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Diet and Neurocognition: Review of Evidence and Methodological Considerations

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Abstract

The relationship between diet and cognitive function has been a topic of increasing interest, as numerous studies have shown that variations in dietary practices and nutrient intake are may protect against age-related cognitive decline, as well as the development of dementia and Alzheimer's Disease (AD). Various dietary practices and specific nutrient components of these diets have been examined in relation to cognitive performance including 1) dietary fatty acids (including fish oil) and the Mediterranean diet, 2) antioxidants (including vitamins E and C) and fruits and vegetables, 3) vitamins B6, B12 (cobolamine), and folate, and, more recently, 4) caloric restriction. Although observational studies have generally reported significant associations between dietary practices and reduced incidence of cognitive dysfunction, randomized trials of dietary interventions have yielded mixed findings, with many trials yielding small gains or equivocal findings. In addition, findings appear to vary based on sample characteristics, methods of dietary assessment, and length of study follow-up. The influence of dietary practices on cognitive function in middle aged and older adults remains uncertain, and further research is needed to clarify the nature of this relationship and identify mechanisms by which diet may affect neurocognition.

INTRODUCTION

The relationship between diet and cognitive function has been a topic of increasing interest over the past two decades, as numerous observational studies have reported that variations in dietary practices and nutrient intake are predictive of cognitive decline [1], dementia [2], and Alzheimer's disease (AD) [3]. The role of healthy dietary practices in the prevention of late-life cognitive dysfunction carries major public health implications, as the World Health Organization (WHO) predicts that 29 million individuals living with dementia by the year 2020 [4, 5], accompanied by an estimated 83% increase in associated health care costs for individuals with AD. Various dietary practices and specific nutrient components of these diets have been examined in relation to cognitive performance. The present review will focus on four key dietary components in relation to neurocognitive functioning: 1) dietary fatty acids (including fish oil) and the Mediterranean diet, 2) antioxidants (including vitamins E and C), as well as fruits and vegetables, 3) vitamin B6, B12 (cobolamine), and folate, and 4) caloric restriction. Due to the great number of studies examining these relationships, only larger studies and those with particularly important methodological or analytical contributions are discussed in detail throughout the text. Other dietary components not reviewed in detail (alcohol and vitamin D) are also briefly summarized. In

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addition, methodological issues in conducting research in this area will be discussed, along with recommendations for future research.

Studies included in the present review have examined a variety of outcomes, including dementia, AD, vascular dementia (VaD), mild cognitive impairment (MCI), and cognitive decline. Although these outcomes are defined somewhat differently between studies, a brief description is provided here: dementia = impairment in memory with significant functional impairment; AD = impairment in memory and at least one other cognitive domain with significant functional impairment; VaD = dementia with focal neurological signs and/or laboratory evidence of cerebrovascular disease; MCI = significant deficits in one or more cognitive domains that are not of sufficient severity to warrant a diagnosis of dementia ; cognitive decline = a significant decline in cognitive performance relative to premorbid levels that is greater than expectation for age (e.g. > 1 standard deviation relative to age-matched peers or premorbid estimates); age-related cognitve decline = a normative decrease in cognitive performance relative to premorbid levels that is the result of 'normal' age-related processes and is not indicative of a neurodegenerative process.

DIETARY FATTY ACIDS

Dietary fatty acids are classified into two general subtypes: saturated fatty acids and unsaturated fatty acids. Among these subtypes, unsaturated fatty acids may be further divided into monounsaturated (MUFAs) and polyun--saturated fatty acids (PUFAs). Saturated fatty acids are derived primarily from meat and dairy products, but also from cookies and pastries. An important component of dietary fat consumption is the levels of n-3 and n-6 PUFAs, commonly referred to as omega-3 and omega-6 fatty acids. n-3 PUFAs are primarily derived from fish and marine sources and consist of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), whereas n-6 PUFAs are primarily derived from legumes, nuts, and other plant-based sources and consist of α-linolenic acid (ALA). The majority of extant studies have reported a similar pattern of findings: greater fat intake is associated with *greater* risk of cognitive dysfunction and dementia, whereas greater intake of n-3 relative to n-6 fatty acids is associated with *lesser* risk of these outcomes. Greater consumption of n-3 relative to n-6 fatty acids is believed to protect against cognitive decline and dementia through a number of mechanisms, including alterations in cholesterol metabolism, reduced inflammation in the brain, modulating central growth factors, and altering neuronal signal processing [6].

Prospective studies have generally examined the effects of diet in protecting age-related cognitive decline among non-demented samples. Although several studies have utilized extensive test batteries assessing multiple cognitive domains, the majority of extant studies have examined changes in mental status, as indexed by the mini mental status exam (MMSE). In an early population-based study from the Zutphen Elderly Study, Kalmijn and colleagues [7] examined the association between intake of linoleic PUFAs and fish consumption and subsequent cognitive decline and cognitive impairment among 476 men aged 69–89 years. Higher levels of linoleic PUFAs and fish consumption were shown to protect against incident cognitive impairment and cognitive decline, defined by performance on the MMSE. In addition, these findings were strengthened by the studies control of other confounding dietary elements, including total energy intake, alcohol consumption, as well as dietary intake of beta-carotene, vitamins C and E, and flavanoids, none of which were protective against cognitive dysfunction. In a subsequent study from Zutphen, van Gelder and colleagues [8] found that elderly men who consumed greater amounts of fish were significantly less likely to exhibit cognitive decline relative to men who did not consume fish. In addition, greater fish consumption appeared to protect against cognitive decline in a dose-response fashion. Capurso and colleagues [9] reported similar findings in a prospective

study of 278 individuals, followed for approximately 9 years. Examination of changes in MMSE performance demonstrated that individuals with high PUFA (> 220 kJ / day) and MUFA intake (> 2000 kJ / day) were less likely to exhibit cognitive decline relative to individuals with low intake.

