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Perspectives in dementia risk reduction – food for thought

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ABSTRACT

Diet and specific nutritional factors, alone and in combination with other lifestyle approaches, have an important role in decreasing the risk for dementia. Protective factors for dementia risk reduction are important in early as well as late adult life, since pathological processes underlying dementia begin years before clinical symptoms appear. Decreased levels of nutrients, such as B vitamins and omega-3 fatty acids, exacerbate pathological processes contributing to cognitive impairment. Initial work using specific diets, including the MIND diet (which combines elements of the Mediterranean and DASH diets), has shown potential to reduce the risk of cognitive decline and/or improve cognitive function, but further research is required. Although the benefits of single-agent nutrient supplementation are unclear, the LipiDiDiet trial has indicated that multinutrient supplementation with Fortasyn Connect may have the potential to improve cognitive function and decrease disease progression in individuals with prodromal Alzheimer's disease. The worldwide FINGER studies are assessing the potential benefits of multidomain lifestyle-based interventions in the prevention of cognitive decline, including dietary interventions. Evidence for the importance of nutrition in combination with lifestyle approaches in maintaining a healthy brain indicates that public health policy must consider nutrition and diet when targeting dementia risk reduction and healthy aging.

PLAIN LANGUAGE SUMMARY

What is this article about? There is a growing body of evidence that specific diets and specific nutritional components of these diets may be able to reduce the risk of developing dementia or improve brain function in those who already have signs of dementia. This article provides an overview of, and commentary on, what is currently known on this subject.

What were the findings? There is evidence to suggest that some diets, including the MIND diet, may help reduce the risk of developing dementia and/or improve brain function, but further research is needed to clarify this. It is currently unclear whether single nutrient supplements (such as specific vitamins) are beneficial, but there is stronger evidence that Fortasyn Connect—a combination of several specific nutritional factors—may have the potential to improve brain function and slow down the rate of progression of Alzheimer's disease in people who are in its early stages. Studies also show that dietary supplements like Fortasyn Connect may help maintain a 'healthy brain' when used together with other lifestyle approaches, such as exercise and social activities.

What do these findings mean? These findings show how important diet and nutrition are in maintaining not only physical health but also brain health. They also indicate that specific diets and nutritional components, when used alongside other lifestyle approaches, might be helpful in reducing the risk of developing dementia and improving brain function. Public health initiatives to reduce the risk of dementia should therefore include guidance on diet and nutrition.

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Dementia; diet; healthy aging; nutrition; risk reduction

1. Introduction

Dementia is the main cause of disability among older adults, affecting around 50 million people worldwide, with this number expected to increase rapidly to over 150 million by 2050 [1]. The World Health Organization [2] and the Global Burden of Disease Study [3] highlight the growing global public health challenge presented by dementia, the impact on costs to society, and the value of addressing modifiable risk factors for dementia through a public health approach. Estimates of dementia prevalence for individual countries could be used to inform national dementia risk reduction strategies, together with investment in research to better understand the mechanisms that underly these interventions.

There is a growing evidence base for the factors that both increase and decrease the risk of developing dementia and the value of addressing these factors to reduce this risk. The European Academy of Neurology (EAN) has advocated a brain health strategy, entitled '*One Brain, One Life, One Approach*,' which aims to develop a holistic approach to brain health that not only prevents neurological disorders but also preserves brain health and promotes recovery after brain damage, thereby improving an individual's quality of life and productivity throughout their life course [4,5]. Central to such a strategy is recognition that management of modifiable risk factors throughout life is an important way to reduce the risk

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Article highlights

- Decreased levels of certain nutrients (e.g., B vitamins, omega-3 fatty acids) exacerbate pathological processes contributing to cognitive impairment.
- Evidence suggests that certain diets and specific nutritional components of these diets may be able to reduce the risk of developing dementia or improve brain function in those with signs of dementia.
- Importantly, diet and nutrition have the potential to simultaneously address multiple disease processes underlying dementia pathology.
- The Mediterranean-Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay (MIND) diet has shown potential to reduce the risk of cognitive decline and/or improve cognitive function, but further research is needed.
- Although the benefits of single-agent nutrient supplementation are unclear, the LipiDiDiet trial has indicated that multinutrient supplementation with Fortasyn Connect may improve cognitive function and decrease disease progression in individuals with prodromal Alzheimer's disease.
- The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was the first large, long-term, randomized, controlled trial to show that a multidomain lifestyle-based intervention could preserve cognitive function and reduce the risk of cognitive decline among older adults at increased risk of dementia.
- The 6-month, proof-of-concept, Multimodal Preventive Trial for Alzheimer's Disease (MIND-AD$_{mini}$) demonstrated that a multidomain lifestyle intervention that included a multinutrient supplement resulted in significantly more vascular risk reduction and significantly less cognitive-functional decline than the control intervention.
- Ongoing research is further assessing the potential benefits of individualized, multidomain approaches to optimizing and maintaining brain health and the associated impact on dementia risk reduction.
- Overall, current evidence indicates that public health policy must consider nutrition and diet when targeting dementia risk reduction and healthy aging.

of dementia, and that it is never too early or too late to take action to mitigate this risk [6]. An overview of dementia risk and protective factors is shown in Figure 1 [7].

