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Nutritional prevention of cognitive decline and dementia

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Summary. Cognitive impairment results from a complex interplay of many factors. The most important independent predictor of cognitive decline is age but other contributing factors include demographic, genetic, socio-economic, and environmental parameters, including nutrition. The number of persons with cognitive decline and dementia will increase in the next decades in parallel with aging of the world population. Effective pharmaceutical treatments for age-related cognitive decline are lacking, emphasizing the importance of prevention strategies. There is extensive evidence supporting a relationship between diet and cognitive functions. Thus, nutritional approaches to prevent or slow cognitive decline could have a remarkable public health impact. Several dietary components and supplements have been examined in relation to their association with the development of cognitive decline. A number of studies have examined the role of dietary patterns on late-life cognition, with accumulating evidence that combinations of foods and nutrients may act synergistically to provide stronger benefit than those conferred by individual dietary components. Higher adherence to the Mediterranean dietary pattern has been associated with decreased cognitive decline and incident AD. Another dietary pattern with neuroprotective actions is the Dietary Approach to Stop Hypertension (DASH). The combination of these two dietary patterns has been associated with slower rates of cognitive decline and significant reduction in incident AD. This review evaluates the evidence for the effects of some dietary components, supplements, and dietary patterns as neuroprotective, with potential to delay cognitive decline and the onset of dementia. (www.actabiomedica.it)

Key words: Alzheimer, cognitive decline, aging, diet, nutrition, inflammation, oxidative stress

Introduction

Aging of the world population is an undeniable contemporary reality. The recently published World Report on Aging and Health (1) asserts that, for the first time in the history of mankind, most people around the world can expect to live over 60 years. Biodemographic data suggest that half of the children alive in 2010 in countries with the highest life expectancies may reach the age of 100 years (2). The dark side of this successful story is that the number of persons with cognitive decline will increase exponentially in the coming decades (3, 4) in parallel with aging of the world population. This implies remarkable finance and human burden because dementia is one of the greatest causes of disability (4). Worldwide, 47 million persons are currently affected by dementia with about 8 million newly diagnosed cases annually. Most of them, 60-75%, have Alzheimer's disease (AD), followed by vascular and Lewy bodies dementia (3, 4). Even if the general care of people with dementia has improved, the availability of effective interventions to significantly modify the disease is still lacking (5). Even if cognitive decline occur generally in old age, the causal brain pathology develops years before, which gives room to preventive strategies. Not only preventing, but even delaying the onset of dementia, would have profound effects on public health. Nevertheless, a very recent systematic review of 51 trials with low-moderate risk of bias concluded that the available evidence does not

support the use of pharmacological treatments (i.e., dementia medications, antihypertensive and diabetes drugs, anti-inflammatory medications, and estrogen/progestin agents) for the prevention of cognitive decline in persons with normal cognition or with mild cognitive impairment (MCI) (6). Two systematic reviews, one on cognitive training including 11 trials (7), and another on exercise including 16 trials (8), concluded that evidence for prevention of cognitive decline or dementia with these strategies is insufficient. Interestingly, a multidomain intervention including physical activity, diet, and cognitive training improved several cognitive outcomes (9).

The impact of diet and nutrition on age-associated cognitive decline is becoming a growing field as a potential modifiable contributor (10). Various minerals, micronutrients, vitamins with antioxidant/anti-inflammatory properties have been studied (11). Dietary essential fatty acids forming neuronal membranes with antioxidant, anti-excitotoxic, and inti-inflammatory actions have been tested as well (12, 13). Similar studies suggest biological plausibility and cognitive effects of other single or multi-ingredient supplements, which recently has been judged as insufficient (14). In addition, diverse dietary patterns have been studied in relation to their association with cognitive functions alluding that the benefit of nutritional factors may derive from synergistic interactions of different components contained in a food pattern (15).

In this article, we review possible mechanisms and evidence for the actions of dietary components, supplements, and dietary patterns on cognitive decline and dementia.