Although the majority of existing studies have utilized self-reported dietary practices to index consumption, Heude and colleagues [10] examined the association between PUFAs and cognitive decline by examining the fatty acid consumption of erythrocyte membranes from blood samples in 246 adults participating in the Etude du Vieillissement Arteriel cohort study. Although approximately 1,400 men and women participated in the larger cohort study, financial restrictions imposed by erythrocyte assays limited the number of individuals included in this analysis. An inverse association was noted between the ratio of n-3 and n-6 PUFA in erythrocyte membranes and MMSE performance. Specifically, a higher proportion of n-3 PUFAs was associated with a 40% reduced risk of moderate cognitive decline, defined as a decline of two or more points in MMSE performance. Similarly, Dullemeijer and colleagues [11] examined the relationship between n-3 PUFA plasma levels and cognitive decline in a 4-year follow-up of older individuals participating in the Folic Acid and Carotid Intima-Media Thickness study. Greater plasma n-3 PUFA levels were associated with protection against declines in performance for sensorimotor and complex speed, although memory, information-processing, and word fluency did not appear to be impacted.

In one of the largest studies to date to examine the role of fatty acids in cognitive decline, Morris and colleagues [12] examined the relationship between saturated and trans-unsaturated fat in predicting cognitive decline among 2,560 individuals participating in the Chicago Health and Aging Project. Notably, the individuals in this trial were relatively at baseline, as the exclusion criteria for this trial eliminated individuals with a history of stroke, heart disease, or diabetes at baseline. Cognitive decline was assessed using a more comprehensive neuropsychological test battery, which included the East Boston Tests of memory, the MMSE, and the Symbol Digit Modalities Test. Examination of 6-year changes in cognitive function indicated that individuals with higher dietary intake of saturated or trans-unsaturated fats or low nonhydrogenated unsaturated fats were associated with a greater incidence of cognitive decline.

Although studies have varied widely in their inclusion/ exclusion criteria and statistical control of CVRFs, Beydoun and colleagues [13] conducted a notable study in which individuals from the Atherosclerosis in Communities Study (ARIC) who were either hypertensive or dylipidemic were analyzed as an at-risk group. In these 2,251 participants aged 50 years and older were examined at three time points, spanning twelve years. Consistent with previous findings, those individuals with higher plasma levels of n-3 PUFAs were less likely to exhibit decline on cognitive measures of verbal fluency, although these individuals did not exhibit improved performances on measures of delayed memory or psychomotor speed.

In contrast to the assessment of cognitive decline, prospective studies examining the relationship between dietary practice and the development of dementia have typically relied on cognitive performance in conjunction with a clinical diagnosis of dementia. In some cases this data is supplemented with MRI results, when available. In addition to their work on cognitive decline, Kalmijn and colleagues [14] have also demonstrated that the protective effects associated with modest dietary fat consumption and greater fish consumption on dementia. In their study of 5,386 non-demented individuals from the Rotterdam study followed for approximately 2 years, greater dietary intake of total fat, saturated fat, and cholesterol were all found to be predictive of incident dementia and were most strongly

associated with reduced risk of VaD. Similar to their previous study, greater fish consumption was protective against the development of dementia. In contrast to their findings for dietary fat, Kalmijn found that fish consumption appeared to be most protective against the development of AD. Barbeger-Gateau and colleagues [15] also found a protective effect of greater fish consumption among 1,674 older adults aged 68 and over participating in the PAQUID (Personnes Agees QUID) cohort study. Specifically, individuals with greater fish consumption were less likely to develop AD over the 2–7 year follow-up in age and sex-adjusted analyses. Interestingly, this relationship was somewhat attenuated following adjustment for education level and, in contradiction to previous findings, greater meat consumption was not predictive of subsequent dementia. Morris and colleagues [16, 17] have recently conducted several studies examining the effects of diet on the incidence of AD. In both studies, 815 participants from the Chicago Health and Aging project were followed for approximately 4 years, during which 131 sample participants developed AD. Consistent with previous findings, higher intake of saturated and trans-unsaturated fats were associated with a higher risk of AD, whereas higher intake of n-3 and n-6 fatty acids were associated with a lower risk. Finally, Schaefer and colleagues [18] examined the relationship between omega fatty acids and incident dementia among 899 older men and women, specifically with respect to plasma levels of decosahexaenoic acid phosphatidylcholine (DHA-PC) levels in relation to incident dementia during an approximate 9-year follow-up. They found that participants with higher DHA-PC levels (i.e. in the highest quartile) were 47% less likely to develop AD relative to other individuals. Negative findings have also been reported, however [19].

Solfrizzi and colleagues [20] have extended these findings, examining the relationship between PUFA intake and the development of MCI among 464 non-demented older adults participating in the Italian Longitudinal Study of Aging. During an approximate 3-year follow-up of participants, higher intake of PUFAs appeared to protect against the development of MCI. However, this relationship was attenuated following adjustment for possible confounders. Given the small sample size of individuals who developed MCI in this study (n=18), the protective effects of PUFAs for MCI remain to be elucidated.