Nutrition is of increasing interest as an important modifiable risk factor and protective factor for dementia prevention [4,5,8]. This article will focus on the evidence for the ability of nutritional interventions alone, and in combination with other lifestyle approaches such as exercise, to influence the risk and time to onset of dementia.

2. Why is nutrition important?

In many long-term conditions, particularly those involving neurodegeneration, such as the dementia syndromes, the pathological processes underlying disease begin many years before the appearance of clinical symptoms. Nutrition has an important role to play in mitigating the potential negative effects of metabolic and vascular disease during adult life on future dementia risk. Equally important is the need to address adequate nutrition during the course of clinical disease. Compared with cognitively normal people, those with dementia more often have a history of weight loss [9]. Weight loss is not only present in the initial stages of illness but also begins prior to diagnosis and becomes more common with disease progression. The mechanisms underlying weight loss and changes in nutritional patterns in dementia are complex,

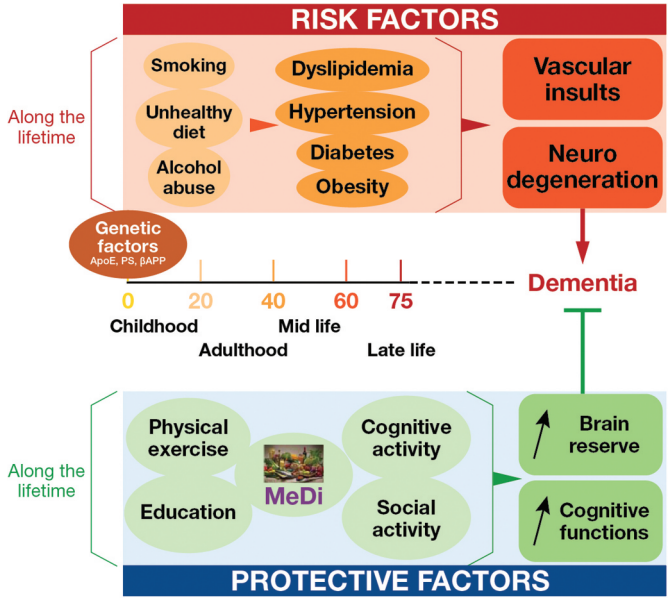

Figure 1. Overview of dementia risk and protective factors.

Figure adapted with permission of Informa UK Ltd, trading as Taylor & Francis Group, from Ravi SK, Narasingappa RB, Vincent B. Neuro-nutrients as anti-alzheimer's disease agents: A critical review. Crit Rev Food Sci Nutr. 2019;59(18):2999–3018 [7].

Abbreviations: APOE, apolipoprotein E; βAPP, beta-amyloid precursor protein; PS, presenilin.

multifactorial and only partly understood [10]. For example: neurodegenerative processes are associated with atrophy in specific brain regions involved in appetite regulation (e.g., the medial temporal cortex and the limbic system); in women with Alzheimer's disease, the *ApoE4* allele is associated with weight loss and decreased body mass index (BMI); inflammation associated with high levels of pro-inflammatory cytokines could contribute to anorexia and weight loss; and changes in the olfactory system (more common in *ApoE4* carriers), often occurring many years before clinical symptoms, are thought to contribute to decreased nutritional intake and weight loss [11,12].

In addition to nutritional problems related specifically to age-related impairments in dementia, disabilities and comorbidities, such as anorexia of aging, chewing problems and depression, can contribute to reduced dietary intake and malnutrition [13]. The brain requires both a source of energy and key nutrients to maintain its functional integrity and metabolism. Deficiencies of nutrients, such as B vitamins (thiamine, folic acid, vitamin B12), omega-3 fatty acids and antioxidants are known to exacerbate pathological processes that contribute to cognitive impairment [14]. Other factors that contribute to the risk of dementia and a more rapid progress of disease, including endothelial dysfunction, vascular damage, oxidative stress and inflammatory processes, are also modulated by specific nutrients [15–19]. Evidence from epidemiological studies has shown that the quality of one's diet can influence the risk of dementia and cognitive impairment [20]. A study conducted by Ousset et al. in patients with very mild Alzheimer's disease showed that poor nutritional status was a predictor of disease progression after 1 year [21]. In the Women's Health Initiative Memory Study (WHIMS) [22], conducted in >7000 participants aged 65–79 years, dietary characterization for pro-inflammatory activity was calculated at

baseline using the Dietary Inflammatory Index [23] and cognitive function was assessed annually over an average of 9.7 years. After adjusting for a range of baseline characteristics (including age, race, geographic region, BMI, physical activity, smoking status, presence of diabetes and hypertension, and the use of non-steroidal anti-inflammatory drugs and cholesterol-lowering medications), diets with the highest pro-inflammatory potential were found to be associated with increased risks for developing mild cognitive impairment (MCI) or dementia [22].

