Nutrition and prevention of cognitive impairment

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Nutrition is an important lifestyle factor that can modify the risk of future cognitive impairment and dementia. Some, but not conclusive, evidence (mostly from observational studies and infrequently from clinical trials) exists of a protective association between certain nutrients (eg, folate, flavonoids, vitamin D, and certain lipids) or food groups (eg, seafood, vegetables, and fruits, and potentially moderate alcohol and caffeine consumption) and cognitive outcomes in older people. For some nutrients and food groups, protection might be greater in individuals with either deficiencies in certain nutrients or a genetic predisposition to cognitive impairment. Identification of potentially different associations between such subgroups should be a priority for future research. At present, evidence of an association between nutrition and cognitive outcomes is somehow stronger for healthy dietary patterns, such as the Mediterranean-type diet, than for individual nutrients and food groups, possibly because of the cumulative beneficial effects of the many ingredients in these diets. Multidomain interventions (including a nutrition component) might also hold some promise for the prevention of cognitive impairment and dementia, but their effectiveness is still uncertain. Use of advanced technologies for nutrition assessment (eg, metabolomics and innovative methods of dietary intake assessment) and recently identified biomarkers of nutrition and neurobiological outcomes will be important to achieve this goal.

Lancet Neurol 2018

Published Online
September 20, 2018
http://dx.doi.org/10.1016/S1474-4422(18)30338-7

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See Online for appendix

Introduction

An analysis of population-based data suggested that a third of Alzheimer's disease cases worldwide might be attributable to potentially modifiable risk factors.[1] Nutrition is a modifiable environmental factor that has been associated with many non-communicable diseases with connections to dementia, such as diabetes and cardiovascular disease.[2,3] Evidence suggests that lifelong nutrition might also have a direct effect on brain function. For example, longitudinal stu dies have identified associations between certain nutrients or dietary patterns and brain-volume loss[4,5] or brain integrity,[6] with some clinical trials[7,8] confirming these results. Additionally, a large body of scientific evidence, mostly from observational studies, suggests a direct role for lifelong nutrition on clinical measures of cognitive status in older adults. A clear overview of the strength of the available research is thus of major importance in clinical practice because it will provide the support needed for clinicians to formulate evidence-based dietary advice for individuals at risk or those already diagnosed with some degree of cognitive impairment.

Here, we provide a comprehensive review of observational studies and clinical trials that have investigated the associations between nutrition and future cognitive decline or dementia in humans. We focus on aspects of nutrition with the strongest evidence base. Given that daily food intake might have multiple effects on health outcomes due to interactions between many foods, we start our Review with individual food components (ie, essential micronutrients or other biologically active compounds and macronutrients). We then move to food groups (which might act via multiple nutrients or food ingredients) and dietary patterns (which might act via combinations of foods). Other emerging aspects of nutrition research, such as caloric restriction, are not covered because of insufficient evidence to date.

Nutrients and biologically active compounds

B vitamins

B vitamins have been studied for their potential effect on cognitive function because of their role in homocysteine metabolism and the well established association between homocysteine concentrations and cognitive decline. Specifically, several clinical studies have found that even moderately raised (within the normal range) concentrations of homocysteine might be associated with increased risk of dementia in people older than 65 years.[9] Homocysteine is produced by methylation of methionine and is eliminated from the body via two pathways, one of which requires folate and vitamin B12 and the other vitamin B6.[10] Major dietary sources of vitamin B6 are grains, pulses, and nuts; of folate are green leafy vegetables; and of vitamin B12 are dairy products, meat, and other animal products (table 1). Most observational studies examining the role of vitamins B6 and B12 have found no clear association with cognitive function (figure; appendix), which could be due to a multitude of methodological reasons and, thus, should be interpreted with caution (panel 1). Such methodological challenges should be kept in mind with regards to all aspects of nutrition reviewed in this paper because they apply almost universally in this field.

Some observational studies examining the role of folate in cognitive function found no association, whereas one study[20] found that elderly people in the highest quintile of folate intake had the fastest rate of cognitive decline (figure; appendix). By contrast, two other observational studies[21,22] in elderly people reported a lower incidence of Alzheimer's disease or dementia in participants in the highest quartile of folate intake, and one study[23] in younger participants (aged 18–30 years) with long-term follow-up (25 years) found that higher folate intake was related to slower decline in psychomotor speed.

Most clinical trials of B vitamins have found no association with cognitive function (figure; appendix).

	Major dietary sources
B vitamins	
B6[11]	Grains (wholegrain corn or maize, brown rice, sorghum, quinoa, and wheat germ), pulses, nuts and seeds, meat, liver and meat products, and fish
B12[12]	Animal products (dairy products, eggs, meats, fish, and liver), foods that contain yeast or have been exposed to microbial fermentation (eg, beer), and fortified foods (eg, ready-to-eat cereals)
Folate[13]	Dark-green leafy vegetables, legumes, oranges and grapefruit, peanuts and almonds, offal (liver and kidney), and baker's yeast
Antioxidants	
Vitamin C[14]	Fruits (berries, citrus fruits, kiwis, lychees, and papayas), vegetables (Brussels sprouts, cauliflowers, cabbages, sweet peppers, and tomatoes), and herbs and spices (parsley, sorrel, and chives)
Vitamin E[15]	Vegetable oils and fat spreads from vegetable oils, nuts and seeds, some fatty fish (eg, sardines, salmon, herring, swordfish, and trout), egg yolk, and wholegrain cereals
Carotenes[16]	Yellow or orange vegetables (sweet potatoes, carrots, and pumpkins), dark leafy vegetables (spinach, broccoli, and endives), and yellow or orange fruits (apricots, peaches, mangoes, and melons)
Flavonoids[17]	Fruits (mainly citrus fruits, bananas, and berries), vegetables (parsley and onions), tea (black and brewed)
Vitamin D[18]	Fish (especially fatty fish) and fish liver, full-fat dairy products (or fortified low-fat ones), egg yolk, meat and meat products, and offal (particularly liver)
n-3 fatty acids[19]	Fish (for eicosapentaenoic acid and docosahexaenoic acid) and some vegetable oils and nuts (eg, linseeds, rapeseed oil, and walnuts for α-linolenic acid)

Table 1: **Nutrients related to cognitive function**

However, in one trial,[24] supplementation with folate 0·8 mg a day (ie, twice the recommended intake) over 3 years was effective in improving cognition in participants aged 50–70 years. Supplementation was more effective in improving information processing speed in those with high baseline homocysteine concentrations (>12·9 µmol/L) and in improving information processing and sensorimotor speed in those with low baseline vitamin B12 concentrations (<250 pmol/L).[24] In a randomised trial,[25] combinations of folate, vitamins B6 and B12, and n-3 fatty acids provided for 4 years to men and women aged 45–80 years were effective in preserving semantic memory or temporal orientation in a subgroup of participants with previous coronary artery disease or ischaemic stroke, but not in the total trial population. These observations suggest that individuals with high baseline homocysteine concentrations (>12·9 µmol/L), low baseline vitamin B concentrations, or established cardiovascular and cerebrovascular disease might benefit most from vitamin B supplementation.

Antioxidants

Many nutrients (mainly vitamin C, vitamin E, and carotenoids) and non-nutrient food ingredients (eg, polyphenols and anthocyanins) have direct antioxidant properties. Additionally, some essential elements, such as selenium, zinc, and copper, serve as cofactors for proteins or enzymes with antioxidative activity. The brain is highly susceptible to oxidative damage, and it has been suggested that oxidative stress or inadequate antioxidant defence might mediate the pathogenesis and progression of dementia.[26] Thus, intake of dietary antioxidants could affect the development of cognitive impairment. Major sources of antioxidants in the diet are fruits such as berries, certain vegetables, tea, and certain fats and vegetable oils (table 1).

Most observational studies have reported no benefit for vitamin C on cognitive function (figure; appendix). However, two studies[27,28] found that the incidence of Alzheimer's disease was reduced in individuals aged 55 years or older who had a high intake of vitamin C and in individuals aged 65 years or older who used vitamin C and D supplements.

Most observational studies have reported no benefit for β carotene in terms of cognitive function (figure; appendix), although one study[29] found that participants with higher plasma carotene concentrations had a lower incidence of dementia and Alzheimer's disease than those with lower plasma concentrations.

The results of studies of vitamin E have been mixed (figure; appendix). Some observational studies[27,30,31] found that the incidence of dementia and Alzheimer's disease decreased with increasing dietary intake of vitamin E in individuals older than 55 years or 65 years. However, five studies[32–36](including one clinical trial) did not detect such protective effects. Of note, in one study[27] that reported a protective effect of vitamins C and E on Alzheimer's disease, the associations were more pronounced in current smokers, possibly suggesting that dietary antioxidants might be more clinically relevant under conditions of high oxidative stress.

Very few studies have assessed antioxidant elements, such as selenium, zinc, and copper. Some observational studies have found potentially beneficial associations between flavonoids and cognitive decline, although these findings are not universal and more evidence is needed. Protective associations for cognitive decline (either individual cognitive domains, such as speed, or global scores) and, more rarely, dementia have been noted with increasing dietary intake of flavonoids in individuals aged 43 years to older than 70 years in observational studies.[35,37–41]

Use of supplements containing antioxidants (rather than obtaining antioxidants from food sources through dietary intake) was associated with a decreased risk of cognitive impairment over 7 years (as measured with the Short Portable Mental Status Questionnaire using specific cutoffs) in both men and women in one observational study,[42] and with a decreased risk of Alzheimer's disease in men in another observational study[28] (figure; appendix). However, these studies did not adjust for overall antioxidant status, in particular dietary intake of antioxidants, and so these findings do not imply a potential benefit from antioxidant supplementation per se. It is possible that health consciousness, access to health services, superior nutrition information, or sociodemographic factors such as income could mediate the observed association. By contrast, clinical trials of supplementation with antioxidant compounds have not observed a beneficial effect on any cognitive outcome (figure).

Vitamin D

Vitamin D has been related to multiple neurobiological pathways, including protection from neurodegeneration induced by inflammation or glucocorticoids, as well as a decrease in amyloid-β production and an increase in its clearance.[43] Major dietary sources of vitamin D are fish, lipids, and full-fat dairy products (or fortified ones in certain countries; table 1), while sunlight exposure can also produce substantial amounts of vitamin D in the epidermis.[43]

Many longitudinal studies have found a protective association between higher blood concentrations of vitamin D and cognitive decline (assessed with various neuropsychological test batteries) or dementia and Alzheimer's disease in men and women aged 65 years or older and occasionally in those aged 55 years or older (figure; appendix). A meta-analysis[44] found an inverse dose–response relationship between serum concentrations of vitamin D and risk of dementia or Alzheimer's disease, with no increase in protection at concentrations higher than 35 ng/mL in both men and women. However, experimental evidence of the effect of vitamin D supplementation is scarce, with a single clinical trial[45] reporting no effect (figure). That trial was in a large cohort and had a long follow-up, but vitamin D was examined only in conjunction with calcium and only in women aged 65 years and older, leaving unanswered questions about calcium potentially masking the beneficial effects of vitamin D and raising external validity concerns.

Macronutrients

Data on the role of macronutrient intake in cognitive function are scarce. In a small observational study[46] in elderly people (aged 70–89 years), high intake of carbohydrates and low intake of fats and proteins (expressed as percentages of energy intake) was associated with increased risk of mild cognitive impairment and dementia.

Unlike protein and carbohydrates, many studies have examined dietary lipids in relation to cognitive outcomes. Most dietary lipids have an important role in cardiovascular and cerebrovascular health, and vascular factors are potentially important contributors to dementia.[47] n-3 fatty acids (particularly docosahexaenoic acid) have indispensable roles in neuronal membranes, are precursors of lipid mediators with anti-inflammatory and neuroprotective functions, and might also have a part in neuronal plasticity.[48] Major dietary sources of n-3 fatty acids include fish and certain vegetable oils (table 1).

Although some studies have found no association, in general, higher blood concentrations of n-3 fatty acids have been associated with a decreased risk of future dementia or Alzheimer's disease in elderly participants (figure; appendix). Higher dietary intake of n-3 fatty acids has also been associated with slower rates of cognitive decline, as assessed with various neuropsychological tests in individuals as young as 43 years (figure; appendix). This potential benefit has been largely shown for docosahexaenoic acid, eicosapentaenoic acid, and α-linolenic acid. In subgroup analyses in one study[49] that found no association between n-3 fatty acids and cognitive function, high dietary intake of α-linolenic acid

Figure: **Summary of the evidence for the effects of nutrients, food groups, and dietary patterns on cognitive outcomes**

Each circle represents a study. Green circles indicate a protective effect, blue circles a neutral (no significant) effect, and red circles a detrimental effect. DASH=Dietary Approaches to Stop Hypertension. MIND=Mediterranean-DASH Intervention for Neurodegenerative Delay.

