction

The global increase in life expectancy has resulted in a growing aging population and with it a growing number of people living with age-related neurodegenerative conditions and dementia, which imposes an enormous societal and emotional burden [1]. In the absence of effective pharmacological treatments to slow the onset and/or progression of age-related cognitive decline, it is necessary to shift focus towards methods of prevention, with cost-effective, modifiable lifestyle approaches, such as dietary modification.

There is a collection of observational and interventional data supporting higher adherence to dietary patterns, specifically the Mediterranean (MEDI), Dietary Approaches to Stop Hypertension (DASH), Mediterranean-DASH Intervention for Neurogenerative Delay (MIND), and ketogenic (KETO) diets, and lower rates of cognitive impairment and decline [1, 2•, 3, 4•, 5•]. Studies suggest that specific nutrients found in the MEDI, DASH, and MIND diets promote brain health [1, 2•, 3, 4•], while the KETO diet shifts the energy substrate in cerebral metabolism from glucose to ketone bodies to provide neuroprotective effects [5•]. However, when it comes to understanding the mechanisms of how diet modification may modulate the risk for cognitive decline, many studies rely on individual, specific nutrient dietary supplements, though supplements cannot always replicate all of the benefits of whole foods. Whole foods are complex and contain nutrients that work together in a variety of ways that supplements cannot always mimic. Therefore, the Dietary Guidelines for Americans suggest nutritional needs be met primarily through diet [6]. To date, research on the cognitive benefits of whole foods associated with these diets is lacking [1, 2•, 3, 4•, 5•].

This article is part of the Topical Collection on *Nutrition and the Brain*

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This review focuses on whether randomized controlled trials (RCTs) in adults support the cognitive benefits of the chronic, whole food consumption of the individual and isolated components of these diets. This is needed to understand if each dietary component alone is effective at altering cognitive function so researchers can ultimately understand how they may act synergistically to target optimal cognitive performance.

Search Strategy and Selection Criteria

PubMed (1946 — current) was searched on December 22, 2021. The syntax for the search was developed in coordination with a health sciences librarian and combines keywords and Medical Subject Headings derived from the concepts in the review question. Terms included the following: "whole foods," "whole grains," "nuts," "DASH," "keto diet," "Mediterranean Diet," and "MIND Diet," in combination with "cognitive function," "dementia," "Alzheimer's," "cognitive assessment," and "elderly," "geriatric," "adult," "frail," and "middle-aged." A pre-built hedge for RCTs was applied [7]. Only trials lasting ≥ 3 weeks, published within the past 10 years, and including foods that were commercially available were included. Results were limited to English language due to time and budget. A gray literature search for unpublished studies and data was not performed. Rayyan (Qatar Computing Research Institute, Doha, Qatar) was used to ensure blinded review. Contact the corresponding author for the complete search string. The PRISMA statement may be viewed in Fig. 1 [8].