3. Are specific diets of value?

3.1. Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets

Evidence, based largely on observational studies of individual diets, has shown that the Mediterranean, DASH and MIND diets are associated with a reduced risk of cognitive decline and a decreased incidence of dementia [24–28]. A Mediterranean diet incorporates the traditional healthy living habits of people from countries bordering the Mediterranean Sea. Although the precise content may vary by country and region, the diet generally includes high amounts of vegetables, fruits, legumes, nuts, beans, cereals, grains, fish and unsaturated fats, such as olive oil. In addition, it usually includes a low intake of meat and dairy products. The DASH diet is somewhat similar to the Mediterranean diet, being rich in vegetables, fruits and whole grains, and also includes fat-free/low-fat dairy products, fish, poultry, beans, and nuts [29], and has been characterized as a low-salt diet option [30]. Both diets have been associated with decreased plasma levels of inflammatory markers [31], and the Mediterranean diet has been associated with improved endothelial function and lower adiposity [32,33].

The Northern Manhattan study demonstrated that the Mediterranean diet was associated with decreased white matter hyperintensity volume (WMHV), a marker of small vessel damage in the brain [34]. More recently, the European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS) showed that adherence to the Mediterranean diet is associated with lower white matter lesion volume in Mediterranean cities and lower cerebrospinal fluid amyloid beta $(A\beta)_{42}$ levels in non-Mediterranean cities [35]. This is of particular interest because cerebrovascular disease is associated with an increased risk of progression of MCI to dementia and a more rapid decline in dementia [36,37]. In other studies, the Mediterranean diet has also been associated with a decreased risk of MCI, Alzheimer's disease and dementia, and reductions in amyloidosis and tau pathology [26,38–40].

The MIND diet is a hybrid eating plan, combining elements of the Mediterranean and DASH diets, which is tailored for brain health, being rich in nutrients with anti-inflammatory, antioxidant, and pro-cognition properties nutrients (e.g., folate, flavonoids, vitamin E), and designed to slow cognitive decline and prevent dementia [41]. Studies have indicated that adherence to the MIND diet may be associated with a reduced rate of cognitive decline, reduced risk of Alzheimer's disease and larger total brain volumes in older adults [28,41–43]. Moreover, a study of autopsied participants in the Rush Memory and Aging Project who had complete dietary information and Alzheimer's disease pathology data found that both the MIND and Mediterranean diets were associated with a reduction in postmortem Alzheimer's disease pathology, primarily due to decreased Aβ load [44].

Recently, an analysis of data from two large prospective US cohorts, which together included over 105,000 participants, examined associations between long-term adherence to eight healthy dietary patterns (DASH, MIND, Alternative Healthy Eating Index, Alternative Mediterranean Index, healthful plant-based diet, Planetary Health Diet Index [PHDI], reversed empirically dietary inflammatory pattern, reversed empirical dietary index for hyperinsulinemia) and healthy aging after 30 years [45]. Higher adherence to all these dietary patterns was associated with greater odds of healthy aging, defined as surviving to the age of 70 years without the presence of 11 major chronic diseases and with no impairment in cognitive function, physical function or mental health [45]. When considering the cognitive health domain, adherence to all the dietary patterns was associated with greater odds of having intact cognitive health, the strongest association being observed for the PHDI, which was derived based on adherence to the reference diet included in the EAT-Lancet Commission Planetary Health Diet [45,46]. The EAT-Lancet Commission Planetary Health Diet is based predominantly on a plant-based dietary pattern, including whole grains, fruits, vegetables, legumes, nuts and unsaturated oils, with limited intake of red meat, added sugars and highly processed foods [46]. Observational studies have indicated that adherence to this type of diet may help support healthier brain aging and cognitive resilience, thereby delaying the risk of dementia [47,48]. More widely, a systematic review and meta-analysis demonstrated that diets that focus on consumption of healthy plant-based foods while limiting consumption of less healthy plant foods and animal products are associated with lower risks of cognitive impairment and dementia, but the results of individual studies were inconsistent, highlighting the need for further high-quality research [49].