Panel 1: **Methodological challenges**

Method of nutritional status assessment
- Dietary assessments (Food Frequency Questionnaire limitations) are limited by requirements for memory and averaging tasks, prespecified food lists, and absence of information about meal patterns and combinations of foods
- Biomarkers are available for few nutrients, expensive, reflect only short-term habits, and provide no information about other aspects of nutrition (eg, chronobiology of diet, eating with company, and social and cultural aspects affecting food choice)

Timing of assessment (duration of follow-up)
- Dietary intake assessed at a specific timepoint but might change over time in long-term follow-up
- Short-term follow-up might not capture early subclinical stages
- Counterbalancing might produce often unconscious changes in dietary intake in clinical trials

Confounding of non-dietary factors
- Physical activity
- Aspects of cognitive reserve (eg, education, occupation, socioeconomic status, intellect, and social activities)

Sample selection
- Many participants have adequate nutrition and some of them might not cognitively benefit from nutrition
- Populations include individuals with variable risk of cognitive decline, which might limit power to detect an association between nutrition and cognition

Multidimensionality of diet
- Multiple nutrients, foods, and food groups that are not eaten in isolation
- Observed effect of a dietary factor might simply reflect the simultaneous intake of another factor

Multidimensionality of underlying mechanisms
- Many causal biological pathways, known and unknown have potentially different (even opposing) effects of each nutritional element on each pathway

Multidimensionality of cognitive function
- Multiple cognitive domains and respective neuropsychological evaluations and tests, apart from the clinical diagnoses

at baseline was associated with a slower global cognitive decline in carriers but not in non-carriers of *APOE* ε4, suggesting a protective effect of n-3 fatty acids only in those with a predisposing genetic background.

By contrast with observational studies, the results of most large (in terms of sample size and duration) clinical trials of supplementation with individual n-3 fatty acids or combinations of them have not suggested a protective effect (figure; appendix). However, in one trial,[50] supplementation with docosahexaenoic acid 900 mg a day for 6 months improved episodic memory (but not working memory or executive function) scores in participants aged 55 years or older. Additionally, a post-hoc analysis[51] of a trial that reported no effect included only participants with a low n-3 fatty acid index at baseline and found a significant difference compared with placebo in executive function (but not in other cognitive domains) in the group that received docosahexaenoic acid 800 mg and eicosapentaenoic acid 225 mg once a day for 3 years. It is possible that only individuals with low concentrations of n-3 fatty acids benefit from supplementation.

No clinical trials were identified for other lipids that have been investigated in the setting of observational studies (figure; appendix). Observational studies of total dietary lipids have had mixed results, with some reporting detrimental associations and others reporting no association. Although most studies that have investigated lipid intake at older ages have found no association, a study[52] with 20 years of follow-up that assessed lipid intake at midlife (mean age of 50 years at initial assessment) reported an increased risk of mild cognitive impairment with higher intake of total lipids. Therefore, the period in life of high lipid intake might be important in relation to cognitive outcomes in later life.

Most observational studies have not found an association between dietary cholesterol and cognitive function (figure; appendix). Although some studies found no association between dementia incidence and monounsaturated or polyunsaturated fatty acids, other studies suggested that cognitive outcomes were improved with increased intake of these fats. Specifically, increased consumption of monounsaturated fats was associated with a slower decline in global cognition in women with type 2 diabetes who were aged 74 years, and with a slower decline in global cognition and verbal memory in women aged 66 years.[53] Higher intake of monounsaturated fats was also shown to protect against mild cognitive impairment in men and women aged 60–64 years.[54] Higher intake of polyunsaturated fats was associated with reduced risk of dementia in individuals aged 50 years.[55] In a study[56] of individuals aged 65 years and older that reported no association, monounsaturated and polyunsaturated fats were associated with reduced cognitive decline in participants older than 72 years (the median of the population).

Findings have been mixed for saturated and trans fatty acids (figure; appendix). Three observational studies found no association between dementia and saturated fats, whereas six studies found that cognitive outcomes worsened with increasing consumption of these fats (figure). Two studies[52,55] in individuals aged 50 years reported that the incidence of mild cognitive impairment, dementia, and Alzheimer's disease were higher in participants who consumed more saturated fats. Similarly, one study[53] in older (age 74 years) women with type 2 diabetes and one[57] in women aged 66 years found that lower intake of saturated fats was associated with a slower decline in global cognitive scores. Higher concentrations of palmitic acid (a saturated fat) in blood were associated with an increased risk of dementia in men aged 50 years who were followed up for 20 years, and with faster cognitive decline in individuals aged 50–65 years.[58,59]

Although two observational studies did not detect an association between trans fats and cognitive outcomes,

one study[53] found that cognitive decline increased with increasing consumption of trans fats in women aged 74 years with type 2 diabetes (figure; appendix). Another observational study[60] in men and women aged 65 years or older reported an interaction between saturated fats, trans fats, and copper. In that study, higher copper intake was associated with a faster decline in cognitive function in the presence of a diet high in saturated and trans fats (appendix).

Food groups and beverages

Fish and seafood

Several observational studies support a potentially beneficial association between fish or seafood consumption and cognitive outcomes (figure; appendix), which is consistent with the results of a 2017 meta-analysis.[61] In one study,[62] a significant protective association was observed between fish consumption and dementia, but only in carriers of *APOE* ε4. Similarly, in a study[49] that reported an overall protective effect of fish consumption on cognitive decline, results were stronger for *APOE* ε4 carriers than for non-carriers. These observations suggest that fish consumption might be particularly beneficial in individuals with a certain genetic background.

Fruits and vegetables

Slower rates of cognitive decline and decreased risk of dementia have been detected in individuals who consume more vegetables (in most observational studies) and fruits (in some observational studies; figure; appendix). Benefits were greatest for green leafy vegetables, a source of folate and flavonoids, and for berries, also a good source of flavonoids. Three observational studies examined fruits and vegetables as a single category and found that the risk of dementia or Alzheimer's disease was reduced with increasing consumption (figure). It is not possible to derive from such studies which of the two food groups is driving the association or whether an interaction is present.

Meat, legumes, and dairy products

No association between meat or legume consumption and cognitive dysfunction has been found in the few studies that have examined these food groups (figure; appendix). Similarly, few studies have investigated the association between dairy products and cognitive dysfunction or dementia. The findings of studies that have investigated this association have been mixed, with one study[63] that followed up participants for 25–30 years reporting a lower incidence of vascular dementia in individuals aged 30 years or older who consumed milk every day than in those who consumed milk less than four times a week. Another study[64] found that the incidence of Alzheimer's disease dementia was reduced in participants aged 60 years or older who reported high consumption of milk and dairy products. In another study,[65] the rate of cognitive decline was faster in participants aged 45–64 years who consumed more than one glass of milk a day than in those who rarely consumed milk (appendix).

Nuts and olive oil

All of the evidence on food groups other than nuts and olive oil stems from observational studies (figure). In two small clinical trials (part of PREDIMED,[66] a trial initially designed with non-cognitive outcomes), supplementation of cognitively healthy individuals aged 55–80 years with nuts 30 g per day or olive oil 1 L per week for 4 years or 6·5 years prevented the decline in cognitive function, as assessed with various neuropsychological tests (figure; appendix). Nevertheless, in these trials, nuts and olive oil were not explored separately but in the context of a Mediterranean-type diet, leaving the question of independent effects unanswered (appendix).

Alcoholic beverages

Although alcohol is not a nutrient or even a substance with a distinct beneficial role in the human body, evidence suggests that light to moderate consumption of some alcoholic beverages (one drink or less per day in women and one to two drinks per day in men) might be related to beneficial health outcomes, particularly cardiovascular outcomes.[67]

Regarding cognitive outcomes, most observational studies have found benefits with moderate alcohol consumption (one to three drinks per day), either in relation to dementia incidence or rates of cognitive decline (figure; appendix). Wine (particularly red) has been shown to have the strongest protective association, whereas beer and spirits have been reported as either not related to, or related to poor, cognitive outcomes.

Confidence in these associations is moderated by the fact that no clinical trial exploring the cognitive benefits of alcoholic beverages has been completed. However, alcohol-use disorders associated with excessive drinking have been linked to poor cognitive outcomes. In a nationwide, retrospective cohort study in France,[68] alcohol-use disorders were the strongest modifiable risk factor among all risk factors (eg, vascular risk factors, presence of cardiovascular diseases, depression, or less education) for onset of all types of dementia, particularly early-onset dementia.

Coffee and tea

Coffee and tea are the most common sources of not only caffeine but also other biologically active compounds, including many polyphenols.[69] Several neuropharmacological activities have been suggested for coffee ingredients, including antioxidant, anti-inflammatory, and neuroprotective effects.[70]

Observational studies of tea and coffee have been done in people of all ages (ranging from 24 years to older than 65 years at baseline), with varying durations of follow-up (up to 28 years; figure; appendix). Overall, coffee, tea, or caffeine intake might have a protective effect on cognitive

	Nutrients	Food groups
Mediterranean diet[73-75]	High intake of folate, vitamin E, carotenoids, flavonoids and other antioxidants, dietary fibre, and monounsaturated fatty acids; balanced intake of unsaturated fatty acids; reasonably high intake of n-3 fatty acids; and low intake of saturated fatty acids	High consumption of fruits, vegetables, wholegrains, and olive oil; everyday consumption of fermented dairy, nuts, seeds, herbs or spices; emphasis on plant proteins (legumes) and seafood instead of red meat; wine in moderation; and daily consumption of herbal infusions
DASH diet[76]	High in potassium, magnesium, calcium, fibre, and protein; low in saturated fatty acids, total lipids, cholesterol, and sodium; and high intake of folate, vitamin E, carotenoids, flavonoids, and other antioxidants	High consumption of fruits, vegetables, low-fat dairy products, and wholegrains; reasonably high consumption of lean animal protein but low consumption of red meat; and emphasis on foods that are low in saturated and trans lipids, sodium, and sugar
MIND diet[77]	High intake of folate, vitamin E, carotenoids, flavonoids and other antioxidants, dietary fibre, and monounsaturated fatty acids, and low intake of saturated and trans fatty acids	Increased consumption of green leafy or other vegetables, nuts, berries, beans, wholegrains, fish, poultry, olive oil, and wine, and decreased consumption of red meats, butter and stick margarine, cheese, pastries, sweets, and fried or fast foods

DASH=Dietary Approaches to Stop Hypertension. MIND=Mediterranean-DASH Intervention for Neurodegenerative Delay.

Table 2: **Dietary patterns related to cognitive function**

decline, although studies frequently report no association (figure; appendix). Evidence is not clear whether the source of caffeine (ie, coffee *vs* tea) or other constituents of coffee or tea are important. Some studies have suggested an increasing dose response, whereas others have found a beneficial association with mild to moderate consumption only (about three cups per day). In a longitudinal study,[71] re-evaluation of coffee consumption close to dementia diagnosis revealed that the risk of dementia was slightly increased with high consumption of coffee at that time, but was not associated with baseline intake. It is possible that any beneficial effect of coffee or tea is established through lifetime consumption, and thus an increase in consumption in later life might not have an effect on, or might even be detrimental to, cognitive health. No clinical trial exploring the cognitive benefits of caffeine has been done.

Dietary patterns, indices, and overall lifestyle

Dietary patterns

Owing to the complex biological interactions between different components of the diet, it has been proposed that the use of a whole-diet approach, through the study of dietary patterns rather than individual nutrients or food groups, might help to understand the role of diet in chronic diseases, such as cognitive impairment in elderly people.[72]

The Mediterranean diet is the most extensively studied dietary pattern (figure, table 2; appendix). The results of most observational studies suggest that higher adherence to the Mediterranean diet is associated with a slower decline in performance on various cognitive test batteries and a reduced risk of dementia, mild cognitive impairment, or progression from mild cognitive impairment to dementia. These findings are supported by two clinical trials[78,79] that tested a Mediterranean dietary pattern in combination with nuts or olive oil against advice to reduce dietary fat. These trials, which were nested within a larger trial (PREDIMED),[66] included relatively few participants but had a reasonably long follow-up (4·1–6·5 years). Another clinical trial[80] in fewer participants and with only 6 months of follow-up showed that a Mediterranean diet did not significantly improve performance on an 11-item neuropsychological test battery compared with the habitual diet control group. At least three meta-analyses of prospective cohort studies investigating the Mediterranean diet have been published and have suggested an overall beneficial effect of adherence to the Mediterranean diet on reducing the risk of mild cognitive impairment, dementia, and Alzheimer's disease,[81,82] or overall neurodegenerative diseases.[83] By contrast, a meta-analysis[84] including only randomised controlled trials concluded that the associations are mostly non-significant, with only small effect sizes.

Other dietary patterns have been also studied in relation to cognitive outcomes (figure, table 2; appendix). Two observational studies reported beneficial associations between cognitive outcomes (decline over time in performance on a single cognitive test and incidence of Alzheimer's disease) and adherence to the Dietary Approaches to Stop Hypertension (DASH) diet in men and women, whereas one study found no association (figure). In four observational studies, high adherence to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet was linked to a decreased risk of Alzheimer's disease or a slower decline in cognitive performance, as assessed either with single cognitive tests or a comprehensive test battery (figure). Two observational studies have examined the Nordic diet, which is characterised by a high intake of vegetables, fruits, fish, and wholegrain products; low to moderate intake of meat and alcohol; and consumption of rapeseed oil as the recommended source of fat. In one study[85] in men and women aged 65 years or older followed up for 6 years, higher adherence to the Nordic diet was associated with reduced cognitive decline compared with low adherence, as assessed with only the Mini-Mental State Examination, whereas another study[86] in men and women aged 57–78 years, who were followed up for 4 years, found no association when using a more comprehensive assessment of cognitive performance.

A few observational studies have investigated other healthy dietary indices based on dietary guidelines, with results suggesting either cognitive protection or no

association (figure; appendix). A-posteriori approaches (ie, data-driven patterns derived from statistical analyses and not defined a priori based on health effects in other medical conditions) have been used in some studies,[87–89] which revealed protective associations for population-specific dietary patterns. Overall, the dietary pattern approach has proven to be the most fruitful in terms of association with cognitive outcomes.

Multidomain interventions

One small and three large multidomain interventions, all including a dietary component, have been assessed in clinical trials (figure; appendix). These trials incorporated nutritional guidance for a healthy diet, as well as coaching regarding modification of other lifestyle factors, such as physical activity, cognitive training, and control of cardiovascular risk factors.