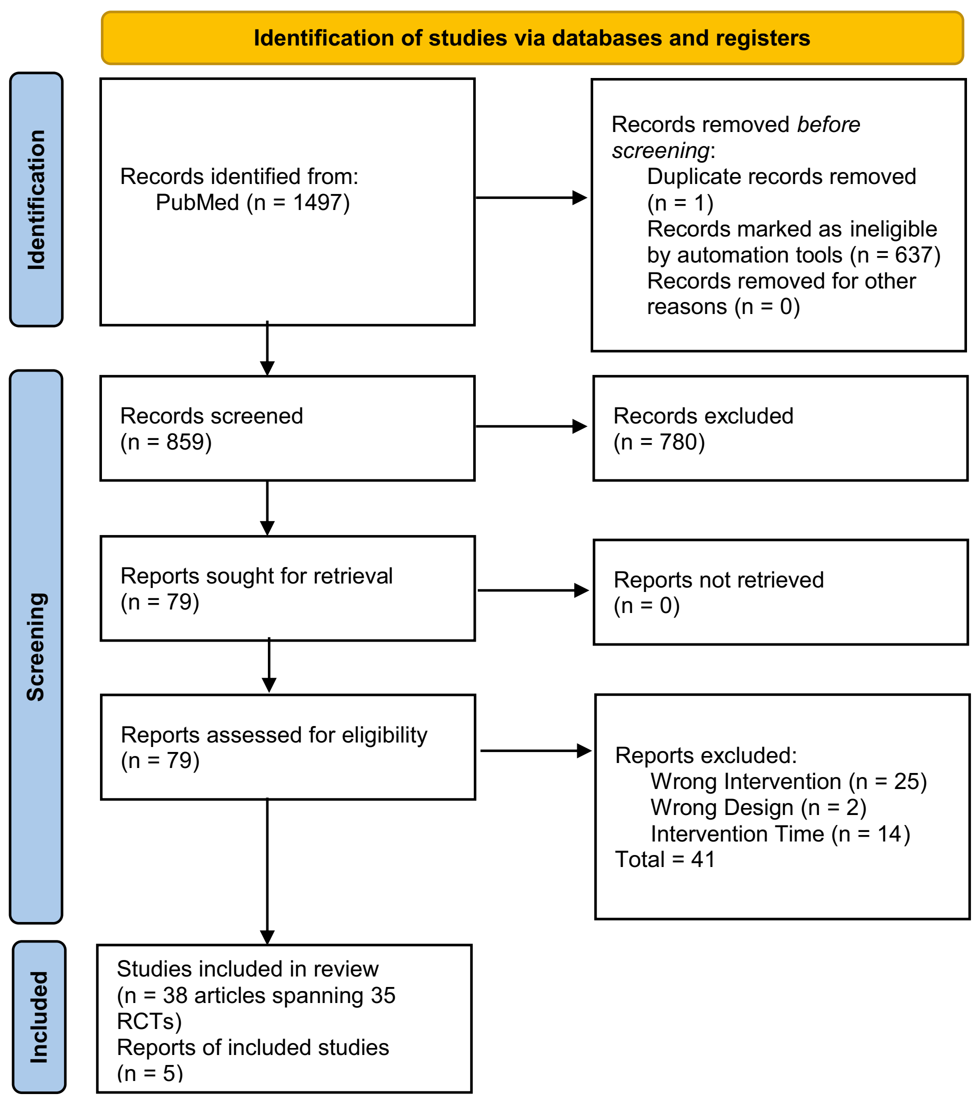

Fig. 1 Flow diagram of the literature selection process

Summary on the Role of the MEDI, DASH and MIND Diets on Cognitive Health

Because a thorough review of each beneficial nutrient of the MEDI, DASH, and MIND diets is beyond the scope of this review, we refer the reader to prior reviews [1, 2•, 3, 4•] and meta-analyses [9, 10], which have detailed the role of these diets on cognitive health, in general supporting a preventative and protective effect of the diets toward reducing the risk of cognitive decline, mild cognitive impairment (MCI), and Alzheimer's disease (AD) [1, 2•, 3, 4•]. We also refer the reader to past detailed reviews, which have outlined the mechanisms that explain the protective effect of these diets on cognitive status, including antioxidative and anti-inflammatory effects and reduced vascular comorbidities [1, 2•, 3•, 4•].

In brief, the protective properties of these diets are mainly believed to be provided through a combination of three main nutritive groups: (1) antioxidants from fruit, vegetables, and wine, (2) high intake of monounsaturated fatty acids (MUFA) and polyphenols from olive oil, and (3) omega 3 (*n*-3) and omega 6 (*n*-6) polyunsaturated fatty acids (PUFA) from fish, nuts, and seeds (2). We discuss additional potential nutrient-specific mechanisms throughout this review. Other components of these diets that may provide cognitive benefits include consumption of whole grains, non- and low-fat dairy, lean meats, legumes, and beans, which we discuss in detail below, and lower consumption of butter, sugary drinks and foods, sodium, and other processed products.

Evidence of Individual Whole Food Components of the MEDI, DASH, and MIND Diets from RCTs on Cognitive Health

We provide a summary of RCTs examining the impact of individual whole food components of the MEDI, DASH, and MIND diets on cognitive health in Table 1.

Olive Oil

Olive oil contains a large amount of MUFA and oleic acid, and also has some phytosterols, vitamin E, and phenolic compounds with anti-inflammatory properties [11]. We identified three recent RCTs, which examined the effects of ~ 50–150 mL/day olive oil intake on cognitive health. Tsolaki et al. [12] compared the effects of 52 weeks on a high phenolic extra virgin olive oil (EVOO), moderate phenolic EVOO, and a MEDI diet control in older adults with MCI. Both high and moderate phenolic EVOO diets were associated with improved cognitive function compared to the MEDI diet. Mazza et al. [13] randomized adults to a MEDI diet including all vegetable oils (control) or a MEDI diet with EVOO. Results showed an improvement in global cognitive function following 52 weeks of EVOO supplementation compared to control. We also draw attention to the PREvención con DIeta MEDiterránea (PREDIMED) study, a large RCT evaluating the effects of cognitively healthy adults assigned to a MEDI diet supplemented with EVOO, a MEDI diet supplemented with mixed nuts, or a low-fat control diet on rates of cognitive change over time. In a PREDIMED substudy, cognitive performance was assessed after a median follow-up of 4.1 years, finding improvements in frontal function (tests of attention, cognitive flexibility, and working memory) and global cognition in those following the MEDI diet plus EVOO and in memory in those following the MEDI diet plus mixed nuts compared with those prescribed the control diet [14]. In PREDIMED follow-up substudies of ~ 6.5 years, the MEDI diet supplemented with either EVOO or nuts was associated with improved global cognitive performance [15] and the MEDI diet with EVOO, but not mixed nuts, was associated with better cognition, especially across fluency and memory tasks, and less incidence of MCI [11] compared to controls. Additionally, those in the EVOO group had significantly better performance on both visual and verbal memory domains compared to those allocated to mixed nut supplementation [11].

Nuts and Seeds

Although moderate consumers of nuts and seeds are reported as having higher total fat intake compared to low consumers, the higher consumption is primarily MUFA and PUFA [16]. Nuts and seeds are high in carotenoids, vitamins C and E, and polyphenols. Although we did not identify any recent RCTs examining seed intake on cognition, we identified six RCTs that evaluated the effects of nut consumption in cognitively intact individuals compared to a control of either habitual dietary intake (devoid of nuts) or an isocaloric carbohydrate-rich control. The diets spanned an assortment of nut varieties, including peanuts [17], walnuts [18•, 19], and almonds [20–22]. In general, the study interventions ranged from 2 to 48 months, involved middle-aged and older adults, and included between 30 and 85 g/day of nuts. Results on cognition were mixed with some reporting improvements in various cognitive outcomes (i.e., short-term and visuospatial working memory, verbal fluency, processing speed, inferential verbal reasoning, and executive function) [17, 19, 22] and others not [18•, 20, 21] compared to the control diet. Data from Rakic et al. [22] suggests that the effect may be dose dependent as no discernable effect was observed at ~ 42 g/day, but was observed at ~ 85 g/day after 6 months. Additionally, Cardoso et al.