Although the results of longitudinal studies have been generally consistent, important negative findings also warrant attention. Engelhart and colleagues [21], in a subsequent analysis of individuals from the Rotterdam study, failed to find an association between high intake of total fat, saturated fat, trans fats, cholesterol, and the subsequent development of dementia. In contrast to the Kalmijn study, this analysis utilized a longer follow-up period (6 years instead of 2). In addition to the negative findings for dietary fat intake, consumption of fatty acids did not appear to protect against the development of dementia. At present these discrepant findings have yet to be reconciled.

Pilot studies of omega-3 fatty acids have reported modest cognitive benefits with fish oil supplementation, although well-controlled RCTs of omega-3 fatty acids have yielded equivocal findings similar to large-scale epidemiological studies [22]. Yehuda and colleagues [23], in an early study, examined whether a combination of n-3 and n-6 fatty acids might improve cognition and quality of life among 100 AD patients. In their double-blind, 4-week study, patients demonstrated modest improvements in short-term memory and quality of life measures. In a 24-week, double-blind pilot study, Chiu and colleagues [24] examined the effects of omega-3 PUFA monotherapy in improving cognitive performance among 46 patients with either AD or MCI relative to placebo controls. Results showed that, among participants completing at least one post-treatment follow-up assessment (76%), treatment group participants showed improvement in the Clinician's Interview-Based Impression of Change Scale (CIBIC-plus). In addition, comparison of individuals with MCI showed that those on omega-3 PUFA monotherapy exhibited cognitive benefits on the AD

Assessment Scale (ADAS-cog) relative to individuals with MCI in the placebo condition. These findings were not significant among individuals with AD, however. Terano and colleagues [25] reported significant improvements in cognition following DHA supplementation among twenty elderly adults with VaD. Participants were randomly assigned to receive 0.72 g/day DHA daily for one year, whereas control participants continued their dietary practices as usual. Cognitive function was assessed every three months by MMSE performance and Hasegawa's dementia rating scale. At three and six months, the treatment group exhibited improved cognitive function as indexed by Hasegawa's dementia rating scale, and this improvement was significantly correlated with serum levels of DHA. After twelve months of treatment, however, these differences were no longer significant. Finally, Kotani and colleagues [26] examined the effects of arachidonic acid (ARA) and DHA in a small group of forty patients with MCI, AD, or organic brain lesions. Patients with MCI were randomly assigned to receive either the active treatment or a placebo. After ninety days of treatment, treated MCI patients showed improvements in immediate memory and attention, while the organic brain lesion group showed improvements in both short and long-term memory performance. In contrast, neither the AD nor MCI patients treated with placebo exhibited improved cognitive performance.

Despite the positive findings of these pilot studies, several large-scale RCTs have failed to find a benefit to fish oil in staving off cognitive decline and/or dementia among adults. In a randomized, double-blind, placebo-controlled trial, van de Rest and colleagues [27] found no effects of omega-3 supplementation among 321 healthy adults, aged 65 years and older. In their study, participants were assigned to a 26-week treatment in which they received 1,800 mg/day, 400 mg/day, or placebo capsules. Prior to treatment and again following the 26-week protocol, participants completed an extensive neuropsychological test battery, including measures of attention, sensorimotor speed, memory, and executive function. Despite substantial increases in plasma concentrations of EPA + DHA, neither of the treatment groups exhibited improvements in cognitive performance. In a 6-month randomized controlled trial of n-3 supplementation, Freund-Levi and colleagues [28] reported similar results among 204 patients with AD. After 6-months of treatment, the groups did not differ in cognitive performance, although sensitivity analyzes revealed that individuals with very mild impairment (i.e. MMSE > 27 points) exhibited modest cognitive benefits.

MEDITERRANEAN DIET

Although the specific components of fatty acid intake remain unclear, recent studies have examined the role of dietary practices that emphasize these components as strategies to prevent dementia. As reviewed in detail elsewhere, the discrepant findings across trials utilizing fatty acid interventions may be explained by the interaction of multiple underlying physiological processes as well as individual differences that have not consistently been examined [29]. Accordingly, the Mediterranean diet has received substantial attention due to its focus on fish intake, vegetables, legumes, fruits, cereals, and unsaturated fatty acids [30, 31]. In addition, this diet is characterized by a low intake of dairy products, meat, and saturated fatty acids, as well as regular, modest intake of alcohol. Recent evidence indicates that the Mediterranean diet is associated with reduced risk of MCI and AD, and that greater adherence to this diet may protect against subsequent cognitive dysfunction in a dose-response fashion [32].

In a study of 2,258 community-dwelling, nondemented New Yorkers, Scarmeas and colleagues [32] examined the association between adherence to the Mediterranean diet and subsequent development of AD during an approximate 4-year follow-up. Greater adherence to the Mediterranean diet was associated with dose-response protection from developing

AD. Notably, compared to individuals in the highest quartile of dietary adherence, individuals with poor Mediterranean dietary practices had an approximately 40% greater risk of developing AD. Interestingly, these results were unchanged in a subsequent study among the same cohort when measures of vascular functioning were accountted for, leading the authors to conclude that the observed relationship between dietary fat and AD is not mediated by vascular health [32].