In a small Korean trial[90] in participants older than 60 years, the multidomain intervention group (in which the nutrition component included increased consumption of fruits, vegetables, and fish) was associated with a slower decline in Mini-Mental State Examination scores than was the control group after 1·5 years. In the FINGER trial,[91] individuals aged 60–77 years with a high risk of dementia received (as part of a multidomain intervention) individual and group sessions with nutritionists who tailored the participants' diets towards increased consumption of fruits, vegetables, wholegrain cereals, fish, low-fat milk, and low-fat meats, and reduced consumption of sucrose and butter. Slower cognitive decline, particularly in executive functioning and speed, was noted for individuals who were assigned to the multidomain intervention.

Secondary analyses in some of the larger trials that did not observe an overall protective effect (preDIVA[92] and MAPT[93] trials) found that the protective effects of multidomain interventions were limited to subgroups of individuals (eg, those with more vascular risk factors, higher future dementia risk scores, or brain amyloid positivity, or carriers of *APOE* ε4). Although the results of secondary analyses should be interpreted with caution, these results could suggest that individuals at higher risk of neurodegeneration or future cognitive decline might benefit most from multidomain interventions. Additionally, the intensity of the intervention and participant adherence to it might affect their outcomes given that these factors seemed to have had a role in the absence of associations noted in some of these trials.[94]

Given the multidomain nature of these interventions, it is not clear whether the nutritional aspect or other components (eg, physical activity, cognitive activities, control of vascular risk factors) are responsible for the noted effects.

Conclusions and future directions

Nutrition is an important modifiable risk factor of cognitive dysfunction. The existing evidence suggests that certain nutrients or food ingredients, such as some B vitamins (particularly folate), flavonoids, vitamin D, and n-3 fatty acids, have the potential to benefit cognitive function. In terms of food groups, fish (and possibly other seafood), vegetables, and to a lesser extent fruit, as well as alcohol and coffee in moderation, might protect against cognitive decline. Somehow, stronger evidence exists for healthy dietary patterns, such as the Mediterranean diet, than for individual nutrients and food groups. Increasing the applicability of healthy dietary patterns to populations with different dietary cultures might be aided by the development of appropriate food guidelines for brain health that not only incorporate scientific knowledge but are also culturally adapted for each population. Several ongoing trials in individuals without cognitive impairment are examining the potential cognitive efficacy of certain dietary patterns, such as the MIND diet (NCT02817074) or the Multicultural Healthy Diet with anti-inflammatory properties (NCT03240406); of food items such as walnuts (NCT01634841); and of natural supplements (ACTRN12611000487910). These trials should help formulate specific food guidelines for prevention of cognitive impairment.

Although we focused on the results of prospective studies that were well powered, most of the available

***Panel 2*: Future research directions**

Dietary assessment

- Use of improved, validated dietary tools and multiple measures (multiple short-term quantitative measures with or without non-quantitative information about usual consumption), possibly improved by new technologies[95,96]
- Use of social media applications and other technologies to record dietary information (although computer literacy is a prerequisite)
- Use of a more extensive list of nutrient biomarkers, possibly aided by new omics approaches, to assess the independent and combined effects of many nutrients and food ingredients
- Exploration of many aspects of the diet not studied thus far (eg, fluid intake and chronobiology of nutrition, such as timing or distribution of food intake during the day)
- Focus on dietary patterns

Study design

- Consideration of pertinent confounders not related to diet
- Studies with long-term follow-up or in various periods of life using multiple dietary assessments
- Emphasis on populations susceptible to diet inadequacy, cognitive decline, or both
- Careful selection of populations with neurobiological pathologies that are reasonably homogeneous
- Replication of findings in populations with different genetic backgrounds and exposures to environmental factors
- Implementation of pilot, biomarker-guided clinical trials, with feasibility components
- Clinical trials targeting earlier windows of exposure, before onset of age-related cognitive decline or neurodegeneration
- Implementation of large-scale preventive interventions based on already identified brain healthy dietary patterns
- Examination of potential sex differences in the effect of dietary components on cognitive outcomes

Search strategy and selection criteria

We aimed to provide a comprehensive review of the role of nutrition in dementia development or cognitive decline associated with ageing in humans. We searched PubMed up to Feb 28, 2018, for full-text, English-language articles using "dementia", "cognitive function", "diet", and "nutrition" as initial keywords. Subsequent searches were performed for each diet component separately, and we also manually searched the reference lists of identified relevant reviews. We included longitudinal studies and clinical trials reporting clinical outcomes (ie, cognitive performance, mild cognitive impairment, dementia, and dementia types), but not neurobiological mechanisms or biomarker outcomes (ie, CSF biomarkers and brain imaging biomarkers). To minimise the possibility of insufficient power or type 2 error, longitudinal studies had to have a minimum sample size of around 1000 participants and clinical trials of around 100 participants. Additionally, clinical trials had to have a minimum follow-up of 6 months. Given that this Review focuses on prevention rather than on prognosis, we excluded studies in which participants had dementia, mild cognitive impairment, or another form of cognitive impairment at baseline. This Review is not exhaustive or a meta-analysis. Excluded studies involving individuals with cognitive impairment at baseline or with insufficient power (ie, trials of fewer participants or shorter duration) might still have provided useful information.

evidence is observational, with data from large, long-term clinical trials rarely available. For many dietary factors, even high-quality observational studies are extremely scarce. As a result, caution is necessary when interpreting the existing literature given that the absence of proof does not equate to proof of absence. Methodological challenges associated with nutrition research need to be addressed before reliable and detailed clinical recommendations can be made (panel 1). Improvements in methods for nutrition assessment and study design could address many of these challenges (panel 2). For example, many dietary assessment methods associated with mobile phones or wearable devices have been developed and allow meals to be recorded using images, videos, or voice recordings, enabling a more accurate automated or manual analysis of dietary intake.[97] Omics technologies have opened new avenues in the field of nutritional biomarkers through measurement of biochemical changes at the level of DNA or RNA, proteins, and the metabolome, thus providing comprehensive insights into the cellular processes that mediate diet-related responses. However, biomarker approaches have limitations that mean that self-reported dietary intake data must also be collected because they not only capture the intake of nutrients but also crucial and valuable information about the foods and beverages consumed and the related context (panel 1).[98]

Future nutrition research will have the opportunity to examine aspects of nutrition that have been rarely explored thus far and for which data relating to cognitive function are scarce (panel 2). For example, water intake, hydration status, chronobiology of food intake (eg, time of eating), and the distribution of nutrient or food intake during the day have been linked to other health outcomes. Analysis of certain populations, such as those with poor dietary patterns or other risk factors (genetic, physiological, or lifestyle), might enable detection of more robust associations between diet and cognitive health.

The use of biomarkers of different underlying neurobiological processes (ie, amyloid-β, τ protein, vascular pathologies, connectivity, and neuroinflammation) that can be detected in the CSF or by neuroimaging might help mitigate some of the limitations associated with clinical trials of nutrition by aiding the selection of subgroups or by providing intermediate outcomes that are more sensitive to change than are clinical outcomes. Pilot intervention studies involving biomarkers will provide the necessary preliminary evidence to design and implement larger experimental investigations.

Contributors

All authors contributed equally to the literature search, figure design, data collection, data analysis, data interpretation, and writing of the Review.

Declaration of interests

NS reports grants from Alzheimer's Association, European Social Fund, and Ministry for Health Greece, during the conduct of the study, and personal fees from Merck Consumer Health and National Institutes of Health, outside the submitted work. CAA reports grants from the Greek State Scholarships Foundation (MIS: 5001552), during the conduct of the study. MY declares no competing interests.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Scarmeas N, Anastasiou CA, Yannakoulia M. Nutrition and prevention of cognitive impairment. *Lancet Neurol* 2018; published online Sept 20. http://dx.doi.org/10.1016/S1474-4422(18)30338-7.

Supplement

Tables

Table 1

Selective Evidence on the Association between B Vitamins and Cognitive Function						
Longitudinal Studies						
Reference	**Sample Characteristics at baseline**	**Nutritional assessment**	**Outcomes**	**Years of follow-up**	**Results**	**Effect**
Qin et. al., Am J Clin Nutr, 2017 [1] *Coronary Artery Risk Development in Young Adults (CARDIA) study, USA*	3,136 men and women , age 18-30 ys	interviewer-administered CARDIA Diet History at years 0, 7 and 20	Rey Auditory Verbal Learning Test (verbal memory), Digit Symbol Substitution Test (psychomotor speed), Modified Stroop Interference Test (executive function)	25 ys	**Folate** intake associated with less decline in psychomotor speed. **B6** intake associated with less decline in psychomotor speed. **B12** intake associated with less decline in psychomotor speed. **Niacin** intake associated with less decline in psychomotor speed and executive function.	↑ ↑ ↑ ↑
Luchsinger et. al., ArchNeurol, 2007 [2] *Northern Manhattan, USA*	965 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	AD diagnosis	6.1 ys	HR for dementia in the higher vs. lower quartile of **folate** 0.5. NS for **B6**. NS for **B12**.	↑ — —
Lefevre-Arbogast et. al., Nutrients, 2016 [3] *Three-City, Study, France*	1,321 men and women, age 75.8 ys	24-hour dietary recall	Dementia diagnosis	7.4 ys	HR for dementia in the higher vs. lower quartile of **folate** 0.5. NS for **B6**. NS for **B12**.	↑ — —
Haan et. al., Am J Clin Nutr, 2007 [4] *Sacramento Area Latino Study on Aging, USA*	1,779 men and women, age 60-101 ys	plasma B12, RBC folate	Dementia diagnosis and neuropsychological test battery	4.5 ys	HR for combined dementia and cognitive impairment NS for **folate**. **B12** increased the risk for combined dementia and cognitive impairment (HR of 1.07 per unit), however low B12 levels increased the HR for homocysteine. HR for homocysteine 2.39 (per unit).	— ↑
Morris et. al., J	1,041 men and	Semiquantitative	AD diagnosis	3.9 ys	HRs for AD in higher vs. lower quintile of **folate** (total	—

Alz Dis, 2006 [5] *Chicago Health and Aging Project, USA*	women, age ≥65 ys	food-frequency questionnaire			or dietary) NS. HRs for AD in higher vs. lower quintile of **B6** (total or dietary) NS. HRs for AD in higher vs. lower quintile of **B12** (total or dietary) NS.	— —
Nelson et. al., J Nutr Health Aging, 2009 [6] *Cache County Memory, Health and Aging Study, USA*	3,634 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	dementia and AD diagnosis	9 ys	ORs for dementia or AD NS by increasing quintiles of **folate** (diet or supplements) ORs for dementia or AD NS by increasing quintiles of **B6** (diet or supplements) ORs for dementia or AD NS by increasing quintiles of **B12** (diet or supplements)	— — —
Morris et. al., Arch Neurol., 2005 [7] *Chicago Health and Aging Project, USA*	3,718 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	East Boston Tests of Immediate Memory and Delayed Recall, Mini-Mental State Examination, Symbol Digit Modalities Test	6 ys	Higher rate of cognitive decline in the higher vs. lower quintile of total or dietary **folate** intake. NS for **B12** in the total population.	⬇ —
Clinical Trials						
Reference	**Sample Characteristics at baseline**	**Intervention**	**Outcomes**	**Duration**	**Results**	**Effect**
Durga et. al., Lancet, 2007 [8] *FACIT trial, Netherlands*	818 men and women, age 50-70 ys	0.8 mg **folate** vs. placebo	5 separate tests used in the Maastricht Aging Study (memory, sensorimotor speed, complex speed, information processing speed, and word fluency) and Mini-Mental State Examination State	3 ys	Significant effects of supplementation on global cognition, memory, and information processing speed. Supplementation more effective for those with high baseline homocysteine levels in information processing speed and in those with low baseline B12 status in sensorimotor speed and in information processing speed.	⬆
Andreeva et. al., Am J Clin Nutr 2011 [9] *SU.FOL.OM3 Study, France*	1,748 men and women, age 45-80 ys with a history of myocardial infarction,	0.56 mg **folate** + 3 mg **B6** + 0.02 mg **B12** vs. 600 mg **EPA + DHA** vs. vitamins + omega-3 fatty	French version of the modified Telephone Interview for Cognitive Status	4 ys	NS main group effects on cognitive function. In individuals with myocardial infarction or unstable angina participants assigned to supplementation with **B vitamins** plus omega-3 fatty acids were significantly less likely to score lower on semantic memory, while those with ischemic stroke less likely	— ⬆ **(coronary syndromes)**

	unstable angina, or ischemic stroke	acids vs. placebo.			to score lower on temporal orientation. Same results when treatment groups were pooled into B vitamins or no B vitamins supplementation.	
Ford et. al., Neurology 2010 [10] *Australia*	299 hypertensive men, age ≥75 ys	2 mg **folate** + 0.4 mg **B12** + 25 mg **B6**	Change in the cognitive sub-scale of the Alzheimer's Disease Assessment Scale (ADAS-cog).	2 ys	NS difference in ADAS-cog change between groups.	–
Eussen et. al., Am J Clin Nutr, 2006 [11] *Netherlands*	195 men and women, age 70 y with mild vitamin B12 deficiency	1000 _µg vitamin **B12** vs. 1000 _µg, vitamin **B12** + 400 _ _µg **folate** vs. placebo	Cognitive performance by Mini-Mental State Examination, Clinical Dementia Rating Scale, and Geriatric Depression Scale	0.5 ys	NS differences in cognitive performance change.	–
McMahon et. al., NEJM, 2006 [12] *New Zealand*	276 men and women, age ≥65 ys, with plasma homocysteine concentrations of ≥13 µmol/L	Daily **folate** (1000 µg) and vitamins **B12** (500 µg) and **B6** (10 mg) vs. placebo	Cognitive performance by Mini-Mental State Examination, Rey Auditory Verbal Learning Test, Wechsler Memory Scales, Controlled Oral Word Association Test of the Multilingual Aphasia Examination, Reitan Trail Making Test	2 ys	NS differences in cognitive performance change.	–

↑: denotes a protective effect; ↓: denotes a detrimental effect; -: denotes no statistically significantly effect.

