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Dietary Factors and Cognitive Decline

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Abstract

Cognitive decline is an increasingly important public health problem, with more than 100 million adults worldwide projected to develop dementia by 2050. Accordingly, there has been an increased interest in preventive strategies that diminish this risk. It has been recognized that lifestyle factors including dietary patterns, may be important in the prevention of cognitive decline and dementia in later life. Several dietary components have been examined, including antioxidants, fatty acids, and B vitamins. In addition, whole dietary eating plans, including the Mediterranean diet (MeDi), and the Dietary Approaches to Stop Hypertension (DASH) diet, with and without weight loss, have become areas of increasing interest. Although prospective epidemiological studies have observed that antioxidants, fatty acids, and B vitamins are associated with better cognitive functioning, randomized clinical trials have generally failed to confirm the value of any specific dietary component in improving neurocognition. Several randomized trials have examined the impact of changing 'whole' diets on cognitive outcomes. The MeDi and DASH diets offer promising preliminary results, but data are limited and more research in this area is needed.

Keywords

Dietary patterns; nutrition; cognitive function; dementia

Background

Epidemiology of Cognitive Impairment

Cognitive impairment is an increasingly pressing public health problem worldwide (1). The World Health Organization has estimated that 35.6 million individuals worldwide had dementia in 2011 and that the prevalence of dementia will double every 20 years, corresponding to an alarming 65.7 million individuals living with dementia in 2030 and 115.4 million adults worldwide by 2050 (2, 3). In addition, the public health cost of dementia is staggering, with an estimated $604 billion dollars spent on dementia care in 2010 (4). In addition to prevalence and significant public health impact of dementia, an additional 5.4 million individuals have cognitive impairment that does not reach the threshold for dementia (e.g., cognitive impairment, no dementia [CIND] and mild cognitive

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impairment [MCI]) (5). Taken together, cognitive impairment is becoming increasingly common as the population in the United States ages and represents a significant public health problem.

Lifestyle modification as a means of protecting against cognitive decline has only recently been embraced as a possible, alternative strategy to reduce the incidence of cognitive decline (6). Due to increasing epidemiological(7-10) and experimental evidence linking lifestyle factors to preservation of cognitive function, recent conference and consensus reports have emphasized the importance of dietary factors (reduced intake of saturated and trans fats, increased vegetable and fruit consumption, and dietary intake of vitamins E and B12)(11) and regular exercise (40 minutes of brisk walking 3 times per week), as public health recommendations to reduce the risk of Alzheimer's Disease (AD) (6, 11). Lifestyle interventions have tended to focus on the impact of aerobic exercise, although recent studies have also suggested that dietary patterns may play an important role (12).

Methodological Considerations

As noted below, methodological differences appear to have an important role in understanding the impact of dietary intake on cognitive function. The most important methodological difference is observational vs. interventional methodologies: although observational studies have tended to support a relationship between greater intake of various nutritional components, interventional studies have generally reported equivocal findings. It is also worth noting that assessments of dietary intake and cognitive function have also varied significantly across studies, which may impact the overall pattern of findings.

Definitions of Cognitive Decline, Cognitive Impairment, and Dementia

Studies included in the present review have used varying definitions of dementia, cognitive impairment, and cognitive decline. Cognitive decline represents a ‘significant’ change in cognitive performance from a premorbid, baseline level (13-16). Cognitive impairment typically refers to one of a number of different clinical conditions specified by consensus statements and is typically diagnosed based on clinical criteria (cognitive performance, clinician interview, and/or neuroimaging), including mild cognitive impairment (MCI: cognitive deficits that do not reach dementia severity and preserved activities of daily living) (17), vascular dementia (VaD)(18), and AD (19). In addition to the above, categorical definitions of cognitive function, many studies have used a continuous measure of cognitive performance within various cognitive domains, including memory, attention, processing speed, visuospatial performance, and executive functioning, although memory and executive function are more often used as the primary cognitive outcome measures (20).

Methods for Assessing Dietary Habits

Several different assessment methods have been used to quantify patterns of dietary habits. These methods have primarily been self-report measures, such as food frequency questionnaires and diaries, although serum biomarkers have also been used in a handful of studies (21, 22). Food frequency questionnaires (FFQs) are one of the most commonly used methods to assess the relationship between dietary patterns and medical outcomes (23).