Possible mechanisms mediating the effects of diet on cognitive decline and AD

Overweight and obesity in adulthood and late-onset cognitive decline

Traditional risk factors for cardiovascular disease (CVD) and type 2 diabetes (T2D), both in isolation and combined, are also risk factors for the development of cognitive decline and AD (16). The clustering of risk factors (i.e., central obesity, hyperglycemia, hypertension, atherogenic dyslipidemia, and a prothrombotic state), or metabolic syndrome, is directly related to the accumulation of visceral adiposity in midlife linked to overeating and sedentarism with deleterious consequences in late-life (17). Obesity has become an epidemic at all ages. In the current industrial era, there is extensive accessibility to abundant inexpensive calorie-rich food, which together with a sedentary lifestyle has paradoxically contributed to the increased life expectancy in the last century. Overeating and sedentarism have led to chronic non-communicable diseases (18), which develop easily but are very challenging to treat and may become unsustainable. A systematic review of 28 longitudinal studies conducted from 2003 to 2013 with follow-up of 5-40 years showed an increased risk of late-onset dementia in overweight and obese participants in midlife (up to 2.44 fold risk) (19). The mechanism behind this association is not yet clarified, but several possible mediators have been suggested. Overweight and obesity-related vascular consequences, i.e., hypertension, atherogenic dyslipidemia, and/or diabetes, are also risk factors for dementia (16). Yet, most analyses in the studies take into account these potential confounder. High levels of plasma amyloid proteins have been found in obese persons (20). A longitudinal study showed that being overweight or obese in midlife was associated with lower blood brain barrier (BBB) integrity almost 25 years later (21).

The accumulation and activation of macrophages in outsized adipose tissue may trigger systemic and neuroinflammation. Immune cells in adipose tissue can secrete pro-inflammatory [e.g., tumor necrosis factor (TNF), interleukin (IL)-1b, IL-6] and anti-inflammatory cytokines (adiponectin and IL-10), which maintain low-grade chronic inflammation (22). Obesity has been also linked to a switch from M2 macrophages to the proinflammatory M1 phenotype (23).

Dietary fats, specially saturated fatty acids (SFA), induce inflammatory responses on microglia, with local cytokine production, i.e., hypothalamic nuclear factor kappa B (NF-kB), which may lead to apoptosis of neurons involved in body weight control, central regulation of energy balance, blood pressure, and glucose homeostasis (24). Obesity may also induce modifications in the developing brain of children and adolescents (25), with long-term negative consequences.

Conversely, low-calorie diets, weight reduction or frequent consumption of food rich in antioxidant/anti-inflammatory properties, or food patterns with combinations of them, have been associated with reduced markers of systemic and adipose tissue inflammation (26). Diet studies in humans have shown a link between insulin resistance and cognition (27), as well as T2D glucose regulation abnormalities and cognitive function (28). Diet interventions that improved insulin resistance have been associated with decreased inflammatory cytokines and improved cognition (29, 30).

Oxidative stress and chronic metabolic inflammation

A pro-oxidant, pro-inflammatory state is characteristic of aging and age-related degenerative diseases resulting in harmful damage on cellular components. The brain is particularly susceptible to oxidative damage. Cerebral metabolism needs large amounts of energy, and it is dependent on aerobic conditions; it is also rich in polyunsaturated fatty acids (PUFAs), which are oxidizable, and in transition metals, which facilitate free radicals generation. Moreover, the brain has low levels of antioxidant systems compared to other body structures. This might render brain tissue prone to damage due to accumulation of neurotoxic peptides such as amyloid-beta (31). Autoptic studies have shown increased protein oxidative damage, lipid peroxidation, glycol-oxidation, and reduced antioxidant enzyme systems in brain tissue from AD patients (32).