Table 1 Evidence on the relationship between cognitive function and adherence to the individual components of the MEDI, DASH and MIND diets through whole foods

Citations	Sample characteristics (*N* = study completers)	Intervention	Significant main findings related to cognition
Olive oil			
[12]	*N* = 50; age 70 ± 7 yrs; participants with impaired cognition	Double-blinded prospective RCT. Participants were randomized to a MEDI diet plus 50 mL of high (975 mg/kg total secoiridoid phenols) or moderate (271 mg/kg total secoiridoid phenols) natural phenolic EVOO vs. a MEDI diet without olive oil (control) for 52 wks	Compared to control, high and moderate phenolic olive oil resulted in greater improvements in attention and working memory and phonemic and semantic fluency, but not global cognition, episodic or long-term memory, executive function, or visuospatial ability
[13]	*N* = 110; 70 ± 4 yrs; participants with intact cognition	Single-blinded prospective RCT. Participants were randomized (1:2 allocation) to a MEDI diet plus EVOO (20–30 g/day) or a MEDI diet including all vegetable oils (control) for 52 wks	Compared to control, MEDI diet supplemented with extra virgin olive oil led to greater improvement in global cognition
[11] [14] [15]	PREvención con DIeta MEDiterránea (PREDIMED) follow-up studies (11): *N* = 267; age 67 ± 6 yrs (14): *N* = 334; age 70 ± 5 yrs (15): *N* = 522; age 75 ± 6 yrs Participants with cardiovascular risk, intact cognition	Single-blinded prospective RCT. Participants were randomized to a MEDI diet plus EVOO (1 L/wk), a MEDI diet plus mixed nuts (30 g/day), or a low-fat (control) diet	(11): Compared to control, MEDI diet with olive oil, but not mixed nut group, had better cognition, especially across fluency, memory task, and less incidence of MCI. In addition, olive oil group had better performance on both visual and verbal memory during a mean follow-up of 6.5 yrs (14): Compared to control, greater improvements in frontal function (tests of attention, cognitive flexibility, and working memory) and global cognition were observed following the MEDI diet plus EVOO and in memory following the MEDI diet plus nuts during a median follow-up of 4 yrs (15): Compared to control, MEDI diet supplemented with either olive oil or mixed nuts was associated with improved global cognitive performance during a mean follow-up of 6.5 yrs
Nuts and seed			
[17]	*N* = 61; age 65 ± 7 yrs; participants with overweight, obesity, intact cognition	Non-blinded crossover RCT. Participants were randomized to a high-oleic peanut diet (56 g/day females and 84 g/day males) 6 d/wk. vs. a nut-free diet for 12 wks. each (no standardized washout)	Compared to control, measures of memory, verbal fluency, and processing speed improved to a greater extent following peanut intake
[19]	*N* = 47; age 21 ± 2 yrs; undergraduate students, cognitive status unknown	Double-blinded crossover RCT. Participants were randomized to a daily meal containing banana bread with (60 g/day nuts, 6.8 g/day α-linolenic acid) or without walnuts (control) for 8 wks. each, with a 6 wk. washout	No differences were observed between groups for non-verbal reasoning or memory; however, inferential verbal reasoning increased following nut intake to a greater extent than control
[18•]	*N* = 657; age 63–79 yrs; mean ~ 69 yrs; participants with intact cognition	Single-blinded prospective RCT. Participants were randomized to a diet supplemented with walnuts (15% of energy; ~ 30–60 g/day) vs. an isocaloric nut-free diet for 104 wks	No group differences for global cognition, memory, language, perception, or frontal function were observed
[20]	N = 79; age 31 ± 13 yrs; participants with overweight, obesity, cognitive status unknown	Non-blinded prospective RCT. In addition to weight loss (500 kcal/day deficit), participants were randomized to a diet supplemented with almonds (15% of energy) vs. an isocaloric nut-free diet for 12 wks	Memory and attention improved similarly between groups over the 12-wk weight loss intervention period

Table 1 (continued)