Multiple FFQs are available, including the Willett FFQ developed at Harvard (24) and the Block FFQ(25). FFQs are typically structured such that the participants 'typical' dietary patterns are measured over the course of a period of several months to a year. The primary advantage of FFQs over dietary diaries is that they provide a measure of dietary intake over a longer period of time, although these instruments also rely heavily on patient recall and may therefore be subject to recall biases (26), which is particularly important in the study of cognitive function (27). Diet diaries are used to provide a more comprehensive, if more time-limited, assessment of dietary intake and are considered by some to be the 'gold standard' of assessment of dietary patterns (28, 29), despite known limitations (30-34). Participants are typically required to record everything they eat over a period of several days, typically including both weekdays and weekend days; sometimes the 'most representative' days are selected for analysis. The primary advantages of diet diaries are that they provide a comprehensive assessment of dietary intake and, when completed properly, are less vulnerable to recall biases (35, 36). The primary limitation of these techniques is that they only provide an assessment of dietary intake over a period of a few days and the diet may be affected by the increased awareness of food consumption and may therefore not be representative of regular dietary habits (34).

Although less commonly used, biomarkers provide a somewhat more objective measure of actual serum nutrient composition, providing a quantification of the amount of B vitamins, antioxidants, and fatty acids, among others from plasma samples. However, biochemical markers are also biased by individual differences in metabolism and absorption levels, and can also be affected by illnesses, medications, and genetic factors. Nevertheless, several studies have used these measures to examine the relationship between objective markers of nutrient intake and cognitive outcomes (37, 38). The primary advantage of biomarkers is their objective assessment of nutrient composition presumed to have been consumed, although these results may only reflect dietary intake at a particular time point and may be cumbersome, expensive, or infeasible in some epidemiological studies.

Dietary Components and Neurocognition

B Vitamins and Folate

Observational Studies—The relationship between folic acid (B9), pyridoxine (B6), and cobalamin (B12) has been the subject of extensive study, with multiple epidemiological studies demonstrating that individuals with higher blood levels of these nutrients demonstrating a lower likelihood of cognitive decline (39-47). B vitamins and folate are thought to exert a beneficial effect on cognition through metabolism of homocysteine (48), a protein that has been associated with greater cardiovascular risk and cognitive impairment. The relationship between poor nutritional status and cognitive decline was first described by Goodwin and colleagues (49), who noted that individuals with low levels of vitamins C and B12 scored more poorly on the Wechsler Memory Test. Following this initial publication, multiple epidemiological studies have reported a relationship between higher levels of B vitamins and folate and lower rates of incident dementia. Among older adults participating in the Kungsholmen longitudinal study in Sweden who were not being treated with B vitamin supplementation (50), those with low levels of both B12 and folate were more than

twice as likely to develop dementia over a three-year follow-up and this relationship was even stronger in sub-analyses among individuals with higher baseline cognitive function. Similar results were reported in a sample of older adults living in Manhattan (51): individuals in the highest quartile of folate intake were 50% less likely to develop AD over a six year follow-up and these results remained significant after controlling for total energy intake, cardiac disease, and APOE genotype. Not all epidemiological studies have reported similar findings, however: Morris and colleagues failed to find an association between B-6, B-12, and incident Alzheimer's disease in more than 1,000 older adults participating in the Chicago Health and Aging Project (CHAP) (52).

Interventional Studies—Despite the encouraging findings of prospective studies, randomized trials have generally failed to replicate these positive findings. Multiple randomized trials have been conducted and several associated meta-analyses have also examined these findings (40-42). A recent meta-analytic review found no improvement following treatment with folic acid, with or without B vitamins, on cognitive function within four different domains of performance (memory, language, speed, and executive function) (53). In a systematic review of randomized controlled trials (RCT), Balk and colleagues (54) noted that existing trials have generally been small and have included heterogeneous outcome measures with few clinically validated outcomes. After identifying 14 trials, three trials of vitamin B6 and six trials of B12 were found to be acceptable for analysis. None of the available interventions reported cognitive benefits associated with supplementation across a variety of doses, modes of administration, and populations. 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, all six trials that utilized various combinations of B vitamins concluded that the interventions had no impact 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 a systematic literature review, Malouf and Grimley (42) 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 boosting B12 levels and, accordingly, reducing homocysteine concentrations. Among healthy, older adults, there was no consistent evidence that folic acid supplementation with or without vitamin B12 improved cognitive function. A separate Cochrane database review conducted by Malouf and Sastre (41) 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 (40) 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, the authors 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 (55) examined the effects of B6, B12, and folic acid among 2,009 women aged 65 years and older with cerebrovascular disease (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.