Increasing evidence suggests neuroinflammation as the origin of AD. Aggregated and misfolded proteins (e.g., amyloid) bind to microglia toll-like receptors (TLRs) and CD4, initiating innate immune responses with production of inflammatory mediators (33). Microglia surrounding amyloid plaques and tangles were already described by Alois Alzheimer, but only in recent times the role of microglia inflammation has been studied. Neuroinflammation is a key protective mechanism; yet, when uncontrolled and chronic, it may become harmful by the incessant release of free radicals, proteolytic enzymes, nitric oxide, complementary factors, cytokines, or excitatory amino acids (34). Amyloid-beta accretion induces neuroinflammation, which consecutively produces more amyloid-beta, propagating the injury (35). Increased neuroinflammation has been shown in MCI and AD patients vs. healthy controls using positron emission tomography and imaging with radioligand C-11-DAA1106 (36). Amyloid-beta may lead to a preponderance of M1 cells vs. M2 (anti-inflammatory cells) and loss of the ability to switch phenotypes and lessen destruction (34). Nitric oxide (NO) in excess may induce inflammatory signals, identified as key players in neurodegenerative diseases with consequent neuronal death (37).

Autophagy and prothrombotic state

Autophagy mediates degradation and recycling and of cellular proteins, whose efficiency declines with age. It involves clearance of misfolded proteins and aggregates such as amyloid, which is altered in AD (38). There is evidence that the mammalian target of rapamycin (mTOR) signaling, a key player of cellular senescence, affects glucose metabolism, energy production, mitochondrial function, and autophagy in the brain. These events are central in age-associated cognitive decline and AD (39).

Other features of AD are vascular disorders (e.g., decreased cerebral blood flow, BBB disruption, and cerebrovascular dysfunction) and a prothrombotic state (e.g., clot formation, activated platelets, decreased fibrinolysis). Fibrinogen accumulates with amyloid-beta, which promotes amyloid beta fibrillization and generation of fibrin resistant to degradation. A recent study showed higher platelet activating factor acetylhydrolase activity and higher oxidized-LDL levels when compared AD patients with control subjects (40).

Dietary components and supplements with suggested effects on cognitive decline and AD

Omega-3 fatty acids

The PUFAs are essential constituents of neuronal cell membranes, preserving membrane fluidity for neurotransmitter communication and synaptic vesicle fusion. They may be precursors for lipid messengers in

signaling processes to promote neuroprotection or neuronal damage (41). There is evidence of PUFAs deficit in the hippocampus, cortex, and cerebellum in the aged brain, which may be worse in AD (42). The most widely studied PUFAs regarding cognitive decline are omega-3 PUFAs with dissimilar results. A systematic review reported data supporting a role for long-chain omega-3 PUFAs in the reduction of cognitive decline in persons without dementia (43). Nevertheless, other trials have shown negative results. The "Supplementation with Folate, vitamin B6 and B12 and/or OMega-3 fatty acids" trial including 1,748 participants with a history of CVD reported no significant effects of vitamin B and omega-3 fatty acid supplementation on cognitive function (44). A double-blind RCT involving 302 cognitively intact persons aged ≥65 years assigned to 1,8 g/day eicosapentaenoic (EPA)-docosahexaenoic (DHA), 0.4 g/day EPA-DHA, or placebo for a short period (26 weeks) found no significant effects (45). A meta-analysis of results from 3,536 persons aged >60 years without cognitive dysfunction at baseline supplemented with omega-3 PUFAs reported no significant effects on cognitive function (46). An epidemiological study of Chinese adults showed that persons aged ≥65 years who consumed ≥100 g/week of fish had a reduction of about 65% in the mean annual rate of global cognitive decline with no associations among adults aged 55-64 years (47). Recently, the "Multidomain Alzheimer Preventive Trial" reported that multidomain intervention and omega-3 PUFAs supplementation, either alone or in combination, had no significant effects on cognitive decline over 3 years in 1525 participants (48).

Curcuminoids

Curcumin is a polyphenolic compound from the rhizome of *Curcuma longa c*ontained in curry spice turmeric, considered an effective therapy for several conditions in traditional Indian medicine, widely used in that population, and a potent antioxidant (49). In 2000, a study by Ganguli et al. (50) reported a lower prevalence of AD in the Indian population compared to the US population. Ng et al. found that older healthy people who consume more frequently curry had better cognitive performance (51). Numerous experimental studies confirmed the potent anti-oxidant and anti-inflammatory properties of curcumin and its protection on AD animal models. Three RCTs have been so far completed. Baum et al. (52) enrolled 34 patients with AD receiving either 1 or 4 g/day of curcumin or placebo for 6 months and reported no significant effects in Mini Mental State Examination (MMSE). Ringman et al. (53), randomized 36 patients with dementia to 2 or 4 g/day of Curcumin C3 Complex (95% of curcuminoids) or placebo for 24 weeks, extended to 48 weeks as an open-label trial with Curcumin C3 Complex for the placebo arm. The authors did not observe any significant difference between treatment groups and placebo in any of the scores (ADAS-Cog, NPI, ADCS-ADL, MMSE) or cerebrospinal fluid markers. Hishikawa et al. (54) showed that 3 dementia patients treated with 100 mg/day of curcumin and donepezil had a lower NPI score after 12 weeks of therapy. Supplements of curcumin have limited bioavailability, which has been suggested to improve with lipidated formulations (55).