Citations	Sample characteristics (N = study completers)	Intervention	Significant main findings related to cognition
[21]	N = 128; age 65 ± 8 yrs; participants with overweight, obesity, intact cognition	Single-blinded prospective RCT. Participants were randomized to a diet supplemented with almonds (15% of energy) vs. an isocaloric nut-free diet (i.e., sweet biscuits and potato chips) 6 d/wk. for 12 wks	No difference between the groups in numerous cognitive performance measures, including, but not limited to accuracy, recall, memory, information processing, and executive function
[22]	N = 60; age ~ 60 ± 6 yrs; participants with intact cognition	Single-blinded prospective RCT. Participants were randomized to 42 g/day or 84 g/day of almonds vs. 100 g/day of snack mix (cereal snack mix; similar in caloric content to 42 g/day of almonds) for 26 wks	At 26 wks, 84 g/day of almonds resulted in improved memory and executive function; however, these cognitive changes did not differ among the 3 dietary groups
[23]	N = 20; age 78 ± 5 yrs; participants with intact cognition	Non-blinded prospective RCT. Participants were randomized to one Brazil nut/day (288.75 µg/day) vs. a no Brazil nut (control) for 26 wks	Compared to control, the nut group had greater improvements in verbal fluency and constructional praxis; however, not for word list learning or recall
Fatty fish			
[25, 26]	N = 84; age 41 ± 9 yrs; male forensic inpatients with a psychiatric disorder and IQ > 75	Non-blinded prospective RCT. Participants were assigned to a meal of 150–300 g fatty fish (Atlantic salmon) vs. control (i.e., chicken, pork, beef) 3 × /wk for 23 wks	(26): The fish group showed improved performance on decision-making and planning tasks compared to the control (25): Neither group improved working memory performance
Lean meat			
[29]	N = 48; age 78 ± 6 yrs; participants with no serious cognitive impairment	Non-blinded prospective RCT. Participants were randomized to a meal of pork vs. chicken (control) 4 × / wk for 12 wks	The chicken (control) group had greater improvements in verbal learning and memory scores than the pork group at 6, but not 12 wks
[30]	N = 43; age 21 ± 8 yrs; undergraduate women; cognitive status unknown	Single-blinded prospective RCT. Participants were randomized to a meal of beef vs. non-beef protein (100 g protein/meal) 3 × /wk for 16 wks	Both groups showed improvements in planning speed, spatial working memory strategy, and attention
[32]	N = 33; age 61 ± 7 yrs; participants at increased risk of cognitive impairment	Non-blinded crossover RCT. Participants were randomized to a MedPork diet (MEDI + 250 g lean pork/wk) vs. a low-fat diet (control) for 8 wks each, with an 8-wk washout	Compared to control, MedPork led to a greater increase in processing speed performance, but not memory, attention, or planning
[33]	N = 154; age 71 ± 4 yrs; participants with intact cognition	Non-blinded prospective RCT. In addition to exercising, participants were randomized to lean red meat (160 g/ servings) vs. a carbohydrate (i.e., ~ 1/2 cup cooked of rice, pasta) 3 × /wk for 24 wks	No differences between groups were observed for global cognition or executive function; however, working memory and learning improved to a greater extent following the control than lean meat at 12 and 24 wks, while psychomotor and attention composite decreased in control with no change in lean meat at 12, but not 24 wks
Fruits and vegetables			
[34]	N = 84; age ~ 34 ± 6 yrs; participants with overweight, obesity, unknown cognitive status	Single-blind prospective RCT. Participants were randomized to consume a meal with one Hass avocado (140 g/day for females and 175 g/day for males) or an isocaloric meal with no avocado (control) for 12 wks	Compared to control, there was greater improvement in attentional inhibition following avocado intake, but not response inhibition
[35]	N = 40; age ~ 63 ± 10 yrs; participants with unknown cognitive status	Single-blinded prospective RCT. Participants were randomized to one avocado/day (0.5 mg lutein) or potato/chickpeas (control with no lutein) for 26 wks	There was a similar improvement in memory and spatial working memory in both groups following 26 wks of intervention

Table 1 (continued)

Citations	Sample characteristics (N = study completers)	Intervention	Significant main findings related to cognition
[36]	N = 154; age 26–70 yrs; participants with unknown cognitive status	Double-blinded prospective RCT. Participants were randomized to high or low-flavonoid fruit and vegetables vs. a habitual (control) diet. Portion sizes were incrementally increased over three consecutive 6-wk periods (18 wk total) from two to four, and finally six portions/day (portion = 80 g fresh, frozen, or canned, 40 g dried, or 150 mL fresh juice) of fruits and vegetables to provide 49–198 mg/day (high flavonoid) and 3–7 mg/day (low flavonoid) total flavonoids	Compared to low-flavonoid and control diets, the high-flavonoid group showed a greater increase in global cognitive function at 12 and 18 wks
[37]	N = 21; age 77 ± 6 yrs; participants with impaired cognition	Double-blind, prospective RCT. Participants were randomized to consume 6.3–7.8 mL/kg/day of Concord grape juice (2091 mg/L total polyphenolics) or an isocaloric placebo beverage (control no anthocyanins) for 16 wks	Compared to control, the Concord grape group performed less interference errors during a recognition memory task
[38]	N = 19; age ~ 43 ± 3 yrs; healthy mothers of children < 13 yrs of age; unknown cognitive status	Double-blinded crossover RCT. Participants were randomized to 355 mL/day of Concord grape juice (777 mg total polyphenolics) or an isocaloric placebo beverage for 12 wks each, with a 4-wk washout	Compared to control, there was a greater improvement in immediate verbal recall with Concord grape juice intake
[39]	N = 26; age 68 ± 3 yrs; participants with intact cognition	Double-blind prospective RCT. Participants were randomized to consume 30 mL/day of blueberry concentrate (387 mg anthocyanins) or isocaloric placebo for 12 wks	Both groups improved similarly in speed of visual processing, verbal learning, and delayed recall. There also were small improvements in reaction time and accuracy that were greater in the blueberry than placebo group
[34]	N = 40; age 63 ± 6 yrs; participants with intact cognition	Non-blinded crossover RCT. Participants were randomized to 600 ml/day of a mixed berry beverage (150 g blueberries, 50 g blackcurrant, 50 g elderberry, 50 g lingonberries, 50 g strawberry, and ~ 100 g tomatoes diluted with water: 1325 mg/L total polyphenols) or a carbohydrate-matched control beverage for 5 wks each, with a 5-wk washout	No changes in cognition were identified after berry or control beverage consumption
[41]	N = 200; age ~ 60 ± 6 yrs; participants with intact and impaired cognition	Double-blind prospective RCT. Participants were randomized to 236.5 mL/day of pomegranate juice (93 mg anthocyanins) or an identical placebo drink (no polyphenols) for 52 wks	Placebo group showed a decline in visual memory, but was preserved with pomegranate supplementation at 26 and 52 wks. Changes in visual learning, recall, and verbal memory did not differ between groups
[42]	N = 37; age ~ 67 ± 5 yrs; participants with intact cognition	Double-blind crossover RCT. Participants were randomized to 500 mL/day of a natural high (305 mg/day) vs. low (37 mg/day) flavanone orange juice for 8 wks each, with a 4-wk washout	Compared to the low flavanone group, there was greater improvement in global cognition and executive function, but not episodic memory, following high flavanone orange juice consumption
Legumes and beans			
[49]	N = 23; age 64 ± 3 yrs; participants with unknown cognitive status	Single-blinded crossover RCT. Participants were randomized to a soy nut group (25.5 g soy protein/d, 174 mg isoflavones) vs. no soy nut (control) group for 16 wks each, with a 6–12-wk washout	Compared to control, soy nut consumption led to improvements in psychomotor speed improved, but not executive function or memory tests