These findings were recently extended to demonstrate that Mediterranean diet adherence is associated with protection against incident MCI in a similar fashion. Scarmeas and colleagues [22] recently examined this relationship in a similar sample of 1,393 New Yorkers over an approximate 5-year follow-up. Results were similar to the relationship observed with AD: greater adherence to the Mediterranean diet was associated with dose-response protection against incident MCI. Specifically, for every one-unit increase in the authors' Mediterranean diet adherence score, the risk of subsequent MCI was reduced 8%. These findings were confirmed by Feart and colleagues [33], who demonstrated that better adherence to the DASH diet was associated with slower cognitive decline as measured by scores on the MMSE, although the incidence of AD was not reduced. A recent observational study by Scarmeas and colleagues [34] extended their earlier findings, demonstrating that greater adherence to the Mediterranean diet combined with higher levels of physical activity had an additive protective effect in reducing the subsequent risk of AD.

ANTIOXIDANTS, FRUITS, AND VEGETABLES

Antioxidants are found naturally in fruits and vegetables and can also be taken as supplements. Greater antioxidant intake is hypothesized to prevent age-related neurologic dysfunction because brain tissue contains low levels of endogenous antioxidants and is therefore particularly vulnerable to free-radical damage [35]. Moreover, oxidative stress has been implicated as one of the primary mechanisms of age-related neuronal decline [36, 37]. Accordingly, there has been great interest in the role of antioxidants in the prevention of age-related cognitive decline and the development of neurocognitive disorders.

Early studies of antioxidants emerged from uncontrolled observational studies in which greater consumption of fruits and vegetables were shown to be associated with better cognitive function [38] and reduced incidence of ischemic stroke [39]. Ortega and colleagues [40], for example, demonstrated that high intakes of fruit, folate, carbohydrate, thiamine, and vitamin C were associated with reduced rates of cognitive impairment among 260 elderly individuals, aged 65 to 90 years. Morris and colleagues [41] extended these findings, noting that greater intake of vegetables, but not fruits, was associated with improved cognitive performance among 3,718 older adults participating in the Chicago Health and Aging Study, and this effect was not attenuated after controlling for cardiovascular comorbidities. La Rue and colleagues [42] reported similar findings in an examination of 137 older adults participating in the New Mexico Aging Project Study. Nutritional status was assessed at a baseline exam and again 6 years later. At the 6-year assessment, a comprehensive neuropsychological exam was administered, assessing visuospatial performance, abstract reasoning, and memory. Examination of simple correlations between dietary and cognitive variables revealed several interesting associations. Higher past intake of vitamins E, A, B-6, and B-12 were associated with better performance on abstractions tests and visuospatial recall. In addition, higher levels of thiamine, riboflavin, niacin, and folate were associated with better abstraction. In contrast, higher plasma ascorbate levels were associated with better visuospatial performance. Vitamin supplementation use was also associated with several tests of visuospatial and abstraction abilities. Fotuhi and colleagues [43] reported similar findings from a prospective examination of 3,376 participants in the Cache County study. Participants using a

combination of vitamins E, C, and non-steroidal anti-inflammatory (NSAIDS) at baseline exhibited the least cognitive decline. Interestingly, when analyses were stratified by APOE genotype, the protective effect of supplementation was driven by individuals with the APOE ε-4 genotype.

In an attempt to examine the components of diet that are most protective against cognitive decline, Morris and colleagues [44] examined the relationship between vitamin E use and cognitive decline among 2,889 older adults (aged 65 years and above) from the same cohort. Participants completed cognitive assessments at baseline and again 18 months later. Cognitive function was indexed by using a composite score derived from four cognitive tests that assessed memory, mental status, and psychomotor speed / executive function. The study was strengthened by its careful control of confounding variables, including other dietary factors such as carotene and vitamin C. Results revealed a dose-dependent protective effect of vitamin E intake, either from diet or supplement use, and lower rates of cognitive decline. Secondary analyses revealed that the protective effects of vitamin E were strongest among individuals with higher intakes of vitamin E from dietary sources relative to individuals with low vitamin E dietary consumption taking supplements. Interestingly, vitamin C was not protective against cognitive decline in this study. Wengreen and colleagues [45] reported similar findings in a prospective study of 3,831 older individuals participating in the Cache County study. During the seven-year follow-up, individuals with greater dietary intake of vitamins E and C exhibited less cognitive decline and a similar trend, although weaker, was observed for vitamin supplements.

Masaki and colleagues [46] have examined the effects of vitamin E and C supplementation specifically in protecting cognitive function and reducing risk for the development of VaD, stroke, and AD. In their examination of 3,385 men participating in the Honolulu-Asia Aging Study, use of either vitamin C or E was associated with better cognitive performance when participants were assessed 6–8 years later. Participants who were taking both vitamin C and E tended to exhibit better cognitive performance than individuals taking only one of these supplements. In contrast, individuals taking both supplements were less likely to develop VaD, and mixed/other dementias, although the use of supplements did not appear to protect against the development of AD. In contrast, Zandi and colleagues [47] found that the combination of vitamins E and C use was associated with an approximate 65% reduced risk of incident AD in sample of 3,227 Cache County participants. Although vitamins E and C appeared to be protective against AD individually, neither antioxidant was statistically significant in its association.