Table 2

Selective Evidence on the Association between Antioxidants and Cognitive Function						
Longitudinal Studies						
Reference	**Sample Characteristics at baseline**	**Nutritional assessment**	**Outcomes**	**Years of follow-up**	**Results**	**Effect**
Featr et. al., J Gerontol A Biol Sci Med Sci, 2016 [13] *Three-City-Bordeaux Study, France*	1,092 men and women,	plasma carotenes	dementia and AD diagnosis	**9.5 ys**	**Total carotenes**, **beta-carotene** and **lutein** increased the risk for dementia only when expressed as a function of plasma lipids	⬆
Akbaraly et. al., Epidemiology, 2007 [14] *EVA study, France*	1,389 subjects, age 60-71 ys	plasma selenium	Mini-Mental Status Examination, Trail Making Test part B, Digit Symbol Substitution	9 ys	**Selenium** decreases over 9ys, but not over 2 ys, were associated with decline in all cognitive tests.	⬆
Morris et. al., Am J Clin Nutr, 2005 [15] *Chicago Health and Aging Project, USA*	3,718 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	AD diagnosis; East Boston Tests of Immediate and Delayed Recall, Mini-Mental State Examination, Symbol Digit Modalities Test	4 ys, 6 ys	RR for AD at 4 ys per 5 mg/day increase in total **vitamin E** intake 0.74. Statistically significant difference in cognitive decline per increase in **vitamin E** intake at 6 ys.	⬆
Engelhart et. al., JAMA, 2002 [16] *Rotterdam Study, Netherlands*	5,395 men and women, age ≥55 ys	Semiquantitative food-frequency questionnaire	dementia and AD diagnosis	6 ys	RR for AD per 1 SD increase in intake of **vitamin C** 0.82 RR for AD per 1 SD increase in intake of **vitamin E** 0.82 NS for **beta carotene** NS for **flavonoids**. More pronounced associations for current smokers, in which associations were also found for beta carotene and flavonoids (RRs of 0.49 and 0.54 respectively).	⬆ ⬆ — —
Devore et. al., Arch Neurol, 2010	5,395 men and women, age ≥55	Semiquantitative food-frequency	dementia and AD diagnosis	9.6 ys	HR for dementia in the lowest vs. higher tertile of **vitamin E** intake 0.75.	⬆

[17] *Rotterdam Study, Netherlands*	ys	questionnaire			NS for **vitamin C** NS for **beta carotene**.	— —
Luchsinger et. al., JAMA, 2003 [18] *Washington Heights-Inwood Columbia Aging Project, USA*	980 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	AD diagnosis	4 ys	Intake of **vitamin C** in supplements, diet or in both not related to the risk of AD. Intake of **vitamin E** in supplements, diet or in both not related to the risk of AD. Intake of **caroteres** in supplements, diet or in both not related to the risk of AD.	— — —
Dai et. al., Am J Med, 2006 [19] *Kame Project, USA*	1,836 Japanese-Americans, age ≥65 ys	Semiquantitative food-frequency questionnaire	AD diagnosis	8 ys	HR for AD not associated with intake of **vitamin C** HR for AD not associated with intake of **vitamin E** HR for AD not associated with intake of **beta-carotene**	— — —
Laurin et. al., Am J Epidemiol, 2004 [20] *Honolulu-Asia Aging Study, USA*	2,459 Japanese-American men, age 45-68 ys	24-hour dietary recall	dementia and AD diagnosis	30.2 ys	RR for dementia or AD by quartiles of intake of **vitamin C** NS RR for dementia or AD by quartiles of intake of **vitamin E** NS RR for dementia or AD by quartiles of intake of **beta-carotene** NS RR for dementia or AD by quartiles of intake of **flavonoids** NS	— — — —
Nooyens et. al., Br J Nutr, 2015 [21] *Doetinchem Cohort Study, Netherlands*	2,613 men and women, age 43-70 ys	Semiquantitative food-frequency questionnaire	15 Words Verbal Learning Test (memory: immediate and delayed recall), Stroop Colour-Word Test (speed and cognitive flexibility), Word Fluency Test (semantic memory) and Letter Digit Substitution Test (speed)	5 ys	**Flavonoids** intake associated with a decrease in decline in speed. **Lignans** intake associated with a decrease in decline in global cognition and all cognitive domains. NS for **vitamin C** NS for **vitamin E** NS for **beta-carotene** and **lutein**	⬆ — — —
Morris et. al., Arch Neurol., 2006 [22] *Chicago Health and Aging Project, USA*	3,718 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	East Boston Tests of Immediate Memory and Delayed Recall, Mini-Mental State Examination, Symbol Digit Modalities Test	6 ys	Annual rate of change in cognitive function in higher vs. lower quintile of total **copper** intake NS. Under a diet high in saturated and trans fat, higher intake of copper was associated with more cognitive decline	— ⬇
Commenges et.	1,367 men and	Semiquantitative	Dementia diagnosis	5 ys	RR for dementia in the highest vs. lowest tertile of	⬆

al., Eur J Epidemiol, 2000 [23] *PAQUID Study, France*	women, age ≥65 ys	food-frequency questionnaire			**flavonoids** intake 0.49.	
Letenneur et. al., Am J Epidemiol, 2007 [24] *PAQUID Study, France*	1,990 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	Mini-Mental State Examination, Benton's Visual Retention Test (BVRT), ''Isaacs'' Set Test (IST), Zazzo's cancellation test, Wechsler's Digit Symbol Test	10 ys	Subjects with the lowest **flavonoid** intake had lost on average 2.1 points on the Mini-Mental State Examination, whereas subjects with the highest quartile had lost 1.2 points	⬆
Kesse-Guyot et. al., J Nutr, 2012 [25] *SU.VI.MAX trail, USA*	2,574 men (45-60 ys) and women (35-60 ys)	at least six 24-h dietary records	RI-48, a delayed, cued recall test for episodic memory, two verbal fluency tasks for lexical-semantic memory and Forward and Backward Digit Span for working memory. Mental flexibility was assessed via the Delis-Kaplan TMT	13 ys	High total **polyphenol** intake was associated with better language and verbal memory, but not with executive functioning. Intake of **catechins, theaflavins, flavonols,** and **hydroxybenzoic acids** was positively associated with language and verbal memory, especially with episodic memory. Negative associations between scores on executive functioning and intake of **dihydrochalcones, catechins, proanthocyanidins,** and **flavonols**.	⬆/⬇
Root et. al., J Med Food, 2015 [26]	10,041 men and women, age 45-64 ys	Semiquantitative food-frequency questionnaire	delayed word recall test, the revised Wechsler Adult Intelligence Scale digit symbol subtest, and the word fluency test of the Multilingual Aphasia Examination	6 ys	Total **flavonols** (or individual flavonols: myricetin, kaempferol, and quercetin) across quintiles of intake were positively associated with preserved combined cognitive function.	⬆
Devore et. al., Ann Neurol, 2012 [27] Nurses' Health Study, USA	16,010 men and women, age ≥70 years	Semiquantitative food-frequency questionnaire	Telephone Interview of Cognitive Status, East Boston Memory Test (immediate and delayed recalls), category fluency; delayed recall of the Telephone	4.2 ys	Greater intakes of **anthocyanidins** and total **flavonoids** were associated with slower rates of cognitive decline.	⬆

			Interview of Cognitive Status 10-word list and digit span backward			
Gray et. al., Am J Ger Pharmacotherapy, 2003 [28] *Established Populations for Epidemiologic Studies of the Elderly, USA*	2,082 men and women, cognitively normal	use of supplemental antioxidants (vitamins A, C, or E, plus selenium or zinc)	Short Portable Mental Status Questionnaire (SPMSQ)	3 and 7 ys	OR for development of cognitive impairment in **antioxidant users** vs. non-antioxidant users 0.66	⬆
Zandi et. al., Arch Neurol, 2004 [29] *Cache County Study, USA*	4,740 men and women, age ≥65 ys	At initial assessment questions about use of supplements during the presiding 2 wks	AD diagnosis	3 ys	HR for AD in **vitamin C and D supplement users** vs. no users of any supplement 0.36. NS for only E, or only C, or any B complex or any multivitamin use.	⬆
Clinical Trials						
Reference	**Sample Characteristics at baseline**	**Intervention**	**Outcomes**	**Duration**	**Results**	**Effect**
Wolters et. al., Preventive Medicine, 2005 [30], *Germany*	220 healthy, free-living women, 60-91 ys	**Multivitamin** capsule (including antioxidant nutrients at physiological doses) vs. placebo	Wechsler Adult Intelligence Scale-Revised (WAIS-III)	0.5 ys	NS changes in cognitive performance between groups.	—
Grostein et. al., Ann Intern Med, 2013 [31] *Physicians' Health Study II, USA*	5,947 men, age ≥65 ys	**Multivitamin** capsule (including antioxidant nutrients at physiological doses) vs. placebo	Telephone Interview for Cognitive Status (TICS), a telephone adaptation of the Mini-Mental State Examination, Immediate and Delayed recalls of the East Boston Memory Test, Delayed recall of a 10-word	8.5 ys	NS difference in the mean cognitive change over time between groups.	—

			list in the TICS, a category fluency task			
Kang et. al., Circulation 2009 [32] *Women's Antioxidant Cardiovascular Study, USA*	2,824 men and women, age ≥65 ys	Vitamin **E** (402 mg every other day) + **beta-carotene** (50 mg every other day) + vitamin **C** (500 mg daily) vs. placebo	Telephone Interview of Cognitive Status (TICS) and delayed recall of the TICS 10-word list, immediate and delayed recalls of the East Boston Memory Test, test of category fluency	5.4 ys	Supplementation was not associated with slower rates of cognitive change vs. placebo.	–
Kryscio et. al., JAMA Neurology, 2017 [33] *PREADViSE Trial, USA*	7,540 men, ≥60 ys	Vitamin **E** (400 IU/d) vs. **selenium** (200 µg/d) vs. Vitamin E and selenium vs. placebo	Dementia diagnosis	10 ys	NS difference in incident dementia among groups.	–

↑: denotes a protective effect; ↓: denotes a detrimental effect; -: denotes no statistically significantly effect.

Table 3

Selective Evidence on the Association between Vitamin D and Cognitive Function						
Longitudinal Studies						
Reference	**Sample Characteristics at baseline**	**Nutritional assessment**	**Outcomes**	**Years of follow-up**	**Results**	**Effect**
Feart et. al., Alzheimers Dement, 2017 [34]Three-City Bordeaux Study, France	916 men and women, age ≥65 ys	25(OH)D blood levels	Dementia and AD diagnosis, Mini-Mental State Examination, Isaacs Set Test, Benton Visual Retention Test, Trail Making Test A and B, Free and Cued Selective Reminding Test	median of 11.4 ys	Participants with **vitamin D deficiency** exhibited faster rates of cognitive decline vs. sufficient levels. HR for dementia or AD in vitamin D deficiency vs. sufficiency 2.12 and 2.85 respectively.	↑ ↑
Karakis et al., J Alzheimer's Disease,2016 [35] *Framingham Heart Study, USA*	1,663 men and women, age 72.4 ys (dementia incidence)/59.5 ys (cognitive testing)	25(OH)D blood levels	Dementia diagnosis, Trail Making A and B, Logical Memory delayed, Visual Reproductions delayed, Similarities, Hooper Visual Organization Test. Cognitive tests performed only at follow up.	9 ys (dementia incidence)/ 1.9 ys (cognitive testing)	Low levels of **vitamin D** associated with poorer cognitive performance at follow up. Low levels of **vitamin D** not associated with incident dementia.	↑ —
Breitling et. al., Experimental Gerontology, 2012 [36] *ESTHER study, Germany*	1,639 men and women, age ≥65 ys	25(OH)D blood levels	COGTEL phone interview, applied only 5 ys after baseline	5 ys	Women in the lowest quintile of **vitamin D blood levels** showed a 2.1 units lower COGTEL score than women in the highest quintile. NS for men.	↑ **(women)** — **(men)**
Toffanello et. al., Neurology, 2015 [37]*Pro.V.A. Study, Italy*	1,927 men and women, age 74 ys	25(OH)D blood levels	Mini-Mental State Examination	4.4 ys	RR for substantial cognitive decline in cognitively intact individuals at baseline 1.29 and 1.36 for **vitamin D insufficiency** and **deficiency** at baseline respectively.	↑
Zandi et. al., Arch Neurol, 2004 [29] *Cache County*	4,740 men and women, age ≥65 ys	At initial assessment questions about	AD diagnosis	3 ys	HR for AD in **vitamin C** and **D supplement users** vs. no users of any supplement 0.36. NS for only E, or only C, or any B complex or any multivitamin use	↑