3.2. Ketogenic diet

The ketogenic diet is a very high-fat, low-carbohydrate diet, which has a fasting-like effect, bringing the body into a state of ketosis. Similarly, ketogenic supplementation with medium-chain triglycerides results in the production of ketones. Ketones provide an alternative metabolic pathway to glucose for brain energy. Unlike glucose, uptake of ketones remains normal in MCI, and this might therefore help counterbalance the glucose hypometabolism seen in individuals with MCI and Alzheimer's disease, and those at risk of future dementia [50]. A ketogenic diet may also have beneficial effects on mitochondrial function, neurotransmitter release, oxidative stress and inflammatory processes [51]. In a small proof-of-concept study, in which individuals with MCI were randomized to receive 30 g/day of a ketogenic medium-chain triglyceride (kMCT) drink or matching placebo for 6 months, those who received the

kMCT drink showed significant improvement in cognitive outcomes targeting attention, processing speed, episodic memory, language and executive function, in comparison with those who received placebo [52–54]. This improvement correlated with increased ketone uptake, white matter connectivity and fiber density in the dorsal attentional network. More recent reviews of the evidence suggest that the ketogenic diet or ketogenic supplementation may help prevent the cognitive symptoms of Alzheimer's disease, particularly in its prodromal stage, and enhance cognitive function in those with Alzheimer's disease [55,56].

4. Dietary supplements: omega-3 fatty acids, vitamins and minerals

Vitamins, minerals and omega-3 fatty acids have multiple functions within the central nervous system and important roles in maintaining brain health and cognitive function. Dietary supplements of these substances have been suggested as a means of preserving cognition and reducing the risk of dementia [57]. Oily fish, such as herring, mackerel, tuna, and sardines, are the main dietary source of omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) and are components of the Mediterranean and MIND diets. Although a number of randomized controlled trials have reported mixed findings with DHA supplementation for up to 3 years, prospective cohort studies have shown improved cognition and a 10–30% reduced risk of Alzheimer's disease [58,59]. Oily fish are also a source of other key nutrients required by the brain, including vitamin B12, vitamin D and selenium.

A Cochrane review of evidence for the use of vitamin and mineral supplementation for maintaining cognitive function in cognitively healthy people in mid and late life, which included studies investigating a range of supplements and combinations, including folic acid, vitamin B12, vitamin B6, antioxidant vitamins (β-carotene, vitamin C or E), vitamin D3 (400 IU/day) plus calcium, and minerals (copper, zinc, and selenium), did not find evidence that any vitamin or mineral supplementation strategy has a meaningful effect on cognitive decline or dementia prevention [60]. These findings are in accord with a review of single-agent nutrient supplements by Muñoz Fernández et al., which included vitamin E, vitamin C, B vitamins, vitamin D, flavonoids, carotenoids, and omega-3 fatty acids [61]. In this, the authors concluded that, based on results of existing clinical trials, there is insufficient evidence to support the use of single-agent nutrients to modify the course of cognitive decline in patients with MCI [61]. However, a review conducted by Zhang et al. found folic acid to be a protective factor against Alzheimer's disease [62].

5. Multinutrients: evidence from the LipiDiDiet trial

In contrast to the current evidence for single-agent nutrients, systematic reviews, and meta-analyses have demonstrated that multinutrient interventions, particularly those containing omega-3 polyunsaturated fatty acids, may be beneficial in slowing the progression of cognitive decline in those with MCI and Alzheimer's disease and attenuating the risk of dementia in older adults without MCI [63–66].

The nutritional product Souvenaid (Danone Nutricia) is a once-daily medical food (formulated as a drink) containing the active component Fortasyn Connect. Fortasyn Connect comprises a multinutrient combination of specific fatty acids, vitamins and other key nutrients that are known to be decreased in patients with Alzheimer's disease [67]. This multinutrient combination contains a mixture of precursors and cofactors that support the formation and function of neuronal membranes and synapses (folic acid, DHA, EPA, uridine monophosphate, choline, phospholipids, selenium, and vitamins B12, B6, C, and E), since synaptic loss is an important feature of early Alzheimer's disease and the formation of new synapses is dependent on the availability of these nutritional elements [68]. Based on the results of an earlier short-term trial (Souvenir I [69]), the European Commission funded a new trial (LipiDiDiet) that investigated the longer term use of the Fortasyn Connect multinutrient combination for memory and cognitive function in MCI due to Alzheimer's disease (prodromal Alzheimer's disease) [70]. The LipiDiDiet trial was the first randomized, placebo-controlled, double-blind, multicenter study of a non-pharmacological intervention in MCI due to Alzheimer's disease [70]. People were to be followed for up to 8 years, making this the longest intervention trial in MCI.

A total of 311 patients with MCI due to Alzheimer's disease were recruited to a 24-month treatment period with an optional 12-month double-blind extensions for up to 6 years, followed by additional open-label treatment for up to 2 years [70]. At the 36-month analysis point, significant reductions in decline were observed in the active versus control group on the Neuropsychological Test Battery (NTB) 5-item composite (−60%; $p = 0.014$), Clinical Dementia Rating-Sum of Boxes (CDR-SB; −45%; $p = 0.014$), NTB memory domain (−76%; $p = 0.008$), and brain atrophy measures (hippocampal volume, $p = 0.002$; whole brain volume, $p = 0.021$; ventricular volume, $p = 0.042$) [71]. An exploratory analysis of the CDR-SB outcome indicated that the CDR-SB benefit was greater in those with higher versus lower baseline Mini-Mental State Examination score (i.e., early MCI) [71], consistent with previous observations that Fortasyn Connect has the greatest effect when used early in the course of Alzheimer's disease [69,72–74]. The good tolerability and safety profile of Fortasyn Connect shown over 24 months was maintained over 36 months [71]. *Post-hoc* analyses of the 24- and 36-month data demonstrated significant benefits for the active versus control group on the Alzheimer's Disease Composite Score (ADCOMS) [75,76].