Magnesium

Compelling evidence shows that magnesium (Mg) deficiency results in increased free radicals production in various tissues, increased oxidative tissue damage, increased superoxide anion production by inflammatory cells, decreased antioxidant enzyme expression and activity, decreased cellular and tissue antioxidant levels, and increased oxygen peroxide production (56, 57); Mg is essential for synaptic conduction, affects N-methyl-D-aspartate (NMDA) receptor response to excitatory amino acids (58), inhibits calcium channels, calcium influx, and glutamate release, and has effects on stability and viscosity of cell membranes (56). Mg insufficiency produces vasospasm while elevated Mg induces tone relaxation in cerebral arteries (59). Due to the above mentioned reasons, the role of Mg in cognitive decline and dementia has been examined in recent years. Former studies showed low serum Mg levels (60) and autoptic brain tissue concentrations in AD patients (61). We observed reduced ionized free Mg concentrations in plasma obtained from AD patients (62), which were related to cognitive dysfunction severity. Cilliler et al. (63) reported negative associations of serum Mg levels and 2 rating AD severity scales (Global Deterioration Scale and Clinical Dementia

Rating), further confirming a potential protective role of Mg on cognitive function. There are no specific trials with Mg supplements in the prevention or therapy of cognitive disorders; hence, whether Mg supplementation may exert protective effects against AD remains to be further elucidated in well-design trials.

Cocoa and cocoa-derived products

Cocoa is a rich source of flavonoids, which has shown cardiovascular benefits. Some small acute and short-term chronic trials have suggested neuroprotective properties. A study in 18 persons aged 50-65 years reported significant increases in regional perfusion across the brain following consumption of the high flavanol drink (494 mg), particularly in the anterior cingulate cortex and the central opercular cortex of the parietal lobe measured with spin labelling functional MRI (64). A small study of 34 healthy persons (mean age 72±6 years) showed an increased blood flow velocity in the middle cerebral artery after one (8%) and two weeks (10%) of flavanol-rich cocoa consumption using transcranial Doppler ultrasound (65). In an RCT, healthy persons aged 50-69 years who consumed a high cocoa flavanol-containing diet for 3 months exhibited enhanced dentate gyrus function, as measured by functional MRI and by cognitive testing (66). A prospective study involving 531 participants aged ≥65 years followed for median 48 months showed that chocolate intake was associated with a 41% lower risk of cognitive decline after adjustment for confounders (67).

The mechanisms proposed to explain the potential benefit of cocoa and derived products are: 1) direct interactions with cellular signaling that promote neurogenesis, neuronal function and brain connectivity, and 2) blood-flow improvement and angiogenesis in the brain and sensory systems. The preliminary evidence shown above underscores the need for further well-design and large RCT on these interesting compounds.

Tea and (-)-Epigallocatechin-3-gallate (EGCG)

Tea is traditionally indicated as a cognitive stimulator in Asian cultures. This effect has been confirmed in some studies and has been linked to antioxidants contained in tea, such as EGCG, L-theanine, and caffeine (68). Tea may also exert neuroprotective actions by regulation of stress hormones and inhibition of acetylcholinesterase (69). However, there is currently inconsistent evidence with no definitive conclusion on its neuroprotective actions (70). Bioactive compounds, such as L-theanine and EGCG, may have some potential due to their anti-amyloidogenic and antioxidant properties in vitro, but the evidence for their use as nutraceuticals is limited and there is no recommendation currently for their use in clinical practice.