Study, USA		use of supplements during the presiding 2 wks				
Licher et. al., J Alzheimer's Disease,2017 [38] *The Rotterdam Study, The Netherlands*	6,087 men and women, age ≥55 ys	25(OH)D blood levels	Dementia and AD diagnosis	median of 13.3 ys	OR for dementia or AD per SD decrease in **25(OH)D levels** 1.11 and 1.13 respectively.	↑
Slinin et. al., J Gerontol A Biol SCi Med, 2012 [39] *Osteoporotic Fractures Study, USA*	6,257 women, , age ≥65 ys	25(OH)D and 1,25(OH)D blood levels	Modified Mini-MentalState Examination (3MS) and Trail Making Test Part B	4 ys	OR for cognitive decline by MMSE in **sufficient vs.deficient or severely deficient vitamin D levels** 1.31 and 1.58 respectively. NS for trails B test.	↑ **(MMSE)** – **(Trail B)**

Overman et.al., Eur J Nutr, 2016 [40] *European Male Ageing Study, Europe*	2,430 men, age 59 ys	25(OH)D and 1,25(OH)D blood levels	Rey-Osterrieth Complex Figure Test, Camden Topographical Recognition Memory, Digit Symbol Substitution Test	4.4 ys	Decline in performance in cognitive tests not significantly associated with **25(OH)D or 1,25(OH)D blood levels**.	–
Olsson et. al., Am J Clin Nutr, 2017 [41] *Uppsala Longitudinal Study of Adult men, Sweden*	1,182 men, age 71 ys	7-d dietary records, plasma 25-hydroxyvitamin D	Dementia dignosis, Mini-Mental State Examination	median of 12 ys	HR for all cause dementia NS for high vs. low plasma concentrations or dietary intake of **vitamin D**	–
Slinin et. al., Neurology 2010 [42] *Osteoporotic Fractures Study, USA*	1,604 men, age ≥65 ys	25(OH)D and 1,25(OH)D blood levels	Modified Mini-MentalState Examination (3MS) and Trail Making Test Part B	4.6 ys	OR for cognitive impairment in the higher vs. lower quintile of **25(OH)D levels** NS.	–
Clinical Trials						
Reference	**Sample**	**Intervention**	**Outcomes**	**Duration**	**Results**	**Effect**

	Characteristics at baseline					
Rossom et. al., J Am Geriatr Soc . 2012 [43] *Women's Health Initiative, USA*	4,143 women, age ≥65 ys	1000 mg of **calcium carbonate** + 400 IU of **vitamin D3** vs. placebo	Dementia and mild cognitive impairment incidence, cognitive function by Modified Mini Mental State Examination and WHISCA cognitive battery	7.8 ys	No significant differences in incident dementia or mild cognitive impairment, or in global or domain specific cognitive function between groups	–

↑: denotes a protective effect; ↓: denotes a detrimental effect; -: denotes no statistically significantly effect.

Table 4

Selective Evidence on the Association between Macro-nutrients and Cognitive Function						
Longitudinal Studies						
Reference	**Sample Characteristics at baseline**	**Nutritional assessment**	**Outcomes**	**Years of follow-up**	**Results**	**Effect**
Roberts et. al., J Alzheimers Dis., 2012 [44] *USA*	937 men and women, mean age 79.5 ys	Semiquantitative food frequency questionnaire	Dementia diagnosis and MCI	3.7 ys	OR for dementia and MCI in the upper vs. lower quartile of **%carbohydrate** intake 1.89 OR for dementia and MCI in the upper vs. lower quartile of **%lipid** intake 0.56 OR for dementia and MCI in the upper vs. lower quartile of **%protein** intake 0.79.	⬇ ⬆ ⬆
Schaefer et. al., Arch Neurol., 2006 [45] *Framingham Heart Study, USA*	899 men and women, mean age 76.0 ys, free of dementia	Plasma phosphatidylcholine (PC) Docosahexaenoic acid (DHA)	All-cause dementia and AD	Mean of 9.1 ys	Subjects in the upper quartile of baseline plasma PC **DHA** levels, compared with subjects in the lower 3 quartiles, had a relative risk of 0.53 of developing all-cause dementia and 0.61 of developing Alzheimer disease	⬆
Kyle et. al., Lipids, 1999 [46] *USA*	1,118 men and women, mean age 75 ys	Plasma fatty acids of phospholipids	AD diagnosis and MMSE	10 ys	Subjects whose serum PC-**DHA** was in the lower half of the distribution, but who had no AD at the time the blood sample was taken had a 67% greater likelihood of developing AD. NS for other ω-3 fats.	⬆
Samieri et. al., Am J Clin Nutr, 2008 [47] *Three-City Study from Bordeaux, France*	1,214 non-demented men and women, age ≥65 ys	plasma PUFAs	Dementia diagnosis	4 ys	HR for 1 SD of plasma proportion for **EPA** 0.69, not significant for total ω-3 and DHA. HR for 1 unit of ω-6 to total ω-3 fats 1.09 (non-depressive subjects).	⬆
Ronnemaa et. al., Eur J Clin Nutr, 2012 [48] *Uppsala Longitudinal Study of Adult Men, Sweden*	2,009 men, age 50 ys	Fasting serum cholesteryl ester fatty acid (FA) composition	Dementia and AD diagnosis	20 ys	HR for the risk of AD NS for **ω-3** fatty acids. HR for the risk of AD for a 1-s.d. increase in **palmitic acid** (saturated) 0.72..	⬌ ⬇
van de Rest,	915 men and	Semiquantitative	A standardized battery	Mean of	In ApoE ε4 carriers only, slower rates of decline in	⬌

Neurology, 2016[49] *Rush Memory and Aging Project, USA*	women, age 81.4 ys	food frequency questionnaire	including 21 cognitive tests	4.9 ys	global cognition was observed with high intake (tertile 3 vs. 1) of **a-linolenic acid**, but not long chain ω-3 fatty acids (**DHA+EPA**). NS on the total population.	⬆ (ε4)
Morris et. al., Arch Neurol, 2005 [50] *Chicago Health and Aging Project, USA*	3,718 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	East Boston Tests of Immediate and Delayed Recall, Mini-Mental State Examination, and the Symbol Digit Modalities Test.	6 ys	Rate of change in cognitive score NS for total **ω-3, DHA**, **EPA**, **a-linolenic acid** intake.	-
Eskelinen et. al., Int J Geriatr Psychiatry, 2008[51] *CAIDE Study, Finland*	1,349 men and women free of dementia and MCI, age 50.2 ys	Questionnaire of 20 multiple choice questions about dietary habits	MCI diagnosis	Mean of 21 ys	OR of MCI for highest vs. two lower tertiles of intake of **total lipids** 1.69 OR of MCI for highest vs. two lower tertiles of intake of **SFA** 2.36	⬇ ⬇
Laitinen et. al., Dement Geriatr Cogn Disord, 2006 [52] *CAIDE Study, Finland*	1,449 men and women, age 50.4 ys	Questionnaire of 20 multiple choice questions about dietary habits	Dementia and AD diagnosis	21 ys	OR of dementia for **PUFA** in 2nd vs. 1st quartile of intake 0.40 OR of dementia for **SFA** in 2nd vs. 1st quartile of intake 2.45. OR for AD for **SFA** in 2nd vs. 1st quartile of intake 3.82	⬆ ⬇
Devore et. al., Diabetes Care, 2009 [53] *Nurses' Health Study, USA*	1,486 women diagnosed with T2D at age 74.3 ys	Semiquantitative food-frequency questionnaire (multiple assessments, beginning at middle-life)	Telephone East Boston Memory Test (immediate and delayed recalls), category fluency, delayed recall of 10-word list, and digit span backward. Assessment at Type 2 diabetes diagnosis and 2 ys later.	2 ys	Mean difference in global score for **SFA** in 3rd vs. 1st tertile -0.12. Mean difference in global score for **MUFA** fa in 3rd vs. 1st tertile 0.12 Mean difference in global score for **trans** fatty acids in 3rd vs. 1st tertile -0.15. Mean difference in verbal score for trans fa in 3rd vs. 1st tertile -0.15	⬇ ⬆ ⬇
Cherbuin et. al., Am J Geriatr Psychiatry, 2012[54] *PATH Through Life Study, Australia*	1,528 men and women, 60-64 ys	Semiquantitative food-frequency questionnaire, population specific MeDi score	MCI diagnosis	4 ys	High **MUFA** intake was protective of MCI.	⬆

Beydoun et. al., Am J Clin Nutr, 2007 [55] *Baltimore Longitudinal Study of Aging, USA*	2,251 men and women, age 50–65 ys	Plasma fatty acids in cholesteryl esters and phospholipids.	Delayed Word Recall Test, Digit Symbol Substitution Test portion of the Wechsler Adult Intelligence Scale–Revised (DSST/WAIS-R), Word Fluency Test (WFT) of the Multilingual Aphasia Examination	Plasma fatty acids measurement at visit 1, cognitive decline during 6 years, 3 years after visit 1	ORs for reliable change in global cognitive decline for **palmitic** acid cholesteryl esters and phospholipids 1.28 and 1.24. ORs for reliable change in global cognitive decline for **PUFA** cholesteryl esters 0.55 NS for **MUFA**	⬇ ⬆ —
Vercambre et. al., Eur J Clin Nutr, 2010 [56] *Women's Antioxidant Cardiovascular Study, USA*	2,551 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	Telephone Interview of Cognitive Status (TICS), TICS 10-word list delayed recall, East Boston Memory Test immediate recall, East Boston Memory Test delayed recall and animal naming test.	three follow ups at 2-ys intervals	**Total lipids** intake not related to cognitive decline. **MUFA** not related to cognitive decline in the total sample, but high intake was inversely related to cognitive decline in the oldest participants. **PUFA** not related to cognitive decline in the total sample, but high intake was inversely related to cognitive decline in the oldest participants.	— — ⬆ **(oldest)** — ⬆ **(oldest)**
Morris et. al, Neurology, 2004[57] *Chicago Health and Aging Project, USA*	2,560 men and women, age >65 ys	Semiquantitative food-frequency questionnaire	East Boston Tests of Immediate and Delayed Recall, the Mini-Mental State Examination, and the Symbol Digit Modalities Test	6 ys	Difference in rate of change in cognitive score in the 5th vs. 1st quintile of **saturated** fat -0.035. NS for **MUFA** NS for **trans**	⬇ — —
Nooyens et. al., Eur J Nutr, 2017[58] *Doetinchem Cohort Study, Netherlands*	2,612 men and women, age 43-70 ys	Semiquantitative food-frequency questionnaire	15 Words Verbal Learning Test (memory: immediate and delayed recall), Stroop Colour-Word Test (speed and cognitive flexibility), Word Fluency Test (semantic memory) and Letter Digit Substitution Test (speed)	5ys	**Total lipids** intake not associated with changes in cognitive outcomes **Saturated** lipids not associated with changes in cognitive outcomes **PUFA** not associated with changes in cognitive outcomes **a-linolenic** (**ω-3**) associated with less global cognitive decline and memory. EPA+DHA associated with less decline in apoE ε4 carriers only. **Cholesterol** negatively associated with decline in all cognitive outcomes.	— — — ⬆ ⬇

Kalmijn et. al., Ann Neurol, 1997[59] *Rotterdam Study, Netherlands*	5,386 men and women, non-demented, age 67.7 ys	Semiquantitative food-frequency questionnaire	dementia and AD	2 ys	RR of dementia in the 3rd vs. 1st tertile of **total lipids intake** was 2.4 NS for **saturated** lipids NS for **linoleic** acid NS for **cholesterol**	↓ — — —
Okereke et. al., Ann Neurol, 2012[60] *Women's Health Study, USA*	6,183 women, age 66 ys	Semiquantitative food-frequency questionnaire	Telephone Interview for Cognitive Status, East Boston Memory Test, delayed recall trial of the TICS 10-word list, category fluency	4 ys	Mean difference in global score for **SFA** in 5th vs. 1st quintile -0.12. Similar observations for verbal memory. Mean difference in global score for **MUFA** in 5th vs. 1st quintile 0.17. Similar observations for verbal memory.	↓ ↑
Engelhart et. al., Neurology, 2002[61] *Rotterdam Study, Netherlands*	5,395 men and women, age 67.7 ys	Semiquantitative food-frequency questionnaire	Dementia diagnosis	6 ys	**Total lipids** not associated with dementia risk. **SFA** not associated with dementia risk. **Trans** lipids not associated with dementia risk. **Cholesterol** not associated with dementia risk. **MUFA** not associated with dementia risk. **PUFA** not associated with dementia risk. **ω-6** PUFA not associated with dementia risk. **ω-3** PUFA not associated with dementia risk.	— — — — — — — —
Ylilauri et. al., Am J Clin Nutr, 2017[62] *Kuopio Ischaemic Heart Disease Risk Factor Study, Finland*	2,497 non-demented men, age 42-60 ys	4-day guided food record	Mini-Mental State Examination, Trail Making Test, Verbal Fluency Test, Selective Reminding Test, and Russell's adaptation of the Visual Reproduction Test	21.9 ys	**Cholesterol** intake not associated with indecent dementia or changes in cognitive function.	—
Clinical Trials						
Reference	**Sample Characteristics at baseline**	**Intervention**	**Outcomes**	**Duration**	**Results**	**Effect**
Yurko-Mauro et. al., Alzheimer's & Dementia, 2010[63] *USA*	485 men and women, age ≥55 ys	900 mg/d **DHA** vs. placebo	CANTAB Paired Associate Learning (PAL), a visuospatial learning and episodic memory test	0.5 ys	Fewer PAL six pattern errors with DHA versus placebo at 24 weeks. DHA supplementation was associated with improved immediate and delayed Verbal Recognition Memory	↑