Several individual trials warrant comment. In a 2-year randomized trial of folic acid, vitamin B-12, and physical activity, folic acid supplementation was associated with improvements in the Telephone Interview for Cognitive Status-Modified (TICS-M) (56). In a randomized trial of 271 older adults with MCI (168 of whom had magnetic resonance imaging assessments), treatment with high dose folic acid, B12, and B6 was associated with lower brain atrophy following two years of treatment (57). A three-year RCT among individuals with elevated homocysteine conducted in the Netherlands also reported positive findings. Participants randomized to receive folic acid showed improvements in memory, information processing speed, and sensorimotor speed compared with placebo (58). However, not all trials among individuals with elevated homocysteine have reported positive findings(59). In addition, two pilot studies among individuals with cognitive impairment have reported positive findings. Among individuals with AD, folic acid supplementation improved response to cholinesterase inhibitors and was associated with cognitive gains in instrumental activities of daily living and social behavior (60). Similarly, a small pilot study of 12 patients with mild-to-moderate AD showed cognitive gains following nine months of supplementation (61). Taken together, existing evidence linking folate and B vitamin supplementation with cognitive benefits is mixed. Although there is weak evidence that supplementation may be beneficial among individuals with pre-existing cognitive impairment or elevated homocysteine, these results have not been consistent.

Fatty Acids

Observational Studies—Dietary fatty acids are classified by two general subtypes: saturated fatty acids and unsaturated fatty acids. Among these subtypes, unsaturated fatty acids may be further divided into monounsaturated (MUFAs) and polyunsaturated fatty acids (PUFAs). Saturated fatty acids are derived primarily from meat and dairy products, as well as other dietary sources utilizing animal fats. 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 (62). n-3 PUFAs are primarily derived from fish and marine sources and consist of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α-linoleic acid (ALA), among others. In contrast, n-6 PUFAs are primarily derived from legumes, nuts, and other plant-based sources and consist of linolenic acid and arachidonic acid, among others.

n-3 fatty acids may be associated with lower incidence of cognitive impairment through their direct influence on neuronal membrane integrity. The brain is enriched in DHA, which

accounts for about eight percent of its dry weight (63), and DHA, a long-chain n-3, helps support both structural integrity and functionality of neurons. Cross-sectional studies have linked greater intake of n-3 fatty acids to greater total brain volume (64) and lower prevalence of white matter hyperintensities (38). Evidence from animal models also suggests that greater n-3 intake may impact cognitive decline by lessening the impact on amyloid deposition within the brain (65). In addition, n-3 consumption is known to reduce the impact cardiovascular morbidity (66, 67) and inflammation (68-71), although not all existing evidence supports this hypothesis (72).

Multiple prospective studies have examined the relative intake of these dietary components and subsequent cognitive dysfunction (69, 73). 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. Results have also been relatively consistent across outcomes, with studies examining changes in cognitive function reporting similar findings to those studies examining the incidence of MCI, VaD, AD, and other types of dementia.