Although the relationship between antioxidant supplements and AD has been less conclusive, dietary intake of antioxidants appears to protect against incident AD. Engelhart and colleagues [48] examined this among 5,395 individuals participating in the Rotterdam study, 197 of whom had developed AD after 6 years of follow-up. Among the dietary factors assessed, higher intake of vitamins C and E were associated with dose-dependent reductions in risk for AD and this relationship was strongest among current smokers. In addition, current smokers with higher intakes of beta carotene and flavanoids showed lower rates of AD, although these factors did not appear to be protective among non-smoking participants. This study was strengthened by its careful control of confounding variables including the use of antioxidant supplements, presence of carotid plaques, total energy intake, and baseline MMSE performance.

Flavonoids, phenolic compounds abundant in red wine and various types of berries, have also been examined due to their antioxidant effects on low density lipoprotein (LDL). In an examination of 1,367 older adults participating in the PAQUID cohort study, Commenges and colleagues [49] found that individuals consuming higher levels of flavonoids were

approximately 50% less likely to develop dementia during a 5-year follow-up. Letenneur and colleagues [50] extended these findings by examining the 10-year follow-up from PAQUID, demonstrating that individuals with higher flavonoid intake showed the least age-related decline in cognitive performance, as indexed by the MMSE. Although few prospective studies have investigated the protective effects of flavonoids on cognitive function, there is abundant laboratory data among animals supporting possible mechanisms for this protective relationship [51].

Several RCTs have investigated the effects of Vitamin E and/or C supplementation in the prevention of dementias, such as AD (Table 1). In the most comprehensive review of these trials to date, Isaac and colleagues [52] examined the effects of vitamin E in the treatment and prevention of AD and MCI. Based on their comprehensive literature search, only two trials met inclusion criteria, incorporating data from two studies, one among AD patients [53] and the other among individuals with MCI [54]. In their study of 341 patients with AD of moderate severity, Sano and colleagues [54] examined the effects of selegiline, alpha-tocopherol, or placebo in slowing the progression of AD over a two-year period. Specifically, survival analyses were used to assess the effects of medication on extending the time before a composite end-point of death, institutionalization, or loss of the ability to perform at least two of three basic activities of daily living, as indexed by the Blessed Dementia Scale. Patients on either medication or a combination of both showed slowed rates of cognitive decline relative to individuals in the placebo group. In their study of 769 individuals with MCI, Peterson and colleagues [53] examined whether the administration of either vitamin E supplements or Donepezil might slow the progression to AD. Although neither treatment group appeared to benefit from therapy after 3 years of follow-up, pre-planned analyses every 6-months demonstrated that both treatments showed a slower rate of conversion to AD during the first year of treatment and that this effects was most pronounced among individuals with the APOE-4 genotype. Taken together, current findings from RCTs indicate that antioxidant supplementation may confer small benefits among populations vulnerable to dementia, slowing the rate of disease progression. However, these benefits must be weighed against the increased risk of death associated with vitamin E use among individuals with a history of cardiovascular disease or taking certain cardiac medications [55]. In addition, the effect of antioxidants among healthier samples remains to be examined.

VITAMINS B6, B12 (COBOLAMINE), AND FOLATE

Multiple population-based observational studies have examined the relationship between intake of vitamins B6, B12, and folate as protective against neurocognitive decline and are reviewed elsewhere [56]. Increased intake of B vitamins and folate is thought to improve cognitive function by improving cerebral structural integrity, neurotransmitter function (e.g. cholinergic activity), and indirectly by reducing homocysteine levels [57].

Although a multitude of observational studies have examined this question, results have been mixed, with many studies reporting protective effects and others finding equivocal associations. Among individuals participating in the Kungsholmen Project, a population-based longitudinal study in Sweden, Wang and colleagues [58] examined the association between serum levels of B12 and folate among non-demented, older adults (aged 75 years or greater). Among the 350 participants followed for approximately three years, lower levels of either B12 or folate were associated with a greater than two-fold increase in the risk of developing AD, and these associations were even stronger among individuals with higher baseline cognitive function. Morris and colleagues [59] relationship among 1,041 residents participating in the Chicago Health and Aging Project. Participants were aged 65 or greater and were followed for approximately 4 years. Dietary intake was assessed using self-

reported food frequency practices, indexed by the Food Frequency Questionnaire (FFQ). After controlling for demographic factors, cognitive activities, APOE-4, and other dietary factors such as vitamin E and niacin, neither self-reported B6, B12, or folate intake were predictive of incident dementia. Most recently, Luchsinger and colleagues [60] examined this association among 965 Manhattan residents, through a random sampling of Medicare recipients aged 65 years or older. Individuals with the highest intake of folate exhibited a 50% lower rate of AD compared to participants with lesser intakes. Notably, this association remained significant after controlling for total energy intake, cardiac comorbidities, and APOE-4 genotype. Interestingly, neither self-reported B6 nor B12 intake appeared to protect against the development of AD.

There have been relatively few large-scale, well-controlled RCTs examining the effects of either vitamins B6 or B12 on cognitive function, despite a large number of observational studies in which these nutrients have been examined. In a systematic review of RCTs, Balk and colleagues [61] examined the value of B6, B12, and folate supplementation on cognitive function. Fourteen trials were initially identified, reporting on data from approximately 50 different tests of cognition. Existing studies were marked by small sample sizes, heterogeneity in outcomes, and a lack of data on clinical outcomes related (e.g., conversion to dementia). Three trials of vitamin B6 and six trials of B12 were available for analysis. None of the available interventions reported cognitive benefits associated with supplementation across a variety of doses, modes of administration, and various populations and more recently published trials have reported similar findings [62]. Three trials examined the effects of folic acid, only one of which reported a benefit in cognitive function among individuals with cognitive impairment and low baseline serum folate levels. Interestingly, six trials that utilized combinations of B vitamins all concluded that the interventions had no effect on cognitive function and, among these, half reported that the placebo arm outperformed treatment participants on several cognitive tests.