					scores, but not working memory or executive function tests.	
Rogers et. al, Br J Nutrition, 2007[64] *United Kingdom*	190 men and women, moderate depressed, age 38 ys	630 mg **EPA** + 850 mg DHA vs. placebo	Various cognitive tests	0.25 ys	No improvement in any cognitive domain in supplemented vs. placebo groups.	–
van de Rest et. al., Neurology, 2008 [65] *Netherlands*	302 men and women, age ≥65 ys	1,800 mg/d **EPA-DHA** vs. 400 mg/d EPA-DHA vs. placebo	Cognitive test battery including many tests	0.54 ys	NS difference in cognitive performance among groups.	–
Dangour et. al., Am J Clin Nutrition, 2010 [66] *United Kingdom*	867 men and women cognitively healthy, age 75 ys	200mg/d **EPA** + 500mg/d **DHA** vs. placebo	CVLT and other cognitive test battery	2 ys	No improvement in memory, MMSE or any cognitive domain in supplemented vs. placebo groups.	–
Andrieu et. al., Lancet Neurol, 2017 [67] *MAPT trial, France*	1,680 non-demented men and women with memory complaint, limitations in one instrumental activity of daily living on slow gait speed, age ≥70 ys	800 mg **DHA** vs. **multi domain** intervention (cognitive training, physical activity, nutrition) vs. DHA + multi domain intervention vs. multi domain intervention + placebo vs. placebo alone	4 cognitive tests (free and total recall of the Free and Cued Selective Reminding test, ten Mini-Mental State Examination orientation items, Digit Symbol Substitution Test, and Category Naming Test)	3 ys	NS in cognitive decline between groups. In post-hoc analyses, in brain amyloid positive participants, less cognitive decline was observed in multi domain intervention + DHA or multi domain intervention + placebo groups vs. placebo alone.	–
Hooper et. al., J Nutr. Heatlh Aging, 2017 [68] *MAPT trial sub-analysis, France*	183 men and women with with low baseline ω-3 fatty acids	800 mg **DHA** vs. placebo			Significant difference in executive function in the supplementation vs. control group. NS for other cognitive tests.	↑ **(executive)**
Geleijnse et. al., Alzheimer's & Dementia, 2012[69] *Alpha Omega Trial, Netherlands*	2,911 coronary patients (stable myocardial infarction), 60-80 ys	400 mg/d **EPA-DHA** vs. 2 g/d **ALA** vs. **EPA-DHA + ALA** vs. placebo	Mini-Mental State Examination	3.3 ys	Risk of cognitive decline NS for active groups vs. placebo.	–

↑: denotes a protective effect; ↓: denotes a detrimental effect; -: denotes no statistically significantly effect.

Table 5

Selective Evidence on the Association between Specific Food Groups and Cognitive Function						
Longitudinal Studies						
Reference	**Sample Characteristics at baseline**	**Nutritional assessment**	**Outcomes**	**Years of follow-up**	**Results**	**Effect**
van de Rest, Neurology, 2016[49] *Rush Memory and Aging Project, USA*	915 men and women, age 81.4 ys	Semiquantitative food frequency questionnaire	A standardized battery including 21 cognitive tests	Mean of 4.9 ys	In the total population, consumption of ≥1 vs. <1 **seafood** meal was associated with slower decline in semantic memory and perceptual speed. In ApoE ε4 carriers, slower rates of decline in global cognition was observed with consumption of ≥1 vs. <1 seafood meal.	↑
Barberger-Gateau et. al., BMJ, 2002[70] *PAQUID Study, France*	1,426 men and women, age>68 ys	frequency of consumption of meat and fish or seafood	dementia and AD diagnosis	7 ys	Dementia and AD incidence was 6.61 and 5.29 times higher in those reported no **fish** or **seafood** consumption, compared to those with consumption once a day. NS for **meat**	↑ —
Morris et. al., Arch Neurol, 2005 [50] *Chicago Health and Aging Project, USA*	3,718 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	East Boston Tests of Immediate and Delayed Recall, Mini-Mental State Examination, and the Symbol Digit Modalities Test.	6 ys	Rate of change in cognitive score was 0.017 in 4th quartile, compared to the 1st quartile of **fish** consumption.	↑
Kalmijn et. al., Ann Neurol, 1997[59] *Rotterdam Study, Netherlands*	5,386 men and women, non-demented, age 67.7 ys	Semiquantitative food-frequency questionnaire	dementia and AD	2 ys	RR of dementia in the 3rd (higher) vs.1st tertile of **fish** consumption was 0.4.	↑
Barberger-Gateau et. al., Neurology, 2007 [71] *Three-City Cohort Study in Bordeaux, France*	8,085 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	dementia and AD diagnosis	4 ys	HR for dementia in high vs. low consumption of **fish** significant only in ApoE ε4 negative participants (0.78), not in the total population. HRs for dementia for **fruits and vegetables** 0.72 NS for **meat**	— (all) ↑ **(non ε4)** ↑ —

					NS for **animal fat** NS for **olive oil** NS for **ω-3 rich oils** NS for **ω-6 rich oils**	— — — —
Huang et. al., Neurology, 2005[72] *Cardiovascular Health Cognition Study, USA*	2,223 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	dementia and AD diagnosis	Average of 5.4 ys	HRs for dementia or AD in high vs. low **fish** consumption NS in fully adjusted models.	—
Nooyens et. al., Eur J Nutr, 2017[58] *Doetinchem Cohort Study, Netherlands*	2,612 men and women, age 43-70 ys	Semiquantitative food-frequency questionnaire	15 Words Verbal Learning Test (memory: immediate and delayed recall), Stroop Colour-Word Test (speed and cognitive flexibility), Word Fluency Test (semantic memory) and Letter Digit Substitution Test (speed)	5ys	**Fish** consumption not associated with cognitive outcomes.	—
Morris et. al., Neurology, 2017[73] *Memory and Aging Project, USA*	960 men and women, aged 58-99 ys	Semiquantitative food-frequency questionnaire	a battery of 19 cognitive tests characterising cognition in 5 cognitive domains (episodic memory, working memory, semantic memory, visuospatial ability, and perceptual speed)	mean of 4.7 ys	**Green leafy vegetables** was associated with slower cognitive decline (decline rate in the highest quintile was slower by 0.05 standardised units). Similar associations for individual bioactive compounds of green leafy vegetables (phylloquinone, lutein, folate, a-tocopherol, nitrate, kaempferol).	↑
Dai et. al., Am J Med, 2006 [19] *Kame Project, USA*	1,836 Japanese-Americans, age ≥65 ys	Semiquantitative food-frequency questionnaire	AD diagnosis	8 ys	HR for AD in high (≥3 times/wk) vs. low (<1 wk) consumption of **fruit and vegetable juices** 0.24.	↑
Morris et. al., Neurology, 2006[74] *Chicago Health and Aging Project, USA*	3,718 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	East Boston Tests of Immediate Memory and Delayed Recall, Mini-Mental State Examination, Symbol Digit Modalities Test	6 ys	Annual rate of change in cognitive function in 5th vs. 1st quintile of **green leafy vegetables** consumption 0.018. NS for yellow or cruciferous vegetables. NS for **legumes**,	↑ **(green)** — **(yellow, cruciferous)** —

					NS for **fruits**.	—
Hughes et. al., Am J Geriatr Psychiatry, 2010[75] *Swedish Twin Registry, Sweden*	3,799 men and women, age 48 ys	Semiquantitative food-frequency questionnaire	Dementia and AD diagnosis	31.5 ys	OR for dementia or AD in medium or high **fruits and vegetables** consumption vs. no or small consumption 0.73 and 0.60 respectively.	↑
Kang et. al., Annals Neurology, 2005[76] *USA*	13,388 women, age 74 ys	Semiquantitative food frequency questionnaire	Six cognitive tests by telephone, measuring general cognition, verbal memory, category fluency, and working memory	2 ys	V**egetable** consumption was significantly associated with less decline, especially **green leafy** vegetables. NS for **fruits.**	↑ —
Lee et. al., Age & Aging, 2017 [77] *Japan*	17,700 men and women, free of dementia, age ≥65 ys	Semiquantitative food frequency questionnaire	dementia diagnosis	6 ys	OR for dementia in at least three servings of **vegetables**/day vs. lower 0.88. OR for dementia in at least two servings of **fruits** / day vs. lower 0.86. OR for the **combination** 0.75.	↑ ↑ ↑
Devore et. al., Ann Neurol, 2012 [27] *Nurses' Health Study, USA*	16,010 participants, age ≥70 years	Semiquantitative food-frequency questionnaire	Telephone Interview of Cognitive Status, East Boston Memory Test (immediate and delayed recalls), category fluency; delayed recall of the Telephone Interview of Cognitive Status 10-word list and digit span backward	4.2 ys	Greater consumption of **blueberries** and **strawberries** was associated with slower rates of cognitive decline.	↑
Nooyens et. al., Br J Nutr, 2011[78] *Doetinchem Cohort Study, Netherlands*	2,613 men and women, age 43-70 ys	Semiquantitative food-frequency questionnaire	The 15 Words Verbal Learning Test (VLT), Stroop Colour–Word Test (SCWT), Word Fluency Test and Letter Digit Substitution Test (LDST)	5 ys	Total consumption of **fruits** and **juices** not associated with baseline or change in cognitive function. Consumption of **legumes** not associated with baseline or change in cognitive function.	— —

Yamada et. al., JAGS, 2003 [79] *Adult Health Study, Japan*	1,774 men and women, age ≥30 years	milk consumption frequency	Dementia diagnosis (all-cause, AD, vascular)	25-30 ys	OR for vascular dementia in almost daily **milk** intake (vs. less that 4 times per week) 0.35.	⬆ **(vascular)**
Ozawa et. al., J Am Geriatr Soc, 2013 [80] *Hisayama Study, Japan*	1,081 men and women, age ≥60 ys	Semiquantitative food-frequency questionnaire	Dementia diagnosis (all-cause, AD, vascular)	17 ys	HR for AD in the higher vs. lower quartile of **milk and dairy** consumption 0.69. NS for all-cause and vascular dementia.	⬆ **(AD)**
Petruski-Ivleva et. al., Nutrients, 2017[81] *Atherosclerosis Risk in Communities Study, US*A	13,751 men and women, age 45-64 ys	Semiquantitative food frequency questionnaire	Delayed Word Recall Test (DWRT), Digit Symbol Substitution Test (DSST), Word Fluency Test (WFT), composite score	20 ys	Consumption of >1 glass **milk** / day associated with an additional decline in composite and DSST z-scores by 11% and 12%. NS for DWRT, WFT.	⬇
Clinical Trials						
Reference	**Sample Characteristics at baseline**	**Intervention**	**Outcomes**	**Duration**	**Results**	**Effect**
Valls-Pedret et. al., JAMA Intern Med, *2015* [82] *PREDIMED trial, Spain*	334 cognitively healthy men and women, age 66.9 ys	**MeDi + olive oil** (1 L/wk) vs. **MeDi + nuts** (30 g/d) vs. control (advise to reduce dietary fat)	Mini-Mental State Examination, Rey Auditory Verbal Learning Test (RAVLT), Animals Semantic Fluency, Digit Span subtest from the Wechsler Adult Intelligence Scale, Verbal Paired Associates from theWechsler Memory Scale, and the Color Trail Test. 3 cognitive composites were constructed: memory, frontal (attention and executive function), and global.	4.1 ys	Both the **olive oil** and the **nuts** MeDi arms prevented the decline in cognitive function (global, frontal, memory).	⬆
Martinez-	522 men and	**MeDi + olive oil**	Mini-Mental State	6.5 ys	Both the **olive oil** and the **nuts** MeDi arms scored	⬆

Lapiscina et. al., J Neurol Neurosurg Psychiatry, 2013[83] *PREDIMED-NAVARRA trial, Spain*	women, at high vascular risk, age 67.4 ys	(1 L/wk) vs. **MeDi + nuts** (30 g/d) vs. control (advise to reduce dietary fat)	Examination, Clock Drawing Test. Assessment only at 6.5 ys after the intervention.		higher in the two tests, compared to the control intervention group.	

⬆: denotes a protective effect; ⬇: denotes a detrimental effect; -: denotes no statistically significantly effect.