Two of the largest studies to examine this relationship come from the Cognitive Health and Aging Project (74) and the Atherosclerosis Risk in Communities project (ARIC)(67). Morris and colleagues (74) 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. Individuals in this trial did not have a history of stroke, heart disease, or diabetes at baseline. Examination of 6-year changes in cognitive function indicated that higher dietary intake of saturated or trans-unsaturated fats or low nonhydrogenated unsaturated fats was associated with a greater incidence of cognitive decline. Beydoun and colleagues (67) conducted an analysis of ARIC in which 2,251 patients who were either hypertensive or dyslipidemic were analyzed as an at-risk group 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 addition to the existing relationship with cognitive decline, higher PUFA intake appears to be linked with lower incidence of clinician-diagnosed dementia. Modest dietary fat intake and greater fish consumption were both associated with reduced rates of dementia in a sample of 5,386 individuals participating in the Rotterdam study (75). During a two-year follow-up, the authors found that greater dietary intake of total fat, saturated fat, and cholesterol were all 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 and appeared to be most strongly protective against the development of AD. A protective effect of fish consumption on the development of AD was also reported in the PAQUID (Personnes Agees QUID) cohort study (76) and in the Chicago Health and Aging project (77, 78). Solfrizzi and colleagues (79) 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 (80), 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. These discrepant findings have yet to be reconciled.

Interventional Studies—Despite the encouraging findings from observational data and small pilot trials (81-83), large, well-controlled randomized trials have generally failed to find significant benefits (84). In a randomized, double-blind, placebo-controlled trial, van de Rest and colleagues (85) 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 and 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 (86) 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. Recently a Cochrane analysis was conducted to examine the impact of omega-3 interventions on cognitive function (84). Following a literature review, the author identified three randomized trials for inclusion (87-89) incorporating data from 4,080 individuals. Results showed no differences in cognitive outcomes between treated and control participants when results were combined across the three trials.

Antioxidants

Observational Studies—Antioxidants, including vitamins A, C, and E, are found naturally in many fruits, vegetables, and berries, and also can be taken as supplements. Initial interest in the role of antioxidants in cognitive decline was generated from observational studies demonstrating that greater intake of fruits and vegetables were shown to be associated with better cognitive function and lower risk of cerebrovascular events (90, 91). 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(92). Oxidative stress has been implicated as one of the primary mechanisms of age-related neuronal decline (93, 94). Perhaps not

surprisingly, greater intake of fruits and vegetables has been linked to lower rates of cognitive decline and dementia in multiple prospective studies, including the Chicago Health and Aging study, and this effect appears to be independent of cardiovascular comorbidities (95). Greater vitamin E intake was associated with better cognitive function in the same cohort (96) over an 18-month follow-up, and results suggested 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. Supplementation with either vitamin C or E also appears to be related to reduced risk of cognitive decline (97). In a sample 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.

Several studies have reported protective effects of vitamins C and E on the development of AD, including a study of 5,395 individuals participating in the Rotterdam study (98). Among adults 55 years of age or older, higher intake of vitamins C and E were associated with dose-dependent reductions in risk for AD over a 6-year follow-up, 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. Finally, higher intake of flavonoids, phenolic compounds found in red wine and berries, have been associated with reduced rates of cognitive decline (99) and dementia (100) in several longitudinal studies.

Interventional Studies—Several RCTs have investigated the effects of Vitamin E and/or C supplementation in the prevention of cognitive decline (101, 102). In one of the most comprehensive review of these trials to date, Isaac and colleagues (101) 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 (103) and the other among individuals with MCI (104). In their study of 341 patients with AD of moderate severity, Sano and colleague s (104) examined the effects of selegiline, alpha-tocopherol, or placebo in slowing the progression of AD over a two-year period. Although the study's primary outcome was the effects of medication on a composite end-point of death, institutionalization, or loss of activities of daily living, the authors found in secondary analyses that individuals randomized to receive either selegeline or alpha-tocopherol were less likely to be institutionalized during follow-up. In their study of 769 individuals with MCI, Peterson and

colleagues (105) 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. At least one study has suggested that treatment responsiveness may be a critical factor impacting AD outcomes in these trials. Lloret and colleagues (106) found that patients who responded to vitamin E treatment with reduced oxidative stress were less likely to develop AD(106). However, among individuals who did no experience a decrease in oxidative stress, cognitive function actually appeared to worsen relative to placebo controls, suggesting that patients' response to treatment is an important factor impacting the impact of antioxidants on treatment outcomes. Finally, a recent Cochrane review suggested that progression of MCI to AD was not significantly impacted by vitamin E treatment (102). Taken together, results from the extant literature are mixed and do not provide compelling evidence for a beneficial effect of antioxidants on cognitive decline.