Table 1 (continued)

Citations	Sample characteristics (N = study completers)	Intervention	Significant main findings related to cognition
Non- and low-fat dairy			
[57]	N = 41; age 60 ± 7 yrs; participants with overweight, obesity, at risk for cardiovascular disease, intact cognition	Non-blinded crossover RCT. Participants were randomized to MedDairy (MEDI + 3–4 dairy servings/day: serving = ~ 250 ml low-fat milk) vs. low-fat (control) diet for 8 wks each, with an 8-wk washout	An interaction was observed where processing speed performance increased with MedDairy, but decreased with low-fat diet. No differences among groups in memory, attention, or planning were observed
[58]	N = 38; age 52 ± 13 yrs; participants with overweight, obesity, unknown cognitive status	Non-blinded crossover RCT. Participants were randomized to a high dairy diet (3–4 reduced-fat dairy servings/day) or a low dairy (control) diet (1 reduced-fat dairy serving/day) for 26 wks each without a washout period	Compared to control, high dairy resulted in greater improvements in working memory. No differences among groups in processing speed, attention, or verbal fluency (among others) were observed
[59]	N = 37; age 71 ± 4 yrs; female participants with intact cognition	Single-blinded prospective RCT. Participants were randomized to 250 g fortified yogurt (400 mg calcium and 200 IU vitamin D) vs. non-fortified yogurt 2 ×/day for 12 wks	An interaction was observed where global cognition was maintained with fortified yogurt, but decreased with the control
[60]	N = 53; age 69 ± 5 yrs; participants with intact cognition	Double-blind prospective RCT. Participants were randomized to 200 mL/day enriched milk (297 mg DHA, 137 mg EPA) vs. non-enriched (control) milk for 52 wks	Compared to control, the improvement in global cognition was greater following consumption of enriched milk

[23] evaluated the effects of 24 weeks of supplementation with one Brazil nut daily (versus a habitual diet) in older adults with MCI, and observed that Brazil nut consumption resulted in improvements in verbal fluency and constructional praxis (characterized by an inability or difficulty to draw or build objects) compared to the control group. We also refer the reader to the olive oil section for discussion of the PREDIMED study, which reported positive effects of a MEDI diet plus mixed nuts on memory and global cognition compared to a control diet [14, 15].

Fatty Fish

Fatty fish (i.e., mackerel, salmon) is a primary source of long-chain n-3 PUFAs, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are present in the membranes of brain tissue and modulate neuronal membrane properties [24]. We identified one recent RCT that evaluated the effect of consumption of fatty fish in a sample of forensic participants with mental disorders [25, 26]. Participants were randomly assigned to consume 150–300 g of either Atlantic salmon or other meats (i.e., chicken, pork, or beef) three times a week for 8 weeks. The authors reported improvements in executive function tasks (i.e., decision-making and planning) in the Atlantic salmon group [25, 26]; however, working memory performance did not improve [25].

Lean Meat

Protein-rich lean meats are a good source of creatine, several B-vitamins, iron, and zinc [27, 28]. Creatine and B-vitamins are involved in brain energy metabolism, cellular function, and homeostasis that may influence cognitive function [28, 29]. Further, evidence showed a direct relationship between improved iron status from consuming lean meat and cognition [30]. Additionally, zinc acts as an antioxidant, anti-inflammatory agent and has been linked to improved cognitive function [31]. Four recent RCTs were identified that evaluated the impact of consumption of lean meat on cognition. Wade et al. [32] examined the cognitive benefits of a 24-week MEDI diet with an additional 250 g/week lean pork intake (MedPork) versus a low-fat control in cognitively intact adults. The results showed a significant improvement in processing speed, but not attention, memory, or planning, in the MedPork group compared to control. The three other identified RCTs [29, 30, 33] investigated the effects of 12–26 weeks of consumption of 85–250 g/week lean red meat or pork versus various controls (i.e., chicken, cooked rice). The authors reported no significant difference between the groups at the end of each trial for cognitive function, including memory, learning, attention, and planning speed, and further suggested that merely changing the type of dietary protein does not impact cognitive function.