In addition, a *post-hoc* analysis of the 24-month LipiDiDiet data employed time component tests to assess how cognitive, functional, global and structural outcomes may translate into 'time saved' (i.e., the difference between active and control group in the time to reach a specified degree of worsening) [77]. This demonstrated time savings of 9.0, 10.5, and 7.2 months for NTB, CDR-SB, and hippocampal volume, respectively, with an overall 9.0 months of time saved over 24 months when these three components were combined (Figure 2) [77]. These findings are particularly noteworthy when compared with similar analysis of trial data of pharmacological disease-modifying therapies for Alzheimer's disease:

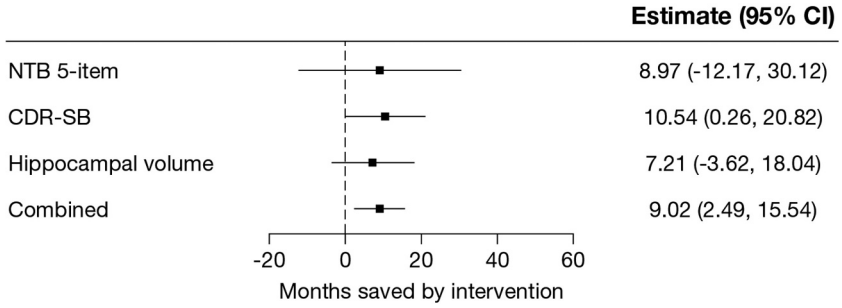

Figure 2. LipiDiDiet: analysis of 'time saved' after 24 months' intervention with Fortasyn Connect versus control.

Figure reprinted with permission of Elsevier from Dickson SP, Solomon A, Kivipelto M, et al. Evaluation of Clinical Meaningfulness of Fortasyn Connect in Terms of "Time Saved." J Prev Alzheimers Dis. 2024;11(4):992–997 [77].

Abbreviations: CDR-SB, Clinical Dementia Rating-Sum of Boxes; CI, confidence interval; NTB, Neuropsychological Test Battery.

for example, a time-saved analysis of donanemab data from the TRAILBLAZER-ALZ trial demonstrated that disease progression was delayed by 5.3 and 5.2 months as measured by the Integrated Alzheimer's Disease Rating Scale (iADRS) and CDR-SB, respectively, at study endpoint (18 months) [78].

Although encouraging, the LipiDiDiet findings should be considered hypothesis-generating at this stage, particularly given the high attrition rate observed in the trial, in addition to other limitations acknowledged by the study investigators, including population heterogeneity and demographic restrictions [70,71]. Future analyses are planned to look at specific subgroups of interest (e.g., people with long-term conditions that increase the risk of disease progression and those carrying the *ApoE4* allele). It will be interesting to see if there is a differential benefit of Fortasyn Connect in those people who are at greater risk of progression. In addition, there is some evidence supporting a synergistic effect when Fortasyn Connect is used in conjunction with acetylcholinesterase inhibitor therapy, which warrants further investigation [79,80].

6. Combined interventions

The majority of clinical trials to date have focused on evaluating the impact of individual interventions to modify risks for dementia or conversion from a 'risk state,' such as MCI, to dementia. These interventions have targeted vascular, metabolic, and other lifestyle-related factors that are known risk factors for late-onset dementia and Alzheimer's disease. Due to the heterogeneous and multifactorial etiology of dementia, it would seem appropriate to target a number of risk factors and mechanisms simultaneously. Such interventions will not be the same for everyone and should be tailored to individual risk profiles for optimal impact on risk reduction. To date, three large European multidomain lifestyle-based prevention trials have been conducted: the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) [81], the French Multidomain Alzheimer Preventive Trial (MAPT) [82], and the Dutch Prevention of Dementia by Intensive Vascular Care (PreDIVA) [83]. In addition, the US Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (US POINTER) was conducted to assess whether the results from FINGER are applicable to a larger and more diverse US population at risk of dementia [84].