Table 6

Selective Evidence on the Association between Alcoholic Beverages Consumption and Cognitive Function						
Longitudinal Studies						
Reference	**Sample Characteristics at baseline**	**Nutritional assessment**	**Outcomes**	**Years of follow-up**	**Results**	**Effect**
Antila et. al., BMJ 2004 [84] *Finland*	1,467 men and women, age 47.7-48.4 ys (means of subgroups)	alcohol consumption categorisation: never, infrequent, frequent drinking	dementia and MCI diagnosis	23 ys	OR for MCI in never and frequent vs**. infrequent drinking** 2.15 and 2.57 respectively. NS for dementia in the total population. In apolipoprotein ε4 carriers OR for dementia in **frequent** (vs. never) drinking 7.97	↑ **(MCI)** — (dementia) ↓ (ε4)
Truelsen et. al., Neurology 2002[85] *The Copenhagen City Heart Study*	1,709 men and women, age ≥65 ys	alcohol consumption categorisation: never, monthly, weekly, daily for beer, wine, spirits	dementia diagnosis	15 ys	OR for dementia in weekly and monthly **wine** consumption (vs. no consumption) 0.33 and 0.43 respectively. OR for dementia in monthly **beer** consumption (vs. no consumption) 2.28. NS for **spirits or total alcohol**.	↑ ↓ —
Nooyens et. al., Br J Nutr, 2014 [86] *Doetinchem Cohort Study, Netherlands*	2,613 men and women, age 43-70 ys	alcohol consumption categorisation: none, 0-2 and >2 glasses/day	15 Words Verbal Learning Test (memory: immediate and delayed recall), Stroop Colour-Word Test (speed and cognitive flexibility), Word Fluency Test (semantic memory) and Letter Digit Substitution Test (speed)	5 ys	**Total** consumption inversely correlated with decline in global cognitive function in women, not in men. In the total population **red wine** consumption was inversely associated with the decline in global cognitive function, memory and flexibility. Smallest declines were observed at a consumption of about 1.5 glasses of red wine per day. NS for **white wine**, **fortified wine**, **beer**, **spirits**.	↑ **(women)** — **(men)** ↑ —
Deng et. al., Clin Neurology & Neurosurgery,	2,632 men and women without neurological	alcohol consumption categorisation:	dementia diagnosis (all, AD, vascular, other)	2 ys	OR for all, AD, vascular dementia in **light to moderate** (vs. non drinkers): 0.52, 0.63 and 0.31 respectively. NS for excessive vs. non-drinkers.	↑

2006 [87] *China*	disorders, age 65.2-69.2 ys (means of subgroups)	non-, light to moderate and excessive drinkers			Light to moderate **wine** consumption decreased the risk of dementia (vs. non-drinkers) (OR of 0.68). Light to moderate **beer** consumption increased the risk for dementia (OR of 2.47). NS for other **spirits**.	⬆ ⬇ —
Weyerer et. al., Age & Ageing, 2011 [88] *Germany*	3,202 men and women, dementia free, age age ≥75 ys	alcohol consumption categorisation: abstinent, 1-9,10-19. 20-29, 30-39, ≥40 g/day or abstinent, wine, beer, mixed	overall and AD dementia	3 ys	HRs for overall and AD dementia in **alcohol** consumption of 20-29 g/day (vs. abstinence) 0.40 and 0.13 respectively. Mixed consumption only significantly associated with overall and AD dementia.	⬆
Lindsay et. al., Am J Epidemiol, 2002 [89] *Canadian Study of Health and Aging, Canada*	4,088 men and women, without cognitive impairment, age 72.9-81.0 ys (means of subgroups)	alcohol consumption categorisation: no consumption and at least weekly consumption (any type, beer, wine, spirits)	AD diagnosis	5 ys	OR for AD in at least weekly of **any type of alcohol** (vs. no consumption) 0.68. OR for AD in at least weekly of **wine** (vs. no consumption) 0.49. NS for **beer** and **spirits**.	⬆ ⬆ —
Espeland et. al.,, Am J Epdemiol, 2005 [90] *Women's Health Initiative Memory Study, USA*	4,461 women, age ≥65 ys	alcohol consumption categorisation: no,<1 drink/day, ≥1 drink/day	dementia and MCI diagnosis, MMSE	4.2 ys	ORs for a significant decline in MMSE score in **<1 drink/day** and in **≥1 drink/day** (vs. no drinking**)** 0.69 and 0.53 respectively. NS for dementia diagnosis or MCI.	⬆ **(MMSE)** — **(dementia, MCI)**
Ruitenberg et. al., Lancet, 2002[61] *Rotterdam Study, Netherlands*	5,395 men and women, age 65.2-69.2 (means of subgroups)	alcohol consumption categorisation: none, <1 drink/wk, ≥1 drink/week, 1-3 drinks/day, ≥4 drinks/day	dementia diagnosis (all, AD, vascular, other)	6 ys	HR for all dementias and vascular dementia in **1-3 drinks/day** (vs. no consumption) 0.58 and 0.30 respectively. NS for AD and other dementias. HRs not different among wine, beer liquor and fortified wine.	⬆ **(all dementia, vascular dementia)**
Handing et. al., J Gerontol A Biol Sci Med Sci,	12,326 men and women, age 54.2 ys	alcohol consumption categorisation:	dementia diagnosis	43 ys	HR for dementia in heavy and very **heavy alcohol consumption** (vs. light consumption) 1.10 and 1.18 respectively.	⬇

2015[91] *Swedish Twin Registry, Sweden*		none, light (≤5 g/day), moderate (≤12 g/day), heavy (≤24 g/day), very heavy > g/day)			Increasing alcohol intake from **wine** decreased the risk for dementia. Increasing alcohol intake from **spirits** increased the risk for dementia.	⬆ ⬇
Langballe et. al., Eu J Epidemiol, 2015 [92] *Nord-Trøndelag Health (HUNT) study*	40,435 men and women, age 60.8 ys	alcohol consumption categorisation (times drinking alcohol last 14 days): abstainer, 1-4 times, ≥5 times, unknown/missing	dementia diagnosis (all, AD, vascular, other)	up to 27 ys	HR for all dementias or AD in **drinking ≥5 times** (vs. drinking 1-4 times) 1.40 and 1.47 respectively.	⬆

⬆: denotes a protective effect; ⬇: denotes a detrimental effect; -: denotes no statistically significantly effect.

Table 7

Selective Evidence on the Association between Coffee or Tea Consumption and Cognitive Function						
Longitudinal Studies						
Reference	**Sample Characteristics at baseline**	**Nutritional assessment**	**Outcomes**	**Years of follow-up**	**Results**	**Effect**
Eskelinen et. al., J Alzheimer's Disease, 2009 [93] *CAID Study, Finland*	1,406 men and women, age 49.8-51.1 ys	coffee and tea consumption categorization: 0-2, 3-5, >5 cups/day	dementia and AD diagnosis	21 ys	OR for dementia in **coffee** consumption of 3-5 cups/day (vs. 0-2 cups per) day 0.30. NS for >5 cups/day vs. 0-2 cups/day. NS for **tea**.	↑ (moderate) – (high) –
van Boxtel, Pharm Bioch Beh, 2003 [94] *Maastricht Aging Study, Netherlands*	1,376 men and women, age 24-81 ys	caffeine intake from coffee and tea	Visual Verbal Learning Test, Motor Choice Reaction Test, Letter-Digit Substitution Test, Fluency Test, Concept Shifting Test	6 ys	**Caffeine intake** associated with change in performance in Motor Choice Reaction Test.	↑
Ng et. al., Am J Clin Nutrition, 2008 [95] *Singapore Longitudinal Ageing Studies, Singapore*	1,438 men and women, age ≥55 ys	coffee and tea consumption categorization: never or rarely, occasionally, ≥1 cups/day	cognitive decline by Mini-Mental State Examination	1-2 ys	OR for cognitive decline in consumption of black and oolong **tea** only (vs. no tea) 0.69. OR for cognitive decline in consumption of black and oolong tea of ≥1 cups/day (vs. never/rarely) 0.68. NS for green tea. NS for **coffee**.	↑ –
Solfrizzi et. al., J Alzheimer's Disease, 2015 [96] *Italian Longitudinal Study on Aging, Italy*	1,445 men and women, age 65-84 ys	coffee + tea consumption categorization: never or rarely, 1, 1-2 and >2 cups/day	MCI diagnosis	median of 3.5 ys	OR for MCI in **tea+coffee** consumption of 1-2 cups per day (vs. never) 0.31. NS for >2 cups/day vs. never. Increase in consumption at follow up associated with an OR for MCI of 1.80 (vs. unchanged) and OR of 2.17 (vs. decreased).	↑ (moderate) – (high) ↓ (increase over time)
Dai et. al., Am J Med, 2006 [19] *Kame Project, USA*	1,836 Japanese-Americans, age ≥65 ys	tea consumption categorization: less often than weekly, 1-2	AD diagnosis	8 ys	OR for dementia NS for **tea** consumption.	–

		times/week, ≥3 times/week				
Feng et. al., J Nutr Health Aging, 2012 [97] *The Chinese Longitudinal Healthy Longevity Survey, China*	7,139 men and women at baseline, age around 60 ys, to 913 participants at 3rd follow up	tea consumption categorisation: non-drinker, occasionally, daily (baseline and at 60 ys old)	verbal fluency test	2, 4, 6 ys	**Tea** drinkers had higher verbal fluency scores at all time points. Steeper slope of cognitive decline as compared with non-drinkers.	⬆
Vercambre et. al., J Alzheimer's Disease, 2013 [98] *Women's Antioxidant Cardiovascular Study, USA*	2,475 women at high vascular risk, age ≥65 ys	caffeine intake from coffee, tea, cola, chocolate	Telephone Interview of Cognitive Status (TICS), TICS 10-word list, East Boston Memory Test, a test of category fluency. Composite score. At 2 ys intervals.	5 ys	Slower rate of cognitive incline with increasing **caffeine intake**. Consumption of **caffeinated coffee** associated inversely with cognitive decline. NS for **tea** or other caffeinated foods.	⬆ ⬆ —
Laitala et. al., Am J Clin Nutrition, 2009 [99] *Finnish Twin Cohort Study, Finland*	2,606 men and women, age ≥65 ys	coffee consumption categorisation: 0-3, 3.5-8, >8 cups/day	telephone interview: TELE screen for dementia identification and Telephone Interview for Cognitive Status	28 ys	Dementia or MCI not associated with **coffee** consumption.	—
Gelber et. al., Alzheimer's Disease, 2011 [100] *Honolulu-Asia Aging Study, Japanese American men*	3,494 men, age 52 ys	coffee consumption (oz/day) and caffeine intake from coffee and cola	diagnosis of all dementias, AD, vascular dementia. Cognitive impairment (Cognitive Abilities Screening Instrument).	25 ys	OR for all dementias, AD or vascular dementia or cognitive impairment NS for **coffee** consumption. NS for **caffeine** intake.	— —
Lindsay et. al., Am J Epidemiol, 2002 [89] *Canadian Study of Health and Aging, Canada*	4,088 men and women, age ≥65 ys	coffee and tea consumption (daily vs. no consumption)	AD diagnosis (527 cases of other dementias or cognitive impairment excluded from the analysis)	5 ys	OR for AD in daily consumption of **coffee** (vs. no consumption) 0.69. NS for **tea** consumption.	⬆ —

Mirza et. al., Eur J Epidemiol, 2014[101] *Rotterdam Study, Netherlands*	5,408 men and women, age 66-3-70.3 ys	Coffee consumption categorisation: continuous or 0-1, 1-3, >3 cups/day. Evaluation at baseline and at 4 ys.	dementia diagnosis	4-6 ys	HRs for dementia NS with **coffee** consumption.	–
Ritchie et. al., Neurology, 2007[102] *The Three Cities Study, France*	7,017 men and women, age ≥65 ys	coffee consumption categorisation: 0-1, 1-2, 2-3, >3 cups/day	Benton Visual Retention Test, Isaacs Set Test. Dementia diagnosis.	4 ys	In women, OR for a decline in Isaacs test in **coffee consumption** >3 cups/day consumption 0.67. The protective effect increased with age. NS in Benton test. NS for all tests in men. NS for dementia incidence.	↑ **(women) (older) (some tests)** – **(men)**
Sugiyama et. al, J Alzheimer's Disease, 2016 [103] *Ohsaki Cohort 2006, Japan*	13,137 men and women, age ≥65 ys	coffee consumption categorisation: never, occasionally, 1-2, ≥3 cups/day	dementia diagnosis	5.7 ys	OR for dementia in occasionally **coffee** consumption and 1-2 cups/day (vs. never) 0.73 and 0.72. NS for ≥3 cups vs. never.	↑ (moderate)

↑: denotes a protective effect; ↓: denotes a detrimental effect; -: denotes no statistically significantly effect.

Table 8

Selective Evidence on the Association between Dietary Patterns and Cognitive Function						
Longitudinal Studies						
Reference	**Sample Characteristics at baseline**	**Nutritional assessment**	**Outcomes**	**Years of follow-up**	**Results**	**Effect**
Featr et. al., JAMA, 2009 [104] *Three-City Study, Bordeaux, France*	1,410 men and women, age ≥65 years	Semiquantitative food-frequency questionnaire, population specific MeDi score	Mini-Mental State Examination (MMSE), Isaacs Set Test (IST), Benton Visual Retention Test (BVRT), Free and Cued Selective Reminding Test (FCSRT). Dementia diagnosis.	5 ys	**MeDi** adherence was not associated with the risk for incident dementia. Change in cognitive scores in MSSE and FCSRT associated with MeDi score.	⬆
Scarmeas et. al., Ann Neurol. 2006[105] *WHICAP Study, USA*	2,258 men and women	Semiquantitative food-frequency questionnaire, population specific MeDi score	Neuropsychological battery with tests of memory, orientation, abstract reasoning, language and construction. Dementia diagnosis.	4 ys	HR for AD in the high vs. low tertile of **MeDi** Score 0.60 and HR for AD in the middle vs low tertile 0.85. MeDi was also associated with rates of cognitive decline.	⬆
Koyama et. al., J Gerontol, 2014 [106] *Health, Aging and Body Composition study, USA*	2,326 men and women, 70-79 ys	Semiquantitative food-frequency questionnaire, *a priori* MeDi score	3MS score	7.9 ys	NS for white participants. Black participants with high **MeDi** scores (top tertile), compared with those with lower MeDi scores (middle and bottom tertiles) had a significantly slower mean rate of decline of 3MS score.	⬌ (White) ⬆ (Black)
Scarmeas et. al., Arch Neurol. 2009[107] *WHICAP Study, USA*	2,364 men and women, 564 with MCI	Semiquantitative food-frequency questionnaire, population specific MeDi score	MCI and AD diagnosis	4.5/4.3 ys	HR for incident MCI in cognitively normal individuals at baseline in the high (vs. low) tertile of **MeDi** Score 0.72. HR for AD (in MCI individuals at baseline) in the high (vs. low) tertile of MeDi Score 0.52.	⬆
Kesse-Guyot et. al., Am. J. Clin Nutr, 2013 [108] *SU.VI.MAX study,*	3,083 men and women, age 52 ys	24-h diet records every 2 months, *a priori* MeDi score	RI-48 for episodic memory, verbal fluency tasks for lexical-semantic memory, forward and backward digit	13 ys	Composite score not associated with **MeDi** adherence in the total sample. Associated only in manual workers, Low adherence to MeDi associated with poorer	⬌ ⬆