Fruit and Vegetables

Fruits and vegetables are an abundant source of dietary fiber, flavonoids, B-vitamins, minerals, and antioxidants, which could play a role in ameliorating cognitive impairment. We identified nine recent RCTs utilizing of fruit and/or vegetable intake to evaluate the effect of dietary intake on cognition. Only three studies utilized whole fruit and/or vegetable consumption [34–36], while the remaining six studies utilized fruit juice from Concord grapes [37, 38], berries [39, 40], pomegranates [41], and oranges [42]. Study participants were generally healthy and older adults, and only two studies included older adults with MCI [37, 41]. The fruit juice studies were < 24 weeks in duration (except one lasting 52 weeks [41], supplemented between 240 and 600 mL/day of juice (active intervention containing between ~ 600 and 1,800 mg of total polyphenols/day), and utilized an isocaloric carbohydrate-rich beverage control. In general, the fruit juice studies showed improvements in at least one measure of global cognition compared to control, with the main improvements specific to various domains of memory (i.e., working and short term) [37–39, 41, 42], except one study [40]. Neshedoust et al. [36] compared the effects of high- or low-flavonoid fruit and vegetables against a habitual diet control. At 12 and 18 weeks, the participants in the high-flavonoid group had an increase in global cognitive function compared to the low-flavonoid and habitual diet groups. Lastly, trials assessing whole, daily avocado consumption demonstrated benefits towards improving domains of cognitive function. One 12-week study in overweight and obese adults found that attention inhibition improved after consuming one meal with an avocado compared to an isocaloric meal without avocado [34], while another 24-week intervention found improvements in spatial planning and spatial working memory within the group consuming one avocado daily compared to control at 24 weeks [35].

Legumes and Beans

Over the past two decades, legumes and beans and their polyphenolic compounds (i.e., isoflavones) have gained attention due to their beneficial effects on cognitive function [43]. A recent review of observational studies reports an inverse association between dietary intake of isoflavones and cognitive decline/dementia [44]. The neuroprotective properties of isoflavones include antioxidant and anti-inflammatory function [45], clearance of amyloid-β plague [46], decrease in tau phosphorylation [47], and inhibition of the mitochondrial apoptotic pathway [48]. Legumes and beans also are rich in fiber and the *n*-3 PUFA, α-linolenic acid, which may benefit brain health. In a study evaluating soy nut consumption, participants were randomized into a crossover trial of either soy nuts versus control (no nuts) for 16 weeks each [49]. With regard to cognition, psychomotor speed improved, but not executive function or memory. This supports the findings of a recent meta-analysis of RCTs that examined the relationship between soy isoflavones on cognitive function and reported an overall positive effect of soy isoflavones on cognitive function in adults [50•]. However, it should be noted that the majority of RCTs to date that evaluated the effects of soy and/or isoflavone intake on cognition are limited to postmenopausal women. More trials are needed to confirm this observation in men.

Whole Grains

Whole grains are rich in dietary fiber, B-vitamins, vitamin E, minerals (i.e., selenium, magnesium), and phytochemicals with antioxidant properties. Although we did not identify any recent RCTs examining the impact of whole grain intake and cognition, evidence from observational studies suggested a dietary intake of whole grains (30–45 g/day) was associated with better cognitive function [51, 52, 53•].

Non- and Low-Fat Dairy

A recent meta-analysis, mostly observational, reported that the current evidence is too poor to draw a firm conclusion regarding the effects of dairy on the risk of cognitive decline in adults [54]. Most processed dairy milk is fortified with ~ 100 IU of vitamin D per serving. Low serum 25-hydroxyvitamin D (25OHD) concentrations and the inefficient utilization of 25OHD increase the risk of AD and cognitive decline in older adults [55]. 25OHD stimulates phagocytic clearance of amyloid-β plaques, prevents apoptosis in hippocampal cells, has direct antioxidant effects, and also upregulates the production of several neurotrophic factors important to cognitive functions, including mood, decision-making, social behavior, excessive worry, and impulse control [56]. In addition to vitamin D, dairy foods commonly contain B-vitamins, vitamin K, bioactive peptides, and calcium, which can have a positive influence on cognition. We identified two recent RCTs utilizing a crossover design to report the relationship between dairy intake and cognitive performance in adults. Wade et al. [57] examined the effects of a MEDI diet with adequate dairy (3–4 servings/day [note, standard MEDI is 1–2 servings of dairy/day]) versus a low-fat control diet for 8 weeks, while Chrichton et al. [58]

compared the effects of high diary (4 servings/day) or low dairy control (≤ 1 serving/day) for 26 weeks. Both studies reported supplementation with dairy foods improved various cognitive performance measures (i.e., working memory and processing speed) compared to the controls. Additionally, two recent RCTs were identified and found that fortification of dairy foods with specific nutrients was important to cognitive health. Beauchet et al. [59] compared the 12-week effects of supplementing older women with one serving of fortified yogurt twice daily (fortified with 400 IU/day of vitamin D_3 and 800 mg/day calcium) versus control of non-fortified yogurt, while Ichinose et al. [60] conducted a 52-week RCT in older participants consuming a milk beverage containing 297 mg DHA and 137 mg EPA, whereas the control group consumed non-fortified milk. Both studies observed global cognitive improvements in the intervention group compared to the control.