Caffeine

There is evidence of antioxidant (71) and amyloid-beta suppressive properties of caffeine in animal models of AD (72). The reduction in amyloid-plaques is associated with a stimulation of protein kinase A activity, increased phosphor-CREB levels, and reduced phosphor-JNK and phosphor-ERK expression in mouse models of AD, promoting survival cascades in the brain (72, 73). It is well-known that coffee and caffeine strengthen short-term memory and cognition, but there is limited evidence suggesting long-term effects. A case-control study of 124 older persons with MCI showed that high serum levels of caffeine were associated with lack of progression to dementia (74). Another study reported that consumption of 3-5 cups of coffee per day reduced incident AD and dementia by 65% (75). Among 3494 men from the Honolulu-Asia Aging Study, deceased men in the highest quartile of caffeine intake were less likely to have any neuropathological dementia lesion vs. men in the lowest quartile. Yet, coffee and caffeine intake in midlife were not associated with risk of cognitive impairment, overall dementia, AD, vascular dementia, or moderate/high levels of neuropathological lesions (76).

A meta-analysis of studies exploring the relationship of caffeine consumption and cognitive decline reported nonsignificant effects (77), but few and largely heterogeneous studies were included. A Portuguese study reported an association of caffeine consumption with slower cognitive decline (78), while a study from France found no association (79). A longitudinal study reported less cognitive decline among coffee consumers but no dose response (80). Another showed no relationship (81). There is no evidence from RCTs.

Phytoestrogen compounds

Studies on soy isoflavones usually include mixtures of them, such as genistein and daidzein, which impede to discriminate the effects of specific components on cognition. Studies of soy consumption and phytoestrogen supplements on cognitive function have reported variable and inconclusive results (82), with overall absence of adverse events (83). An initial positive cognitive effect in adult age appears to reverse in older women; in men the data are even more equivocal (82). Discrepancies may be explained by the use of different isoflavone supplements at variable doses in small short-term trials. Studies showing no effect of phytoestrogens on cognition are mostly from European cohorts, with low dietary soy consumption. Studies of older Asian populations with higher consumption of soy-derived foods show lower rates of cognitive decline. After oral intake of conjugated isoflavones, dadzein is converted to S-equol by a gut biotransformation. About 70% of older Japanese persons are "equol producers" (84), which may help explain the different results in Asian vs. Europeans studies.

In the Women's Isoflavone Soy Health (WISH) trial, 313 postmenopausal women aged 45-92 years were randomized to receive 25 g/d of isoflavone-rich soy protein (containing genistein, daidzein, and glycitein) or milk protein-matched placebo. Cognitive function was assessed at baseline and after 2.5 years. There were no differences between the groups in cognition change from baseline. Nevertheless, women within 5-10 years of menopause in the isoflavone group showed a nonsignificant (p=0.07) trend toward cognitive improvement, and a significant improvement in verbal episodic memory. Consistent producers of urinary S-equol showed a nonsignificant (p=0.08) trend toward cognitive improvement (85). Further studies are necessary to validate these findings. There are no RCTs of phytoestrogens for the prevention or treatment of AD.

Resveratrol

This hytoalexin is a polyphenol contained in berries. Most dietary resveratrol in humans comes from grapes and red wine (86). Biological properties of resveratrol include antioxidant and anti-inflammatory actions (87). Studies in animal models of AD have shown reduced hippocampal neurodegeneration and increased memory performance, but human clinical trials of resveratrol on cognition are limited. A placebo-control study in 22 healthy adults showed a dose-dependent (250-500 mg/day) increase in cerebral blood flow in the prefrontral cortex during cognitive tasks (88). Another small study including 23 overweight persons, aged 50-75 years, receiving resveratrol (200 mg/d) for 26 weeks vs. a group receiving placebo, reported improved memory performance and higher functional connectivity of the hippocampus in neuroimaging with resveratrol treatment (89). There are several ongoing clinical trials on resveratrol investigating its potential effects on cognitive function, MCI and AD (90). At present, there is no data on toxicity of chronic resveratrol supplementation. There is no sufficiently substantiated evidence for prescribing this supplement to improve cognitive function.