Observational Studies of Non-specific Diets: Analysis of Dietary Components

Several studies have examined multiple dietary patterns within a single sample by clustering various components of participants' diets using principal components analysis. In contrast to many of the other studies cited above, these studies have simultaneously examined multiple dietary patterns without an a priori focus. In a study of older adults living in New York, a dietary pattern comprised of higher levels of n-3 and n-6 fatty acids, vitamin E, and folate, and lower levels of saturated fatty acids and B12 was associated with reduced risk of developing AD over a four-year follow-up (107). Individuals in the highest tertile of this dietary pattern were 38% less likely to develop AD compared with those in the lowest tertile. Another study of nutrient biomarkers examined the relationship between nutrient content from plasma samples and their association with brain imaging markers (38). In this study of 104 older adults (mean age 87 years), several nutrient patterns emerged and were found to be associated with both cognitive performance and neuroimaging markers of brain health. Nutrient patterns consisting of high levels of B vitamins, vitamins C, D, and E was associated with greater brain volume and cognitive performance within several domains, whereas dietary patterns consisting of higher levels of n-3 fatty acids were associated with lesser white matter hyperintensities and better executive function. A third pattern consisting of high levels of trans fatty acids was associated with lower total brain volume and also with worse cognitive performance across several domains.

Whole diet Eating Plans and Neurocognition

In contrast to the impact of specific nutrients, more general patterns of dietary intake emphasize the overall consumption of various dietary practices. The primary advantage of examining dietary eating plans compared to specific nutrients is that it allows for an examination of the ‘food matrix’ effect on biological systems, which includes additive, synergistic, and antagonist effects (108, 109). This approach may be particularly important in the study of cognitive decline, which is likely influenced by multiple factors (110). The primary limitations of studying patterns of dietary behavior are that the potential influence

of individual nutrients might be obscured and the quantification of these scores is often sample-dependent. For example, the MeDi score, which is the most commonly used metric for the Mediterranean diet, is based on a sum of sex-specific medians of a population, in which a score of one is given if an individual is above the median for 'beneficial' components of MeDi (e.g. fruits, vegetables, whole grains, etc.) and a score of 0 is given when an individual falls below the median. Not only can two individuals with the same MeDi score have vastly different diets, but the scores may be different when derived from two different samples (108).

Several dietary patterns have been examined as they relate to cognitive decline, principally among them the Mediterranean Diet (MeDi) and the Dietary Approaches to Stop Hypertension Diet (DASH) eating plan. Other studies have examined the Alternative Healthy Eating Index (111), the Healthy Diet Indicato r(112), the Healthy Eating Index and the Canadian Healthy Eating Indices (113), the French National Nutrition and Health Programme Guideline Score (114), the Comprehensive Healthy Dietary Pattern(115), and the Recommended Food Score (116).

Mediterranean Diet (MeDi)

Observational Studies—The Mediterranean diet has received substantial attention due to its focus on fish intake, vegetables, legumes, fruits, cereals, and unsaturated fatty acids (117, 118). 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. Multiple prospective studies have shown that individuals with more Mediterranean diets are less likely to experience cognitive decline or develop dementia (118). Both the Mediterranean and DASH diets, discussed below, are believed to impact cognitive function indirectly through reducing CVD risk factors. The Mediterranean and DASH diets are known to have a beneficial effect on CVD health (119, 120) and there is substantial evidence that increasing CVD risk factors are associated with greater risk of cognitive impairment (121-124). For example, reducing lipid levels has been shown to reduce the incidence of stroke and VaD (125) and insulin resistance has been implicated in the pathogenesis of AD (126).