FINGER was the first large, long-term, randomized, controlled trial to show that a multidomain lifestyle-based intervention had a clinically significant effect on vascular and lifestyle-related risk factors, and could preserve cognitive function and reduce the risk of cognitive decline among older adults at increased risk of dementia [81]. Recently presented 11-year data from the initial FINGER study demonstrate that the 2-year multidomain intervention had beneficial effects on lifestyle and cognition that were sustained for several years, particularly in those who adhered well to the intervention [85]. The worldwide FINGER studies comprise a global network of clinical trials assessing the potential benefits of multidomain lifestyle-based interventions in the prevention of cognitive decline; two of these studies, the Multimodal Preventive Trial for Alzheimer's Disease (MIND-AD$_{mini}$) [86,87] and FINGER-NL [88], have included Fortasyn Connect to investigate the potential additional benefit when added to other multidomain components (e.g., diet, exercise, cognitive training). Results from the 6-month MIND-AD$_{mini}$ proof-of-concept trial, conducted in individuals with prodromal Alzheimer's disease, demonstrated that the lifestyle plus medical food arm experienced significantly more vascular risk reduction ($p = 0.043$) and significantly less cognitive-functional decline (as measured by the CDR-SB; $p < 0.05$) than the control arm [89]. The FINGER-NL trial is comparing a high-intensity multidomain lifestyle intervention, which includes seven lifestyle components (physical activity, cognitive training, cardiovascular risk factor management, nutritional counseling, sleep counseling, stress management, and social activities) plus Fortasyn Connect, with a low-intensity intervention (comprising online access to general lifestyle-related health information) in older Dutch adults at risk of cognitive decline [88]. Among the 1210 participants recruited into FINGER-NL within 17 months (mean age, 67.7 years; 64% female), baseline modifiable risk factors included physical inactivity (89%), low mental/cognitive activity (50%), low social engagement (39%), hypertension (39%), and high alcohol consumption (39%) [88].

Exploratory subgroup analyses of MAPT and PreDIVA studies suggested cognitive benefits in subpopulations of participants with increased risk of dementia [82,83,90]. However, a 12-year follow-up analysis of the PreDIVA population found

no significant difference in dementia incidence between the multidomain intervention and control groups, the authors suggesting that study population may have been too old to compensate for lifetime damage and/or that the high quality of care in the control group may have hampered the detection of a potential interventional effect [91]. US POINTER compared the effects of two 2-year lifestyle interventions (a structured lifestyle intervention and a self-guided lifestyle intervention) on cognitive trajectory in older US adults at risk of cognitive decline and dementia [84]. The structured lifestyle intervention comprised 38 facilitated peer team meetings, with education, goal-setting and accountability to support physical exercise, nutrition (encouragement to follow the MIND diet), computer training and social activities, and guideline-based health coaching [84]. The self-guided lifestyle intervention comprised six facilitated peer team meetings to support education, tangible tools to facilitate self-guided plans, and general support to encourage physical activity, a healthy diet, and cognitive and social stimulation [84]. Over 2 years, the structured intervention had a statistically significant greater benefit on global cognitive function (assessed by a composite measure of executive function, episodic memory, and processing speed) compared with the self-guided intervention [84]. In FINGER, the beneficial intervention effects on cognition were observed regardless of participant characteristics including age, sex, baseline cognitive performance, education level, socioeconomic status, and presence of cardiovascular risk factors/comorbidity [92]. It is hoped that the worldwide FINGER program will provide additional information on the long-term effects of multidomain interventions, as well as helping to inform further research into how various participant characteristics may affect response to the interventions [92].

Other studies of multidomain interventions for dementia risk reduction that include diet are in the early stages and include the Lifestyle Intervention Study for Dementia Risk Reduction (LEISURE) [93], the Body, Brain, Life for Cognitive Decline (BBL-CD) study [94], and the AUstralian multidomain Approach to Reduce dementia Risk by prOtecting brain health With lifestyle intervention study (AU-ARROW; part of the worldwide FINGERS initiative [WW-FINGERS]) [95].

So, what has been learnt from these studies that can assist in the design of future trials of multidomain interventions? Recent multidomain prevention studies are targeting at-risk individuals and people with prodromal Alzheimer's disease rather than general populations. Cummings et al. have suggested that combining nutritional management designed specifically for neuroprotection with other lifestyle interventions (e.g., cognitive stimulation, physical exercise) may well be necessary to demonstrate greater effect sizes [96]. The next aspect to consider is whether separate studies should be conducted in people with particular risk factors (e.g., hypertension, diabetes).

It is important to acknowledge that current evidence for the effects of diet and nutrition in dementia prevention is limited by the nature of the studies conducted, which are often affected by attrition, the subgroup/*post-hoc* nature of some analyses, demographic restrictions, and the interpretive gap between surrogate outcomes and hard clinical endpoints. Such limitations highlight the need for further carefully designed and adequately powered prospective studies, conducted in well-defined populations using validated endpoints.

7. Concluding remarks

Delaying the onset of dementia and Alzheimer's disease even by a few years could have a significant effect on reducing the prevalence and societal and economic burden of the disease [97]. Current evidence indicates that an individualized, multifactorial approach to reducing risk for dementia, which includes addressing individual risk factors at the appropriate time in adult life, should have potential for improving outcomes. The results of current trials, such as the MIND-AD$_{maxi}$ trial, are awaited with interest. The EAN's brain health strategy recognizes the urgent need to promote brain health and prevent neurological disorders across an individual's life span, highlighting key multidomain preventative measures that should be adopted to achieve this aim [4,5]. The EAN has provided an overview of what it views to be the determinants of brain health (some established, some yet to be confirmed; Figure 3) and has outlined the five pillars of its brain health strategy, which are: building a brain health alliance, supporting international and national/regional policy making, fostering research, promoting education, and raising public awareness and understanding [4,5].