Gingko biloba

An RCT included 3,069 participants randomized into Gingko biloba treatment or placebo to determine whether G. biloba supplementation could prevent dementia among older adults who were cognitively intact or had mild cognitive impairment at baseline. Participants were followed for a median of 6.1 years, and study results indicated no difference in the rate of cognitive decline for the two treatment groups (91).

Garlic (Allium sativum)

Garlic extracts have shown antioxidant properties and protection against amyloid-beta-induced neurotoxic effects in experimental animals (92). Allicin, an organosulfur compound contained in garlic, inhibited cholinesterase enzymes and upregulated brain acetylcholine levels in vitro (93). Nevertheless, there are no clinical trials for these compounds. In the Doetinchem Cohort Study, including 2613 participants aged 43-70 years, higher consumption of allium (onion, garlic, and leek) was associated with worse scores on cognitive flexibility and speed of cognitive processes in cross-sectional analyses, while in longitudinal analyses, al-

lium consumption was not associated with cognitive decline (94).

Vitamins

In 4,052 participants from the Physicians' Health Study and Physicians' Health Study II, there was no significant effect on cognitive function with short-term beta-carotene (provitamin A) treatment and beneficial effect with longer-term (18-year) administration (95).

Studies on the effect of vitamin B on cognition have produced mixed results. An RCT of 299 men >75 years showed no significant effect on cognitive function of 2-year supplementation with folic acid, vitamin B6, and B12 (96). Similarly, a meta-analysis of 9 RCTs (n=2,835) indicated no significant effect of folic acid with or without other B vitamins on cognitive function (97). Conversely, an RCT of 900 persons aged 60–74 years showed that folic acid+vitamin B12 were significantly superior vs. placebo for improving cognitive tests (98).

A number of studies have examined the combined effects of vitamins C and E on cognitive function in healthy populations with conflicting results. The Women's Health Study (6,377 women over 65 years) showed no significant effect on cognitive function of vitamin E supplementation (99). Analyses of 616 over 65-years-old participants of the Duke Established Populations for Epidemiologic Studies showed that vitamins C and/or E supplements had no influence on incident dementia or AD (100). On the contrary, the Canadian Study of Health and Aging (894 participants aged ≥65 years) reported that a combination of vitamins C and E significantly decreased the rate of cognitive decline (101). A recent study analyzed the relations of alpha- and gamma-tocopherol brain concentrations with AD neuropathology among 115 deceased participants of the prospective Rush Memory and Aging Project. Gamma-tocopherol concentrations were associated with lower amyloid load and lower neurofibrillary tangle severity, while alpha-tocopherol concentrations were not associated with neuropathology (102).

The Third National Health and Nutrition Examination Survey showed an association of vitamin D deficiency with an increased risk of cognitive decline in the US (103). However, the Women's Health Initiative showed no significant effect of vitamin D and calcium supplementation on cognitive function in 2,034 women aged over 65 years, followed for a mean of 7.8 years (104).

Results from the Age-Related Eye Disease Study including 2,166 participants followed for 6.9 years showed that a combination of antioxidant vitamins (vitamins E and C, beta-carotene), zinc, and copper had no significant effects on any of six tests of cognitive function (105). Similarly, the Women's Antioxidant Cardiovascular Study that included 2,824 women with or at risk for CVD who received a combination of vitamin E, beta-carotene, and vitamin C or placebo showed no effects on cognition with the multivitamin supplementation (106).

Dietary patterns

The incidence of chronic diseases, including dementia and AD, has been assessed in relation to dietary patterns in populations of various ethnicity, culture, or religious beliefs. There is no single dietary or lifestyle intervention proven in RCTs to prevent incident AD. Nevertheless, epidemiological data suggest that adopting a healthy, balanced diet and lifestyle known to improve cardiovascular risk may help delay incident AD (107).

Mediterranean diet (MeDiet)

The dietary pattern consumed traditionally by populations bordering the Mediterranean Sea has been extensively reported as a model of healthy eating. MeDiet characteristics are shown in Table 1. A greater adherence to MeDiet has been associated with a reduced incidence of overall mortality, cardiovascular mortality, cardiovascular events incidence, cancer mortality and/or incidence, and incident Parkinson's disease and AD (108).