Three Cochrane collaboration reports lend further credence to these findings. In one systematic literature review, Malouf and Grimley [63] examined the effects of folate supplementation with and without B12 in the maintenance of cognitive function, as well as the prevention and treatment of dementia. Eight RCTs met inclusion criteria: four among healthy, older adults and four among participants with mild to moderate cognitive impairment or dementia with or without diagnosed folate deficiency; two of these studies utilized a combination of folic acid and vitamin B12 and the majority of existing studies were successful in increasing B12 levels and in reducing homocysteine concentrations. Among healthy, older adults, there was no consistent evidence that folic acid supplementation with or without vitamin B12 improved cognitive function. The one notable exception was a decidedly positive trial by Durga and colleagues [64], which examined this relationship among otherwise healthy elderly adults with elevated homocysteine levels at enrollment. Interestingly, previous RCTs among individuals with elevated homocysteine did not demonstrate cognitive gains [65]. Similarly, the majority of extant trials among individuals with cognitive impairment have failed to demonstrate a benefit in cognitive function with supplementation. Again, a notable exception was a pilot trial among individuals with AD [66], in which folic acid supplementation of one mg/day improved overall response to cholinesterase inhibitors, resulting in cognitive gains in Instrumental Activities of Daily Living and Social Behavior indices. A separate Cochrane database review by Malouf and Areosa [67] reported similar findings in an examination of the effects of B12 on cognition, specifically. Three trials were included, all of which examined this association among individuals with cognitive impairment and low levels of serum B12. None of existing trials reported beneficial effects of B12 supplementation on cognitive function across patient groups and modes of administration.

Malouf and Grimley [68] have also examined the effects of B6 on cognitive function among both healthy, older adults as well as individuals with cognitive impairment and dementia. In their Cochrane review, Malouf and Grimley reported that few RCTs had examined the effects of B6 among older adults and that none had examined these effects among individuals with cognitive impairment. Among the two trials included in their review, neither demonstrated an effect of B6 supplementation on cognitive function. More recently, Kang and colleagues [69] examined the effects of B6, B12, and folic acid among 2,009 women aged 65 years and older with CVD or ≥ 3 cardiovascular risk factors participating in the Women's Antioxidant Cardiovascular Study. Results showed that the trial was largely ineffective in delaying cognitive decline, but that a subgroup of women with low B vitamin levels at baseline demonstrated modest cognitive benefits. Taken together, the vast majority of existing trials have failed to find a benefit of B6, B12, or folate supplementation on cognitive function.

CALORIC RESTRICTION

Recent evidence indicates that lower levels of caloric intake may be associated with improved cognitive performance and reduced rates of dementia. Although several recent examinations have been conducted in humans, this relationship has been studied extensively among animals [70]. Caloric restriction is thought to reduce cognitive dysfunction through its impact on inflammatory processes, reducing oxidative stress, increasing synaptic plasticity, and reducing beta-amyloid pathology [71]. Luchsinger and colleagues [72] examined this relationship among 980 older adults participating in the Washington Heights-Inwood Columbia Aging project. Participants completed a food frequency questionnaire and were then followed yearly to assess for new-onset dementias. Greater caloric intake was associated with a graded increase in risk of AD and this relationship was particularly strong for individuals with the APOE-4 genotype. Although greater dietary fat intake tended to be associated with increased risk of AD, this relationship did not reach statistical significance.

Willcox and colleagues [73] examined the relationship between low caloric intake and neurological function by conducting a retrospective analysis of 54 Okinawans, a population marked by 'successful' aging with a high prevalence of centenarians and low rates of dementia. Participants were recruited from the Okinawa Centenarian Study, an ongoing population-based study of Okinawas over the age of 100 that began in 1976. Archival data from annual physical examinations and dietary data were examined as predictors of current functioning. As a reference group, control participant data was selected from the NHANES I trial in order to provide a normative population reference. Relative to control participants, Okinawans exhibited dietary patterns characterized by markedly low caloric intake and, accordingly, low BMIs (e.g., values < 21 kg /m^2). Indeed, during their 30s, the average Okinawan reported a daily energy intake of 1785 kcal/day and a daily energy expenditure of 2003 kcal / day, representing a 10.9% energy *deficit*. This pattern was relatively consistent during other decades of life and the majority of Okinawans studied reported continued caloric restriction and exhibited similarly low BMIs during later life. Although this study provides ancillary data demonstrating that caloric restriction may protect against age-related decline, it should be noted that little empirical data are available from this population demonstrating a causal relationship between low caloric intake and protection against age-related decline.

Several recent RCTs have examined the effects of caloric restriction in enhancing cognitive function. Witte and colleagues [74] recently examined the effects of caloric restriction on cognitive performance among 50 healthy, elderly participants at either normal weight or mildly overweight. Participants were randomly assigned to either caloric restriction, intake of unsaturated fatty acids (UFAs), or a control condition. Following three months of

treatment, individuals in the caloric restriction group exhibited increased verbal memory scores and these improvements were correlated with decreased levels of fasting insulin and C-reactive protein. Notably, these results were strongest among participants with the best adherence. Brain derived neurotrophic factor (BDNF), a growth factor thought to mediate the effects of aerobic fitness on brain function, also was assessed in this trial, but was not altered with treatment and did not correlate with changes in cognitive performance.