France			span task for short-term and working memory, Delis-Kaplan trail-making test for mental flexibility. Composite score.		backward digit span performance and poorer phonemic fluency performance.	(some cognitive scores) (manual workers)
Tangney et. al., Am J Clin Nutr, 2011 [109] *Chicago Health and Aging Project, USA*	3,790 men and women, age ≥65 years	Semiquantitative food-frequency questionnaire, *a priori* MeDi score, Healthy Eating Index-2005	East Boston tests of immediate and delayed recall, Mini-Mental State Examination (MMSE), Symbol Digit Modalities Test	7.6 ys	Slower rates of global cognitive decline was associated with higher **MeDi** score Rate of global cognitive decline was not associated with **Healthy Eating Index**-2005	↑ –
Wengreen et. al., Am J Clin Nutr, 2013 [110] *Cache County Study on Memory, Health and Aging. USA*	3,831 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire, population specific MeDi score and DASH score	3MS score	11 ys	Individuals in 5th quintile (higher) of **MeDi** averaged 0.94 points higher than those in 1st quintile (lower) in 3 MS score. Individuals in 5th quintile of **DASH** averaged 0.97 points higher than those in 1st quintile in 3 MS score.	↑ ↑
Tsivgoulis et. al., Neurology, 2013 [111] *Reasons for Geographic and Racial Differences in Stroke Study, USA*	17,478 men and women, age ≥45 years	Semiquantitative food-frequency questionnaire, population specific MeDi score	Six-item Screener	4 ys	OR for cognitive impairment in high vs. low adherence to **MeDi** 0.87. NS for individuals with diabetes.	↑
Cherbuin et. al., Am J Geriatr Psychiatry, 2012 [54] *PATH Through Life Study, Australia*	1,528 men and women, 60-64 ys	Semiquantitative food-frequency questionnaire, population specific MeDi score	MCI diagnosis	4 ys	Adherence to **MeDi** not protective of MCI.	–
Samieri et. al., J Nutr, 2013 [112] *Nurses' Health Study, USA*	16,058 women, age ≥70 ys	Semiquantitative food-frequency questionnaire, population specific MeDi score	Telephone Interview for Cognitive Status (TICS), Immediate; and Delayed recalls of the East Boston Memory test (EBMT), Delayed recall of the	6 ys	**MeDi** was not associated with decline in global cognition or verbal memory.	–

			TICS 10-word list, Category fluency and digit span-backward.			
Olsson et. al., J Alzheimer's Dis, 2015 [113] *Sweden*	1,038 men, age 71 ys	7-day dietary records	dementia and AD, MSSE	12 ys	OR for dementia – cognitive impairment in low vs. high adherence NS for **Healthy Diet Indicator** (WHO recommendations), NS for **Mediterranean-like diet** NS for **low carbohydrate high protein diet** In subpopulation with energy intake considerations **Mediterranean-like diet** protective for cognitive impairment	— — — ↑
Morris et. al., Alzheimer's & Dementia, 2015 [114] *Memory and Aging Project, USA*	923 men and women, age 58-98 ys	Semiquantitative food-frequency questionnaire, MinD, MeDi, DASH diet indices	AD diagnosis	4.5 ys	HR for AD lower in high and middle **MIND diet** adherence, compared to low adherence. HR for AD lower in high **MeDi** diet adherence, compared to low adherence. HR for AD lower in high **DASH** diet adherence, compared to low adherence.	↑ ↑ ↑
Morris et. al., Alzheimer's & Dementia, 2015[115] *Memory and Aging Project, USA*	960 elderly men and women	Semiquantitative food-frequency questionnaire, Mind Diet adherence	21 neuro-psychological tests, 19 of which summarised cognition in five cognitive domains (episodic memory, working memory, semantic memory, visuospatial ability, and perceptual speed)	4.7 ys	The **MIND diet** score (including dietary components of the Mediterranean and DASH diets) was positively associated with slower decline in global cognitive score and with each of five cognitive domains.	↑
Berendsen et. al., J Nutr Health Aging, 2018 Nurses' Health Study, USA	16,058 women, age ≥70	Semiquantitative food-frequency questionnaire, Mind Diet score	Telephone Interview for Cognitive Status	6 ys	Higher adherence to **MIND diet** was associated with better cognitive function in later life, but not change in cognitive function.	↑/—
Mannikko et. al., Br J Nutr, 2015[116] *Finnish Dose-Responses to Exercise Training Study, Finland*	1,140 men and women, age 57-78 ys	4-day dietary records, Nordic Diet adherence	CERAD neuropsychological battery and the Mini-mental State Examination	4 ys	No significant association between **Nordic diet** score and cognitive outcomes.	—
Shakersain et. al.,	2,223 men and	Semiquantitative	Mini-Mental State	6 ys	**Nordic diet** score associated with less cognitive	↑

Nutrients, 2018 [117] *Swedish National study on Aging and Care in Kungsholmen, Sweden*	women, age ≥60 ys	food-frequency questionnaire, Nordic Diet, MeDi, DASH, Baltic Sea Diet indices	Examination		decline. Stronger association compared to other scores. **MeDi** associated with less cognitive decline. **MIND** diet associated with less cognitive decline. NS for **DASH**. NS fot **Baltic Sea Diet index**.	↑ ↑ — —
Zhu et. al., J Nutr Health Aging, 2015 [118] *CARDIA Study, USA*	2,435 men and women, age 25.2 ys	Semiquantitative food-frequency questionnaire, *a priori* Dietary Quality Score	Rey Auditory Verbal Learning Test (verbal memory), Digit Symbol Substitution Test (psychomotor speed), Stroop test (executive function) at 25 ys	25 ys	Verbal memory, psychomotor speed and executive function at year 25 associated with *an a priori* **Dietary Quality Score** at year 20. Verbal memory at year 25 only associated with Dietary Quality Score at year 0.	↑
Smyth et. al., Neurology, 2015[119] *ONTARGEN + TRANSCENT International Trials*	27,860 men and women, age 66.2 ys	Qualitative Food Frequency Questionnaire	Mini-Mental State Examination	4.7 ys	Lower risk of cognitive decline among those in the healthiest dietary quintile of modified **Alternative Healthy Eating Index** vs. with lowest quintile (HR 0.76)	↑
Ozawa et. al., An J Clin Nutr, 2013[120] *Hisayama Study, Japan*	1,006 men and women, free of dementia, age 60-79	Semiquantitative food-frequency questionnaire	all dementias, AD and vascular dementia diagnosis	15 ys	A **pattern** characterized by high consumption of soybeans and soybean products, green vegetables, other vegetables, algae, and milk and dairy products, and less rice explained 54.3% of variation. HR for dementia in the 4th vs. 1st quartile of this pattern 0.66. HR for vascular dementia 0.45. HR for AD NS.	↑ — **(Alzheimer)**
Gu et. al., Arch Neurol, 2010 [121] *Washington Heights–Inwood Columbia Aging Project, USA*	2,148 men and women, age ≥65 ys	Semiquantitative food-frequency questionnaire	AD diagnosis	3.9 ys	A dietary **pattern** characterized by higher intakes of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark and green leafy vegetables and a lower intake of high fat dairy products, red meat, organ meat, and butter was associated with risk of AD. HR for AD in the highest vs. lower tertile of adherence to this pattern 0.62.	↑
Shakersain et. al., Alzheimer's &	2,223 men and women, age	Semiquantitative food-frequency	Mini-Mental State Examination Test	6 ys	High adherence to a **prudent diet pattern** (including vegetables, fruits, legumes, oils, low fat dairy, cereals,	↑

Dementia, 2016[122] *Swedish National study on Aging and Care-Kungsholmen, Sweden*	≥65 ys	questionnaire			whole grains, rice/pasta, fish, poultry, water) was associated with less decline in cognitive performance. High adherence to a **western diet pattern** was associated with more decline in cognitive performance.	⬇
Clinical Trials						
Reference	**Sample Characteristics at baseline**	**Intervention**	**Outcomes**	**Duration**	**Results**	**Effect**
Valls-Pedret et. al., JAMA Intern Med, *2015* [82] *PREDIMED trial, Spain*	334 cognitively healthy men and women, age 66.9 ys	**MeDi + olive oil** (1 L/wk) vs. **MeDi + nuts** (30 g/d) vs. control (advise to reduce dietary fat)	Mini-Mental State Examination, Rey Auditory Verbal Learning Test (RAVLT), Animals Semantic Fluency, Digit Span subtest from the Wechsler Adult Intelligence Scale, Verbal Paired Associates from theWechsler Memory Scale, and the Color Trail Test. 3 cognitive composites were constructed: memory, frontal (attention and executive function), and global.	4.1 ys	Both **MeDi** arms prevented the decline in cognitive function (global, frontal, memory).	⬆
Martinez-Lapiscina et. al., J Neurol Neurosurg Psychiatry, 2013[83] *PREDIMED-NAVARRA trial, Spain*	522 men and women, at high vascular risk, age 67.4 ys	**MeDi + olive oil** (1 L/wk) vs. **MeDi + nuts** (30 g/d) vs. control (advise to reduce dietary fat)	Mini-Mental State Examination, Clock Drawing Test. Assessment only at 6.5 ys after the intervention.	6.5 ys	Both **MeDi** arms scored higher in the two tests, compared to control.	⬆
Knight et. al., Nutrients, 2016[123] *MedLey study,*	137 men and women, age ≥65 ys	**MeDi** vs. habitual diet	Comprehensive neuropsychological test battery,	0.5 ys	No significant between-groups mean differences in performance between **MeDi** and habitual diet group.	–

Australia			including 11 individual tests			
Lee et. al., Psychotherapy and Psychosomatics, 2014 [124] *Korea*	460 men and women, age ≥60 ys	**Multi-domain Lifestyle Modification** (physical activity, anti-smoking, social activity, cognitive activity, **alcohol** in moderation**, healthy diet** including encouragement for high consumption of fruits and vegetables and at least 2 portions of fish/week, weight control). Group A: Control; group B = telephone every 2 months; group C = monthly telephone; group D = health worker visit once every 2 months; group E = group D + rewards	Mini-Mental State Examination	1.5 ys	Group E (health worker visit every 2 months + rewards) showed less decline in MMSE score, compared to control group.	⬆
Ngandu et. al., Lancet, 2015 [125] *FINGER trial, Finland*	1,260 men and women with CAIDE Dementia Risk Score of at least 6 points and cognition at mean level or slightly lower than expected for age, age 60-	M**ulti-domain** intervention consisting of **nutritional** guidance (high consumption of fruits and vegetables, consumption of whole grain cereals and low	comprehensive neuropsychological test battery (total NTB z-score plus executive functioning, processing speed, and memory)	2 ys	Mean change in total score, executive functioning and processing speed higher in the intervention vs. control group. NS for memory.	⬆

	77 ys	fat milk and meat, use of vegetable margarine and rapeseed oil instead of butter, fish consumption of at least two portions/week, small reduction in body weight if necessary), exercise, cognitive training and social activity, and management of metabolic and vascular risk factors				
Andrieu et. al., Lancet Neurol, 2017 [67] *MAPT trial, France*	1,680 non-demented men and women with memory complaint, limitations in one instrumental activity of daily living on slow gait speed, age ≥70 ys	800 mg **DHA+225 mg EPA** vs. **multidomain** intervention (cognitive training, physical activity, **nutrition**) vs. **DHA,EPA + multi domain** intervention vs. **multi domain** intervention + placebo vs. placebo alone. Nutrition component included at least 5 portions/day of fruits and vegetables, bread and other cereal-based products in	4 cognitive tests (free and total recall of the Free and Cued Selective Reminding test, ten Mini-Mental State Examination orientation items, Digit Symbol Substitution Test, and Category Naming Test)	3 ys	NS in cognitive decline between groups. *post-hoc analyses:* NS in the effects of interventions between groups according to APOE ε4 status. Cognitive decline in participants with baseline CAIDE≥6 was less in the combined intervention group. In brain amyloid positive participants, less cognitive decline was observed in multi domain intervention + DHA or multi domain intervention + placebo groups vs. placebo alone. NS in cognitive decline did not differ significantly between interventions groups in participants with low vs. high blood red cells ω-3 fatty acids.	**—** **—** **(ε4)** **↑** **(CAIDE≥6)** **↑** **(amyloid positive)** **—** **(blood ω-3 status)**

		each meal, milk or other dairy 3-4 times/day, meat, fish or eggs once or twice daily, limit consumption of added fats and sugar, water 1/5 L/day.				
Moll van Charante, Lancet, 2016 [126] *PreDIVA trial, Netherlands*	3,526 men and women, age 70-78 ys	Individually tailored **lifestyle** advice conforming to Dutch general practitioner guidelines on cardiovascular risk management (for smoking, **diet,** physical activity, weight and blood pressure, supported by motivational interviewing techniques every 4 months) vs. usual care (control)	incidence of dementia and disability score, Mini-Mental State Examination, Geriatric Depression Score	6 ys	No differences in outcomes between intervention and control groups. *post-hoc analyses:* Dementia other than AD occurred less frequently in the intervention group. In participants with untreated hypertension who were adherent to the intervention dementia occurred less frequently in the intervention group.	**–** **⬆ (non-AD dementia)** **⬆ (untreated hypertension, high adherence)**

⬆: denotes a protective effect; ⬇: denotes a detrimental effect; -: denotes no statistically significantly effect.

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