A recent systematic review of longitudinal cohorts examining MeDiet effects on cognition found that participants in the highest tertile of adherence to MeDiet had 33% less risk of MCI or AD when vs. those in the lowest tertile (109). The RCT PREDIMED (Prevención con Dieta Mediterranea), includ-

Table 1. Characteristics of the Mediterranean dietary pattern.

Mediterranean dietary pattern
- Olive oil as the main source of fat
- Fresh fruits and vegetables; legumes, nuts, seeds
- Bread and other grain products (pasta, rice from whole grains)
- Herbs and spices (providing taste and facilitating low use of added salt)
- Foods that have undergone minimal processing, that are fresh and locally produced
- Frequent consumption of fish and seafood (2-3 times per week)
- Dairy products on a daily basis, mainly yogurt (less often small portions of cheese)
- Red meat consumed in moderation, if possible as a part of stews and other recipes, not often (1-2 every month)
- Eggs (providing high quality proteins)
- Fresh fruit everyday as dessert; sweets, cakes and dairy desserts only occasionally in small amounts
- Water
- Wine in moderation, with meals
- Moderate portion size
- Moderate physical active every day
- Meals in the company of others

ing adults aged 55-80 years at high cardiovascular risk, showed that participants on a MeDiet supplemented with either EVOO or nuts, had a reduced incidence of cardiovascular events vs. participants following a low-fat diet over 5-years of follow-up (110). Two subanalysis of this RCT have reported improved cognitive function with the MeDiet supplemented with either EVOO oil or nuts vs. low-fat diet (111, 112).

Several longitudinal studies have examined the effects of MeDiet on AD in cohorts from the US (113-117), and France (118, 119). Two reviews (108, 120) concluded that even if there is some evidence that adherence to MeDiet is associated with a reduced risk of AD, additional confirmation in populations with different ethnicities and dietary habits is necessary. The Personality and Total Health (PATH) through Life longitudinal study (121) of healthy participants from Australia found no protection of MeDiet for cognitive decline, while the Australian Imaging, Biomarkers and Lifestyle (AIBL) study (122) showed that participants with AD and MCI had lower adherence to MeDiet than healthy controls. A 7-year longitudinal study (123) evaluated adherence to HEI-2005 or to MeDiet in relation to cognitive change in 3,790 adults aged >65 years from the ongoing Chicago Health and Aging Project longitudinal study. The results showed that white participants had higher energy-adjusted MeDiet scores but lower HEI-2005 scores compared to black participants. Higher MeDiet scores, adjusted for confounders, were associated with slower rates of cognitive decline, but no association was found for HEI-2005 scores. MeDiet encompasses other cultural and lifestyle components, such as physical activity, adequate rest, social engagement, and culinary activities (124). These lifestyle factors have shown positive effects on delaying cognitive decline. Future studies should consider all MeDiet lifestyle factors into their design.

Dietary approaches to stop hypertension (DASH)

This balanced eating plan effectively lowers cardiovascular outcomes (125). DASH characteristics are shown in Table 2. A prospective study examined the associations between DASH and MeDiet with age-related cognitive changes in 3831 participants aged >65 years, followed for >11 years. Higher adherence to DASH and MeDiet and greater consumption of whole grains, nuts and legumes were significantly associated with higher average MMSE scores (126). A combined dietary pattern of MeDiet and DASH (or MIND) in 960 participants of the Memory and Aging Project followed for a mean of 4.7 years was positively associated with slower decline in global and 5 single cognitive domains, after adjusting for confounders (127). In 923 participants, aged 58-98 years, followed for average 4.5 years, there was a significant reduction in incident AD for the second and third tertile

Table 2. Characteristics of DASH (Dietary Approaches to Stop Hypertension)

Dietary Approaches to Stop Hypertension
– Eating vegetables, fruits, and whole grains
– Including fat-free or low-fat dairy products, fish, poultry, beans, nuts, and vegetable oils
– Limiting foods that are high in saturated fat, such as fatty meats, full-fat dairy products, and tropical oils such as coconut, palm kernel, and palm oils
– Limiting sugar-sweetened beverages and sweets

of adherence scores to MIND diet vs. the lowest tertile (128). Replications of these positive results with DASH and MIND are needed in other populations to confirm their relevance to brain health.