Over the past three or four decades, the major focus of risk reduction has been on cardiovascular health, where dietary modification alone or combined with exercise and/or pharmacotherapy (e.g., statins) has shown significant benefit in reducing cardiovascular morbidity and mortality and stroke in those at risk [98,99]. As outlined earlier in this article, the risk factors for dementia are very similar to those associated with cardiovascular disease (diabetes, hypertension, obesity, smoking, etc.). Indeed, although evidence for a direct effect of diet on dementia risk is currently not strong, the impact of diet on well-established risk factors for dementia – such as diabetes, hypertension and obesity – is unequivocal, and a healthy diet thus plays an important indirect role in dementia risk reduction [100].

A great deal has been learned from the implementation of nutritional change for people at risk of cardiovascular disease – the challenges, barriers and need for a multidisciplinary approach [98]. The considerations of lifestyle, especially nutrition, give much food for thought for both research and clinical practice about how and when to intervene to optimize dementia risk reduction and brain health.

8. Future perspective

We are at a watershed moment where, for the first time, disease-modifying pharmacological treatments are emerging that have the potential to slowdown disease processes underlying the development and progression of dementia [101]. In tandem with this—and as the evidence presented in this article demonstrates—diet and nutritional interventions also have the potential to reduce the risk of dementia and slow cognitive decline