In a study of 2,258 community-dwelling, non-demented New Yorkers (118), adherence to the Mediterranean diet was associated with lower likelihood of developing AD over an approximate four-year follow-up. 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. These results were unchanged in a subsequent study among the same cohort after controlling for measures of vascular functioning, leading the authors to conclude that the observed relationship between dietary fat and AD is not mediated by vascular health (117). Similar results were reported by the same group in examining the relationship between MeDi and the development of MCI: greater adherence was associated with dose-response protection against incident MCI, with an 8% reduction in risk of MCI for every one-unit increase in the MeDi score (127). Greater MeDi adherence has also been associated with lesser cognitive decline in several epidemiological studies (113, 127) as well as lower risk of cognitive impairment in the REGARDS cohort study, particularly among individuals with diabetes (128). Although the precise mechanisms linking the MeDi to

reduced cognitive impairment are still being explored, at least two studies have demonstrated that greater MeDi adherence is associated with preserved cortical thickness (129) and a lower incidence of MRI infarcts. A recent meta-analysis combining results across five studies found that higher adherence to the MeDi diet (highest tertile) was associated with a 27% reduced risk of MCI and a 36% reduced risk of AD among cognitively normal adults (131).

Interventional Studies—Despite the encouraging findings from observational studies, only one RCT has examined the effects of the MeDi on cognitive performance. In the recently completed PREMEDI trial (120), 522 adults with elevated risk of CVD were randomized to receive a MeDi diet supplemented with extra-virgin olive oil, a MeDi diet supplemented with mixed nuts, or a control diet. The primary endpoint in this RCT was major cardiovascular events and the trial was stopped early after a median follow-up of 4.8 years. Results showed that both the MeDi intervention arms had reduced rates of cardiovascular endpoints, particularly stroke, in comparison with the control arm. In addition to improving CVD outcomes, the MeDi interventions improved global cognitive performance as indexed by performance on the Clock Drawing Test and the MMSE (132). At least one other ongoing study is expected to examine the relationship between MeDi and neurocognition (133).

Dietary Approaches to Stop Hypertension (DASH)

Observational Studies—The Dietary Approaches to Stop Hypertension (DASH) eating plan is similar to the MeDi diet in its emphasis on greater intake of fruits, vegetables, and whole grains. Similar to the MeDi, the DASH diet emphasizes consumption of low-fat dairy products, modest meat consumption, and modest alcohol consumption, although the DASH diet also emphasizes low sodium intake. The DASH diet was originally designed to reduce high blood pressure and its effectiveness has been demonstrated in several randomized trials in both ‘feeding studies’ (134, 135) and in free-living individuals (119). Greater DASH adherence has also been associated with greater blood pressure reductions (136) and reduced risk of stroke (137). Preliminary evidence suggests that, like the MeDi, individuals who are more adherent to a DASH-style diet have a lower incidence of cognitive decline. For example, DASH diet adherence was also associated with lower rates of cognitive decline among older adults participating in the Memory and Aging Project during a 4-year follow-up (138).

Interventional Studies—To knowledge, only the ENCORE study (119) has examined the effects of the DASH diet, alone and combined with exercise and caloric restriction, on neurocognition in overweight adults with high blood pressure. In this trial, 144 middle-aged, overweight or obese adults with high blood pressure were randomly assigned to one of three conditions for four months: the Dietary Approaches to Stop Hypertension (DASH) diet alone (DASH-A), the DASH diet in combination with a weight management intervention (DASH+WM), in which participants exercised regularly and reduced their caloric intake, or a Usual diet control group in which participants maintained their usual dietary habits and did not exercise or lose weight. The primary findings from the trial were that the DASH+WM and DASH-A groups showed significant reductions in blood pressure compared to controls,

while the DASH+WM group also showed reductions in bodyweight and improvements in other markers of cardiovascular health including LVH, arterial stiffness, and insulin resistance (119, 139). In addition to measuring CVD health, participants completed a battery of cognitive tests assessing executive function, memory, learning, and psychomotor speed. Following the four-month intervention, individuals in the DASH-A group showed improvements in psychomotor speed compared with controls, while individuals in the DASH+WM group showed improvements in both psychomotor speed and a composite measure of executive function, learning, and memory (140). These improvements appeared to be greatest among individuals with greater levels of intima medial thickness, a surrogate marker of atherosclerosis, and were associated with improvements in fitness and weight loss.

Several ongoing studies are examining the effects of dietary factors on neurocognition. The ENLIGHTEN trial is an ongoing randomized trial examining the effects of the DASH diet and/or aerobic exercise on cognitive function among individuals with vascular CIND (141). In this trial, patients with vascular CIND will be randomized to receive supervised aerobic exercise, the DASH diet, a combined exercise and DASH intervention, or a health education condition for six months. Cognitive function, CVD risk factors, aerobic fitness, and dietary composition will be assessed before and after the intervention to examine mediators of any treatment improvements.