Alcohol/Wine

We did not identify any recent RCTs examining the impact of drinking wine on cognitive health. However, a recent review of cross-sectional and observational studies provided a summary of supportive evidence that light-to-moderate wine consumption, preferentially red wine, has a positive impact on cognition [61•]. The authors highlighted the uncertainty of the role of wine intake and the risk of cognitive dysfunction due to several limitations such as the validity of measurement of alcohol consumption, environmental, socioeconomic, and lifestyle factors. US dietary guidelines report that possible health benefits may only exist with moderate drinking (i.e., "Up to one drink per day for women and up to two drinks per day for men and only for adults of legal drinking age") [6]. The beneficial effects of red wine are attributed principally to dietary polyphenols (resveratrol) and are considered promising for their neuroprotective properties.

Summary on the Role of a KETO Diet on Cognitive Health

We refer the reader to previous reviews, which detailed the role of the KETO diet on cognitive health and neurogenerative disease and in general supporting the diet to improve, delay, or prevent the progression of cognitive decline, MCI, and AD [5•, 62, 63•]. Additionally, we refer readers to reviews of the mechanisms, beneficial protective effects, and therapeutic role of the KETO diet on cognitive status and neurogenerative diseases, including metabolic benefits, increased mitochondrial function, and decreased oxidative stress and inflammation [62, 64–66]. However, we will provide a summary of potential mechanisms.

Under normal conditions, the brain utilizes glucose as the primary energy source [67]. When glucose supply is insufficient or restricted through fasting, the primary energy substrate shifts from glucose to ketone bodies [67]. The KETO diet (high fat and very low carbohydrate) mimics fasting conditions and shifts energy metabolism from glucose to fatty acids resulting in the production of ketone bodies. A common pathological characteristic of neurodegenerative disorders is the disruption of cerebral energy metabolism, whereby glucose uptake and utilization are impaired [68]. Thus, the KETO diet provides a potential nonpharmacological therapy for neurodegenerative disorders with disruptions in glucose metabolism.

Multiple hypotheses on the beneficial mechanisms of the KETO diet have been proposed and align with the current understanding of the role of metabolism and inflammation in cognitive status. A few of these theories include the improvement of metabolic risk factors (i.e., blood sugar, lipid concentrations, obesity) associated with increased risk of cognitive decline and dementia [69]. The KETO diet's systemic anti-inflammatory and antioxidant properties are another proposed mechanism. The antioxidant capacity of ketone bodies and production of less reactive oxygen species when metabolized decreases oxidative stress and increases mitochondrial detoxification efforts, leading to a decreased inflammatory response from toxic free radicals [70, 71]. Additionally, anti-inflammatory proteins (i.e., C terminal binding proteins) produced from ketosis also contribute to a systemic decrease in inflammation [72]. The effect of ketosis on neurotransmitter concentrations and metabolism (i.e., γ-aminobutyric acid), which leads to enhanced communication between neurons, is another proposed mechanism [73]. The KETO diet also may protect against toxic amyloid-β plague production associated with neurogenerative disease [74]. Furthermore, it has been proposed that through carbohydrate restriction and the stabilization of blood glucose concentrations, the KETO diet may attenuate glycation of apolipoproteins (ApoE), specifically ApoE4, and the "cascade effect" that ultimately leads to neuronal dysfunction, oxidative stress, and cell death [75]. ApoE4 is three times more likely to undergo glycation [76] and the strongest genetic risk factor for AD [77]. Thus, the KETO diet is a potential therapeutic strategy to combat cognitive decline and neurological diseases.

Evidence of Whole Food Components of the KETO Diet from RTCs on Cognitive Health

We provide a summary of RCTs examining the whole food components of the KETO diet on cognitive health in Table 2.

Table 2 Evidence on the relationship between cognitive function and adherence to a KETO diet through whole foods

Citation	Sample characteristics (N = study completers)	Intervention	Significant main findings related to cognition
[78]	$N = 21$; age 70 ± 6 yrs; participants with impaired cognition	Non-blinded prospective RCT. Participants were randomized to a low-carbohydrate diet (≤20 g carbohydrate/day) or high-carbohydrate diet for 6 wks	Compared to baseline, low-carbohydrate diet led to improved long-term memory, but not working memory or executive ability. No changes in cognition were observed in the high-carbohydrate group
[79]	$N = 14$; age ~ 55 ± 5 yrs; HIV with participants with impaired cognition	Non-blinded prospective RCT. Participants were randomized to a KETO diet (≤20 g carbohydrate/day) vs. patient choice (control) diet for 12 wks, followed by an ad libitum diet for 6 wks	At 12 wks, the KETO diet led to greater improvements in executive function, speed of processing, attention, and visuospatial tracking, but not verbal learning or memory, compared to control. Results were negated after 6 wks of follow-up
[80]	$N = 21$; age 70 ± 6 yrs; participants with impaired cognition	Single-blinded crossover RCT. Participants were randomized to a modified KETO diet (6% net carbohydrate) vs. a low-fat (control) diet (62% net carbohydrate) for 12 wks each, with a 10-wk washout	Compared to control, the KETO diet showed a modest (non-significant) trend towards improvement in tests of attention, orientation, memory, language, visual perceptual, and visuospatial skills
[81]	$N = 47$; age 47 ± 8.7 yrs; obese participants with unknown cognitive status	Non-blinded prospective RCT. Participants were randomized to a low-carbohydrate diet (20 g carbohydrate/day) for 9 wks, with an increase of 5 g carbohydrate/wk vs. low-fat hypocaloric diet (1200 to 1800 kcal/day; ≤30% calories from fat) for 26 wks	Both diets showed similar improvement in accuracy to inhibit cognitive interference over time. No performance differences between groups or over time were observed for attention, reaction time, short-term memory, or problem solving
[82]	$N = 115$; 58 ± 7 yrs; participants with overweight, obesity, type 2 diabetes; unknown cognitive status	Single-blinded prospective RCT. In addition to exercising, participants were randomized to an energy-restricted low-carbohydrate diet (500–1000 kcal/day deficit, 14% carbohydrate) vs. an isocaloric high-carbohydrates (53% carbohydrate) for 52 wks	No differences in the change of cognitive performance scores between diet groups were observed for reasoning speed, short-term and working memory, speed of memory, inhibition of cognitive interference, perceptual speed, verbal fluency, and reasoning
[83]	$N = 11$; age 30 ± 9 yrs; participants with intact cognition	Non-blinded crossover RCT. Participants were randomized a KETO diet (15% carbohydrate) vs. an isocaloric high-carbohydrate, low-fat (control) diet for 3 wks each, with a 1-wk washout	Compared to control, the KETO diet showed no effect on the speed and accuracy responses in vigilance tasks, visual learning and memory, working memory, and executive function