Martin and colleagues [70] conducted a similar study among 48 overweight adults, aged 25 to 50 years. Participants were randomly assigned to one of four groups: caloric restriction, caloric restriction and exercise, a low-calorie diet condition, or to a control group (weight maintenance). At baseline, 3 months, and again at 6 months, cognitive tests were administered assessing verbal and visual memory, as well as concentration/attention. Overall, cognitive function changed very little across any group and no consistent pattern of change emerged. In addition, changes in cognitive performance were not related to changes in caloric intake (indexed by daily energy deficit) or weight loss.

Bryan and Tiggemann [75] conducted a quasi-randomized study of 63 overweight women participating in a 12-week dietary intervention. Participants in the treatment group undertook a 12-week, 15% fat, weight reducing diet. The diet was designed to produce a 20% energy deficit resulting in a 10–12 kg weight loss over the course of the study. Neuropsychological tests were administered before and following treatment, assessing a wide range of functions including speed of processing, executive function, working memory, and recall abilities. Psychological well-being was also assessed. Although psychological well-being improved throughout the study, only 1 of the 15 neuropsychological tests (Free Recall Intrusions) administered was significantly improved in the treatment group relative to controls, indicating that weight loss was not associated with cognitive gains.

Halyburton and colleagues [76] conducted a randomized trial among 93 overweight or obese men and women comparing the cognitive effects of a low-carbohydrate, high-fat diet (LCHF) with a conventional high-carbohydrate, low-fat (HCLF) diet. Following the 8-week intervention, LCHF participants exhibited greater weight loss relative to controls. In contrast, no treatment differences were observed on tasks of working memory, as both groups showed comparable improvements. Although speed of information processing improved among HCLF participants relative to the LCHF group, these improvements were relatively small and thus interpreted as practice effects.

OTHER DIETARY FACTORS

Emerging evidence indicates that vitamin D may also be associated with cognitive function among older adults [77–79], although relatively few studies have examined this relationship comparable to the other dietary components reviewed here [80]. Despite the limited empirical evidence for this relationship, there are many plausible mechanisms through which greater vitamin D levels would be associated with neuroprotection, including neuronal protection, calcium regulation, reduced cerebrovascular burden, and the presence of vitamin D receptors in important brain areas including the hippocampal and thalamic regions [81]. Despite these encouraging findings, a recent systematic review found that the evidence for an association between vitamin D and cognitive function was inconclusive as few studies had examined this relationship, studies exploring this relationship were mostly cross-sectional and of limited quality, and even those cross-sectional studies examining this relationship reported conflicting findings [80].

In contrast to the limited available evidence linking vitamin D to cognitive function in later life, the relationship between alcohol consumption and neuroprotection has been studied

extensively [82–84]. Regular, modest alcohol intake has been prospectively associated with reduced rates of AD and unspecified dementia, although interestingly it does not appear to protect against cognitive decline [83–84]. Recent observational studies have extended these findings, demonstrating the moderate alcohol consumption slows the progression of dementia among individuals with MCI [85]. The effect of alcohol on VaD has been less conclusive, with one meta-analysis showing a protective but statistically non-significant relationship [84] and a more recent meta-analysis of prospective studies reporting a 25% reduced rate of VaD for light to moderate drinkers compared to non-drinkers [83]. Comparably, the protective effect of alcohol on AD in recent meta-analyses has been reported as ranging from 28% [83] to 43% [84] depending on the inclusion criteria used. Despite these positive findings and plausible physiological mechanisms , the available evidence must be interpreted cautiously due to potential sampling bias and differences across observational studies [82, 86, 87].

METHODOLOGICAL CONSIDERATIONS

Despite the consistent findings from observational studies, RCTs attempting to alter and/or enhance the dietary patterns of older adults have generally reported equivocal findings. As discussed in detail elsewhere [88, 89], the discrepant pattern of findings may result from methodological issues making it difficult to study the development of dementia in t.he context of a randomized trial. Primarily among these are discrepancies in length of follow-up time, enrollment criteria, assessment of dietary intake, and control of confounding variables. Randomized trials examining the relationship between dietary intake and dementia have varied widely in length of follow-up assessments. Due to the insidious nature of dementia progression and variations in the age of participants at study entry, it is possible that many trials have been limited in their ability to detect associations due to a small number of patients who developed dementia during the course of the study's follow-up period. For example, trials have varied in length of follow-up from one month to nine years and the majority of RCTs have used age, not cognitive dysfunction, as a primary criterion for enrollment [89]. Similarly, the majority of extant RCTs have not selected participants based on diet-related criteria (e.g. homocysteinemia, low vitamin B12 levels, etc.). It is plausible that those participants with deficient diets may be the most likely to benefit from dietary modification [65].