Other dietary patterns with no proven or conflicting effects on cognitive function or prevention of cognitive decline

Several dietary patterns with confirmed benefit for diverse health outcomes (e.g., cardiovascular health, total mortality, incident cancer, body weight control) have not definitely proven effects on the prevention of cognitive decline or dementia.

• *Healthy Eating Index-2005 (HEI-2005) (Dietary Guidelines for Americans)* - Two cross-sectional studies (129, 130) showed associations of HEI-2005 and improvements in cognition. However two longitudinal studies (123, 131) followed up to 7.6 years showed no association. A longer study (132) (11-year follow-up) showed less cognitive decline with increased HEI scores, indicating that a longer duration may be needed to disclose effects of diet on cognition.

• *Okinawa Diet* - Notwithstanding this dietary pattern is followed by populations with some of the longest life expectancies in the world, there is still no solid evidence for its effects on prevention of cognitive decline and AD. A study showed a higher incident dementia in 157 migrants from Okinawa to Brazil vs. 2,217 residents of Okinawa (133). The 9-year difference between the studies and dissimilar sample size may have affected the results.

• *Vegetarian Diets* - The incidence of dementia in those consuming vegetarian diets and meat-eating diets was compared in two cohort sub-studies of the Adventist Health Study (134). The first study showed that persons who ate meat were more than twice as likely to become demented as their vegetarian counterparts. A second analysis showed no significant difference in the incidence of dementia between vegetarian and meat-eating subjects, with no clear explanation for the difference between the two sub-studies. There was no clear evidence of any standardized cognitive assessment during the study.

• *Paleolithic Diet* - A study of 20 overweight postmenopausal women compared the effects of Paleolithic diet vs. Nordic Nutrition Recommendations followed for 6 months on parameters of functional MRI, episodic memory tasks, and weight loss. There was a significant improvement in episodic memory performance after both dietary interventions, which was associated with increased hippocampal activity, decreased waist circumference and reduced plasma FFA without differences between the diets (135). There are no studies on the effects of Paleolithic diet on incident AD.

• *Ketogenic Diet* - This dietary pattern has been associated with neuroprotective effects in some forms of epilepsy. While there is no current evidence of AD prevention with ketogenic diet, a small double-blind placebo-controlled study of 20 patients with MCI or AD showed memory scores improvement in patients receiving medium-chain triglycerides in non-*APOE* ε4 patients but not in *APOE* ε4 positive patients (136). A clinical trial of 152 participants showed similar results (137). Most findings with KD come from animal studies and a solid validation in human trials is still warranted.

• *Low-copper Diet* - A longitudinal study of 3718 participants showed that high intakes of copper, mostly supplements, together with a high-fat diet resulted in more rapid cognitive decline after 5.5. years follow-up (138). In 32 patients with mild to moderate AD, those with low plasma Cu had significantly higher ADAS-cog scores (139) Squitti et al. suggest that the

promotion of a low-Cu diet may potentially reduce the risk of AD (140). Nevertheless, there is no evidence that depletion or supplementation of Cu may modify AD incidence or pathology.

Conclusions

Results from large-scale epidemiologic studies and clinical trials generally do not demonstrate an independent role for most of the nutritional and dietary factors that have been examined for the prevention of cognitive decline or AD. Further research is needed to clarify the possible benefits of the single dietary components.

The effects of MeDiet and DASH on cardiovascular health are well established, and there is moderately convincing evidence that adherence to these dietary patterns is associated with a reduced risk of AD, especially with the combination of both dietary patterns. Further confirmation in populations with different ethnicities and different dietary behaviors is needed. There is at present no clear evidence to support effects of HEI-2005, Okinawa, vegetarian, Paleolithic, ketogenic, or low-copper diets on the prevention of cognitive decline or AD.

Studying dietary patterns may help understand possible synergistic actions of foods and nutrients combinations in order to prevent or delay the onset of cognitive decline and dementia.

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