Caloric Restriction

Observational Studies—Accumulating evidence over the past two decades, particularly in animal models, suggests that lower caloric intake may be associated with reduced risk of cognitive decline (142, 143), although emerging evidence in humans suggests that caloric restriction and weight loss may be associated with improved cognitive function (144). Only a handful of studies in humans have been conducted in humans, although preliminary evidence suggests that caloric restriction confers cognitive benefits (145). For example, a prospective study of nearly 1,000 older adults in the United States found that greater caloric intake was associated with increased risk of AD and that this relationship was stronger among individuals with APOE-4 genotype (146). In addition, observational studies of Okinawan adults, the longest living population on the planet, has demonstrated through archival data that Okinawan centenarians have markedly reduced caloric intakes relative to a normative sample selected from the NHANES I study (147).

Interventional Studies—Several RCTs have examined the impact of caloric restriction on cognitive function, with varying results (145, 148-150). In one study, a three-month caloric restriction intervention improved memory performance among fifty healthy, elderly adults who were either normal weight or overweight. Following three months of treatment, individuals randomized to the caloric restriction group showed improvements in verbal memory performance. In addition, these improvements were associated with decreased levels of fasting insulin and C-reactive protein and were strongest among participants with the best adherence. Finally, in the ENCORE randomized trial mentioned above, participants in the exercise and DASH group, who were also asked to reduce their caloric restriction, showed the greatest cognitive benefits (140). Despite these positive findings, three other

trials examining caloric restriction failed to find significant effects, which may partly due to the younger age of participants in these trials (148-150). Several ongoing trials are examining the impact of caloric restriction on cognitive performance among individuals with MCI (151, 152).

Summary and Future Directions

Existing evidence from observational studies suggests that dietary factors including antioxidants, fatty acids, folate, and B vitamins are associated with lower incidence of cognitive decline, stroke, and dementia in the majority of observational studies. However, despite a wealth of data from prospective studies, few interventions have reported positive effects of nutritional supplementation on cognitive outcomes. In contrast to intake of specific nutrients, emerging evidence suggests that dietary patterns may be important for cognitive health (108, 109, 153). Observational studies have noted that the MeDi and DASH diets are associated with lower rates of dementia, and recent interventional trials have suggested that the DASH diet and weight loss (i.e., caloric restriction) may improve cognitive functioning. Several ongoing RCTs are investigating the effects of diet on neurocognition, including healthy older adults and older adults vulnerable to developing dementia (141, 154).

Future studies would benefit from more comprehensive examination of multiple dietary factors concurrently, as well as additional lifestyle factors known to be associated with dietary behavior and cognitive function, such as physical activity (155-158) and intellectual engagement (159, 160). Indeed, few studies have examined these interrelated behavioral factors concurrently, and those that have generally have reported independent associations between dietary factors and other lifestyle indices as they relate to risk of cognitive impairment (158, 161). It will also be important to gain a better understanding of the mechanisms underlying the relationship between nutritional intake and cognitive outcomes from human studies: although multiple causal factors have been hypothesized, including neuroinflammatory pathways (162), reductions in CVD risk factors (121, 141), alterations in cerebrovascular structure (130) and reserve functioning (163-165), and neuroprotection secondary to reductions in homocysteine (57), strikingly few studies have examined these relationships in the context of a randomized trial. Future randomized trials would benefit from multicomponent dietary change, such as that observed with the DASH and MeDi diets, so that the relationship between alterations in dietary intake of various nutrients and cognitive outcomes can be assessed concurrently. Additional mechanistic studies in humans are also needed to better understand the relationship between dietary intake and underlying changes in vascular mediators. Future observational studies would benefit from the adoption of uniform standards for the assessment of both dietary intake and cognitive outcomes, in order to facilitate better interpretation of these relationships across studies. This is particularly important for the adoption of dietary biomarkers that could be used to inform future prevention trials among individuals at risk for cognitive decline (166).

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