In addition to issues related to study design, measurement of dietary adherence and control of confounding variables may also contribute to the present pattern of findings. Observational studies and RCTs may differ in the frequency and manner in which they assess dietary intake and, more importantly, change in dietary intake over time. Although the different methodological considerations and implications for studying diet and energy intake (e.g. food frequency questionnaire, diet diaries, blood assays, etc.) are beyond the scope of the current review, it is likely that variations in dietary assessment are a partial contributor to the discrepant pattern of observed findings [90]. Similarly, many RCTs have been designed to examine the effects of modifying one component or nutrient instead of examining changes in dietary patterns (e.g. vitamin C *vs.* fruit consumption). Although this technique is helpful in isolating the contribution of specific nutrients, studies are increasingly showing that both the nutrient and form of nutrient consumption are important elements to study and may produce different results [44, 45]. Finally, studies have differed widely in their control of confounding variables, particularly with regard to diet. It is possible that dietary intake of various nutrients may have a moderating or synergistic effect on cognitive function, whereas virtually all studies to data have examined dietary intake as a linear predictor of dementia incidence. Similarly, studies have differed in their control for physical activity and cardiovascular risk factors, despite the importance of both factors as predictors of dementia outcomes [91–93].

SUMMARY AND FUTURE RESEARCH DIRECTIONS

Despite numerous prospective and interventional trials, the role of dietary modification in improving cognitive performance remains unclear. Although the vast majority of observational studies have demonstrated protective effects of healthier diets and dietary supplementation, randomized controlled trials have yielded consistently weak or negative findings. As reviewed in detail elsewhere [29], an examination of the current literature is somewhat confounded by differences in the analytical approach taken across studies. Existing studies have varied widely in their attempts to control potential confounders such as body mass index (BMI), dietary factors that were not of primary interest (e.g. total caloric intake), educational level, and baseline cardiovascular health. Furthermore, studies have varied markedly in their attempts to adequately control for the presence of susceptibility factors in their cohorts, such as differences in gender and genotype (e.g. APOE-4).

Finally, few studies have provided evidence of potential mechanisms linking improved diet and cognitive performance. Elucidation of treatment mediators will help clarify intervention targets and design elements, which may provide greater clarity of these effects. To this end, future studies would benefit from assessments more specific to cerebral health, such as structural MRI or diffusion tensor imaging (DTI). In addition, future studies would benefit from careful control of other dietary components, physical activity, and specific health indices in order to better understand the contributions of these potentially confounding variables.

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ABBRIVIATIONS

ALA	α-linolenic acid
AD	Alzheimer’s disease
CVRF	cerebrovascular risk factors
DHA	docosahexaenoic acid
EPA	eicosapentaenoic fatty acid
MCI	mild cognitive impairment
MMSE	Mini Mental Status Exam
MUFA	monounsaturated fatty acid
PUFA	polyunsaturated fatty acid
RCT	randomized controlled trial
VaD	vascular dementia
FFQ	Food Frequency Questionnaire

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Table 1

Randomized Controlled Trials of Dietary Interventions and their Effects on Cognitive Function

First Author	Year	Sample	Dietary Component	Length of Follow-up	Conclusions
Yehuda	1996	100 adults with probable AD	n-3 and n-6 fatty acids	4 weeks	Modest improvement in short-term memory and quality of life
Chiu	2008	46 adults with MCI or AD	n-3 fatty acids	24 weeks	Improvement in clinician rating of cognitive function
Terano	1999	20 elderly adults with VaD	DHA supplementation	1 year	Modest improvement in MMSE and Hasegawa's dementia rating scale after 6 months, but no group differences after 1 year
van de Rest	2008	321 healthy adults ≥ 65 years of age	EPA + DHA	26 weeks	No group differences
Freund-Levi	2006	204 adults with AD	n-3 fatty acids	6 months	No group differences with only modest improvements among a subgroup of mildly impaired patients
Sano	1997	341 patients with moderate AD	Selegiline or alpha-tocopherol (vitamin e)	2 years	Slowed rates of cognitive decline in treatment group relative to placebo
Petersen	2005	769 patients with MCI	Vitamin E supplements or Donepezil	3 years	Both treatments showed slower rates of conversion to AD during the first year and this effect was most pronounced among individuals with the APOE-4 genotype. No group differences after 3 years
Balk	2007	Meta-analysis of 14 RCTs	B6, B12, and Folate	Range: 5 weeks – 1 year	Equivocal findings across a range of doses and administrations
Malouf & Grimley	2008	Meta-analysis of 8 RCTs	Folate supplementation with and without B12	Range: 2–3 years	No evidence that increasing folate and B12 levels improves cognitive function
Malouf & Areosa	2003	Meta-analysis of 3 RCTs	B12	Range: 3 months – 1 year	No evidence that increasing B12 improves cognitive function
Malouf & Grimley	2003	Meta-analysis of 2 RCTs	B6	Range: 12 weeks – 1 year	No evidence that increasing B6 levels improves cognitive function
Kang	2008	2,009 women > 65 years of age with cardiac disease	B6, B12, and folic acid	5.5 years	No overall group difference. Subgroup analyses showed that women with low B vitamin levels exhibited preserved cognitive function relative to controls
Witte	2009	50 normal or overweight, older adults	Caloric restriction or unsaturated fatty acids	3 months	Caloric restriction increased verbal memory and these improvements were correlated with decreased levels of fasting insulin and C-reactive protein
Martin	2007	48 overweight adults, aged 25 – 50 years	Caloric restriction with or without exercise and a low-calorie diet	6 months	No change in cognitive function
Halyburton	2007	93 overweight or obese adults	Low-carbohydrate, high-fat diet	8 weeks	No clinically significant change in cognitive function

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