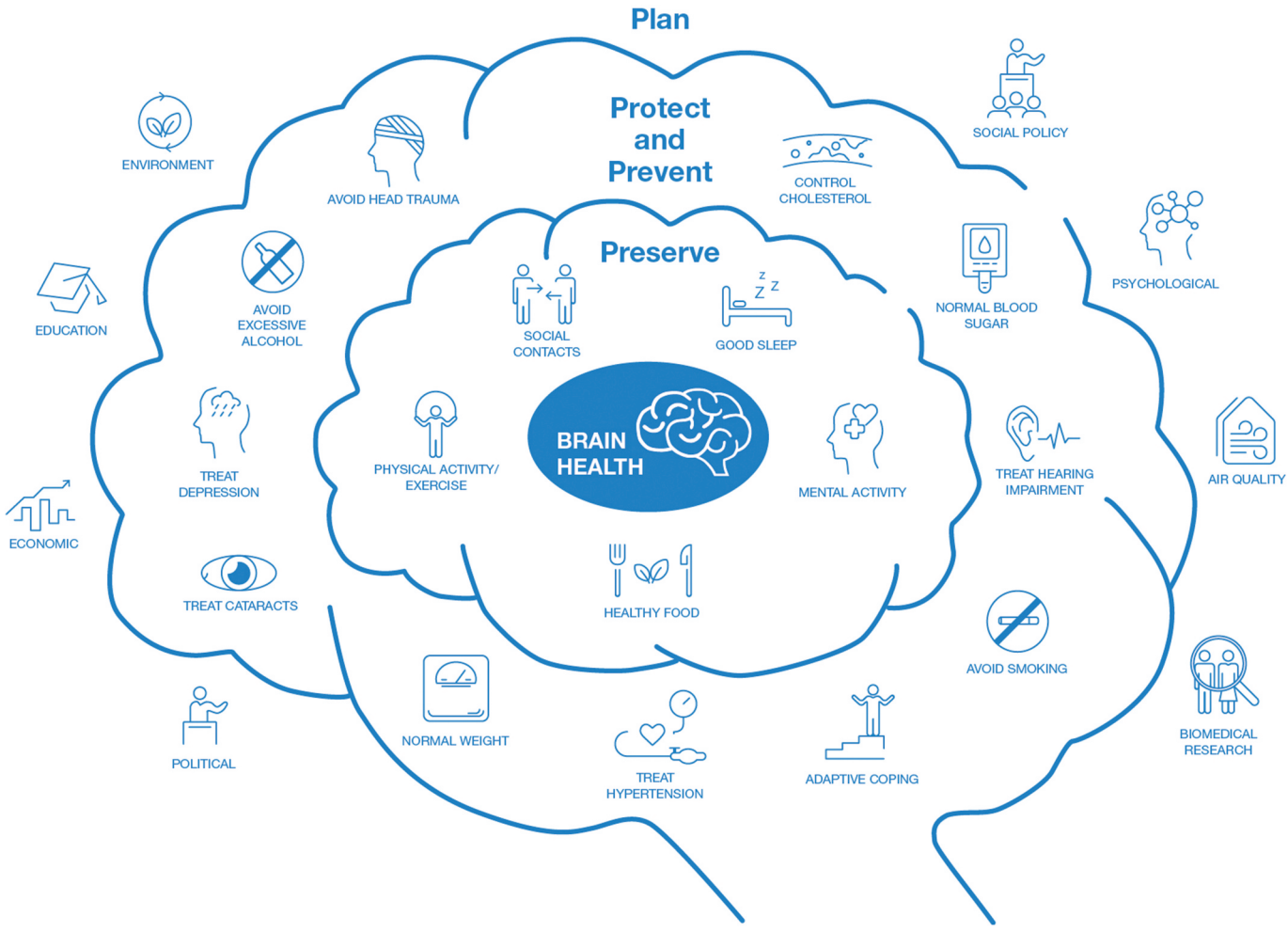

Figure 3. European Academy of Neurology's brain health strategy: brain health and its determinants.

Figure reprinted with permission of John Wiley & Sons from Bassetti CLA, Endres M, Sander A, et al. European Academy of Neurology Brain Health Strategy: One brain, one life, one approach. Eur J Neurol. 2022;29(9):2559–2566 [5].

[102]. It is increasingly recognized that we must look beyond the 'amyloid hypothesis' when considering disease modification, since multiple other mechanisms are involved in the dementia disease process, including oxidative stress, disruption of cholesterol homeostasis, insulin resistance, neuroinflammation, glutamate imbalance, mitochondrial dysfunction, and gut microbiome abnormalities [16–19,103]. Within this context, diet and nutrition can play a key role, since they have the potential to address multiple disease processes simultaneously [104]. Indeed, the fact that multinutrient supplementation has been shown to be effective in reducing dementia risk, whereas the benefits of single-agent nutrient supplementation are less clear, may illustrate the need to target multiple disease processes simultaneously to elicit a meaningful change in dementia risk. Moreover, the current move toward biological characterization of patient populations, based on specific biomarkers, opens the possibility of identifying dietary and nutritional factors that might target specific underlying risk factors and disease pathologies [105,106]. Given the need for robust clinical trial evidence and the fact that the pathological mechanisms underlying the dementia disease process begin much earlier than the emergence of clinical symptoms, future clinical trials may need to be of sufficient duration (e.g., >3 years) to detect the potentially disease-modifying effects of dietary/nutritional interventions.

Future public health policy on risk reduction needs to broaden its focus beyond cardiovascular disease to include education about dementia risk reduction and healthy aging, including specific education on the crucial role that diet and nutrition can play. A recent survey has shown that 'brain health' is a more positive and acceptable message than 'dementia risk reduction,' with more people believing that they can influence their brain health than their dementia risk (75% versus 33%) [107,108]. As for reduction of cardiovascular disease, the evidence supports a life-course model for dementia risk reduction (Figure 1). In primary care, we already review people with long-term conditions that are risk factors for both cardiovascular disease and dementia at least annually. This provides an opportunity for a wider discussion about healthy aging, brain health, and dementia risk reduction. To support this initiative, current guidance, training and education need to reflect the new evidence. A particular challenge is the belief by many health professionals that nothing positive can be done to reduce the risk of dementia. In contrast to the costs of

introducing pharmacological disease-modifying therapies for dementia (and the associated changes required in neuroimaging and laboratory assays), addressing lifestyle factors and improving nutrition are likely to be very cost-effective and simple to introduce [109]. To assist in this endeavor, additional tools are needed to assess 'individual dementia risk' and the quality of one's diet. Some tools for assessing dementia risk have been used in the research setting, but there is currently a lack of validated tools for assessing individual diet quality and/or dementia risk in a busy clinical environment. Currently, few studies of people at risk of dementia or with prodromal dementia have included the composition of a person's diet at baseline as a consideration in analyses of efficacy of an intervention. Equally, we are awaiting with interest further results from the LipiDiDiet trial: the 36-month data suggest greater benefit in milder disease and an increasing benefit over time on brain structures. However, these findings are still at the hypothesis-generating stage and need to be confirmed in future studies. Moreover, the practical implementation and long-term adherence to such medical foods require further validation in real-world clinical settings. Ongoing research will also provide further evidence for the potential benefits of individualized, multidomain approaches to optimizing and maintaining brain health and the associated impact on dementia risk reduction. In clinical practice, clinicians tend to focus on advice and monitoring of individual conditions with little reference to an increased future risk for dementia. If this 'risk' is to be addressed successfully, connection needs to be made between these risk factors and the implications for future brain health and dementia. Optimal management should begin in mid-adult life and include monitoring of individualized risk for dementia for all patients with 'risk factors'. For people identified later in adult life with MCI or prodromal disease, a similar program of advice and regular monitoring need to be in place. The advice should be based on best available data for individual risk factors (long-term conditions) and lifestyle. Research is ongoing about how to predict the timing of future onset of Alzheimer's disease. One of the most interesting methodologies currently being explored is clock modeling of biomarkers related to Alzheimer's disease [110].

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