Over the past decade, there has been a growing interest in the possible association between the KETO diet and cognitive health. We identified six RTCs which examined the effects of the KETO diet induced by whole foods on cognitive function. Of the six identified RCTs, five monitored ketone body concentrations to ensure participants achieved ketosis during the intervention. Krikorian et al. [78] compared the effects of 6 weeks of a very low-carbohydrate KETO diet and a high-carbohydrate diet in older adults with MCI. Compared to baseline, the KETO group showed improvements in long-term memory; however, short-term working memory and executive functions were not affected. Morrison et al. [79] randomized older adults living with HIV and mild-to-moderate cognitive impairment to a KETO diet or patient choice control for 12 weeks followed by a 6-week follow-up period. Results showed no cognitive changes in the control group after 12 weeks, whereas the KETO group showed significant improvement in executive function, processing speed, attention, and visuospatial tracking; however, the improvements were negated after 6 weeks of consuming their usual diet. In a crossover trial, Phillips et al. [80] randomized adults with a diagnosis of AD to either a modified KETO diet or a low-fat control diet for 12 weeks each. Compared to the control diet, the KETO diet group showed a modest trend-level improvement in attention, orientation, memory, language, visual perceptual, and visuospatial skills. The remaining three RCTs examined the effect of the KETO diet in individuals without cognitive impairment. In general, all three studies randomized adults to a KETO diet or a control diet (energy matched, high carbohydrate, low fat) [81–83]. Results were consistent across studies with all reporting no difference in cognitive performance between the KETO and control diets [81–82]. However, it should be noted that none of these studies evaluated glycation of ApoEs, which have been identified as a potential modulator of cognitive function with KETO diets [84].

Adverse side effects, difficulty sustaining, and/or compliance to the KETO diet should be taken into consideration. The main side effects tend to be gastrointestinal and include nausea, vomiting, diarrhea, dehydration, and fatigue; however, long-term health could be affected due to micronutrient deficiencies and lack of phytonutrients. Furthermore, the KETO diet may not be medically appropriate for everyone and should be used with caution in individuals with diabetes and kidney disease.

Conclusion: Limitations and Summary of the Current Evidence and Suggested Future Directions

There are several methodological differences (i.e., variations in study design, blinding, duration, sample sizes, age groups, participants' cognitive status, and doses of the intervention component) of the available literature. The inclusion of several cognitive tests may increase the likelihood of making a type I error [29]. Further, higher adherence to these dietary patterns is associated with better access to socioeconomic resources, which may also be associated with better cognitive outcomes making it difficult to independently distinguish between the effects of diet and socioeconomic status on cognitive health.

Despite these limitations, the majority of RCTs (26/29) of MEDI, DASH, MIND-component studies report promising findings in the areas of olive oil, fruits and vegetables, fatty fish, and legumes on at least one measure of cognition. We found mixed results for nuts and lean meat consumption and cognitive outcomes. In addition, 3/6 KETO diet studies reported positive results on cognition. Generally, the RCTs included in this study were ≤ 6 months (3/35), and included middle-aged and older adults (33/35), and cognitively intact participants (27/35). The current evidence from RCTs generally supported that greater consumption of the individual component of these dietary patterns through whole foods and their neuroprotective properties is a cost-effective, safe, nonpharmacological approach to improve cognitive health.

These are promising findings since the evidence supports that simpler actions are more likely to become habitual more quickly than complex changes and that forming one "small" healthy habit may increase self-confidence in working towards other health-promoting habits [85]. Furthermore, adding the whole dietary pattern would be costly, thus making incremental changes a prudent option to delay age-related cognitive impairments. When these individual dietary components are combined, it is assumed that the interrelated actions of a whole dietary pattern may generate powerful synergistic actions in overall brain health [86]. It is important to note that modifications to dietary habits often occur concurrently with other lifestyle changes, such as incorporating physical activity. These complex multidimensional behaviors and cost-effective measures may reinforce one another to delay age-related cognitive decline

[2]. In summary, there is an urgent need for further empirical research to uncover novel strategies to investigate the individual components of these diets which may promote healthy cognitive aging and minimize the anticipated burden of cognitive impairment in the aging population.

Future research might focus on conducting larger trials that diversify age, baseline cognitive status, race/ethnicity, and sociodemographic backgrounds using standardization of cognitive measures to examine the causal relationship between the dietary components and cognitive outcomes. The implications of this research also may have greater economic significance for society to combat the growing burden of age-related cognitive decline.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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

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