Movement and Nutrition in Health and Disease

Mediterranean diet and Alzheimer's disease | Review

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Abstract: Alzheimer's disease (AD), the most common form of dementia, is a progressive neurodegenerative disease with no effective cure. Lifestyle factors, including nutrition and diet, are attracting increasing attention in AD research. It has been suggested that the Mediterranean diet (MeDi) may protect against cognitive decline and dementia. People adhering to a MeDi showed a decrease in the risk of cognitive disorders in several epidemiological studies. While higher adherence to a MeDi was related to a reduced risk of incident cognitive impairment, lower adherence was associated with an increase in the incidence of AD and mild cognitive impairment. However, the majority of published studies on MeDi and AD are observational and cannot answer the question whether the association is causal. Cohort studies with long follow-up periods and large samples suggest an association between adherence to MeDi and a decrease in the risk of cognitive decline and AD. Lower MeDi adherence has been shown to be associated with progressive AD biomarker abnormalities in middle-aged adults. The lower risk of AD associated with the MeDi could be mediated through reduced vascular risk factors and beneficial effects on glucose and lipid metabolism. Certain components of the MeDi, such as its high fruit and vegetable content, relatively low level of carbohydrates and its use of extra-virgin olive oil as the main source of fat, could provide protective effects against cognitive decline, including AD. These findings call for further investigations of the potential of dietary interventions to protect against brain aging and AD. However, other factors of the Mediterranean lifestyle, such as regular physical exercise and strong social networks, may also contribute to the reduced risk of the disease. Long-term randomized controlled trials are needed to establish a causal relationship between MeDi and the prevention or improvement of cognitive decline in AD. At present, it is not possible to prescribe the MeDi as a preventive measure in AD, since knowledge of the type and quantity of individual food components and bioactives required for effective neuroprotection is lacking.

Keywords: Alzheimer's disease; dementia; Mediterranean diet; nutrition; prevention.

1. Introduction

The dietary habits of populations living on the shores of the Mediterranean Sea have spread out from the Fertile Crescent and have been evolving for 5,000 years. The development of the MeDi over millennia has been influenced by an interaction of factors such as climate, culture, food traditions, and lifestyles. Thus, Mediterranean diet (MeDi) patterns among Mediterranean populations have been neither homogeneous nor static and have undergone many

transformations. A number of factors have contributed to the dietary and lifestyle patterns of people living on the Mediterranean Sea. These include the wide variety of local cultivars used, seasonality, the freshness and home cooking of the food, the frugality and the conviviality of meals as well as a physically active lifestyle [1,2]. There is no single MeDi but rather several variations adapted to the cultures of individual regions. However, all Mediterranean countries share the same key dietary characteristics. Today, the MeDi is a multinutrient dietary profile characterized by a relatively high consumption of fresh fruits, vegetables, legumes, whole grains, nuts and seeds, moderate intake of fish and poultry, low to moderate consumption of dairy products (mainly yogurt and cheese), low intake of red meat, refined grains, refined sugar, and convenience foods, and the use of olive oil as a main source of fat [3−5]. Adherence to the MeDi has been decreasing in recent decades as a consequence of numerous factors, including economic, sociocultural, and lifestyle changes. The easy access to processed foods in Western societies has significantly changed dietary patterns in many parts of the world, with the consumption of a relatively high proportion of foods high in sugar and saturated fats.

A report by the World Health Organization identified the MeDi as a promising strategy in the enhancement of quality of life and prevention of diseases [6]. The MeDi has been linked to a decreased risk of various chronic diseases, such as cardiovascular diseases, type 2 diabetes, obesity, and cancer [7−11], as well as of all-cause mortality [12]. Furthermore, the MeDi has been linked to a reduced risk of age-related cognitive decline and dementia [13,14].

Aging is commonly associated with a decline in cognitive functioning, which ranges from mild cognitive impairment to dementia. Up to 50% of individuals with mild cognitive impairment will develop dementia within 5 years [15]. Given the rapid aging of populations worldwide, health problems related to aging, including dementia, will become a challenge for both societies and healthcare systems, contributing substantially to the high clinical, social, and economic burden of caring for people with dementia [16].

Alzheimer's disease (AD) is an incurable neurodegenerative disorder and the most prevalent cause of dementia. The condition is characterized by a progressive global impairment of cognition, including memory, language, executive and other behavioral functions, severe enough to interfere with daily life [17,18]. The pathological hallmarks in the brain of people with AD are two forms of abnormal proteins: extracellular plaques containing amyloid-β and intracellular neurofibrillary tangles composed of hyperphosphorylated forms of the microtubule-associated protein tau [19−21]. Important patho-physiological mechanisms in AD leading to neuronal dysfunction and death include oxidative stress and chronic inflammation in the brain [22]. The onset of neurodegeneration is believed to precede the clinical symptoms by many years. Effective treatments capable of improving the cognitive impairment or slowing the progression of AD are not available [17]. Preventing or delaying the onset of AD is a major public health challenge [23] and requires the development of novel strategies, such as changes in lifestyle factors.

AD develops over decades, with a long preclinical, asymptomatic phase. It is therefore unclear whether risk factors assessed late in life shortly prior to the onset of clinical symptoms are a cause of the disease or rather a consequence of pathological alterations. Longitudinal studies conducted over decades have examined associations between early-life or midlife risk factors and the risk of cognitive decline and dementia later in life. The majority of these studies suggest a link between vascular health status and the risk of later cognitive decline and dementia [24−27]. Strong evidence suggests that interventions for cardiovascular risk are capable of improving cognitive health at the population level. Primary prevention related to modifiable lifestyle-related risk factors, such as obesity, diabetes, smoking, physical and mental inactivity, depression, low educational attainment, and diet, is likely to play an important role in AD [28]. It has been estimated that the elimination of these risk factors could reduce the incidence of dementia by 30% [29]

Among lifestyle factors, nutrition and diet have attracted increasing attention in AD research. Nutritional approaches to AD include "healthy" dietary patterns (e.g. Mediterranean diet) with individual components that may produce positive effects on pathophysiological processes of AD [30], ketogenic dietary approaches which target energetic deficits and reduced glucose utilization in AD [31], and medical foods meeting specific nutritional needs of individuals with AD [32,33].

2. MeDi and cognitive decline

Adherence to the Mediterranean diet has been posited to contribute to improved cognitive performance and to be an important modifiable protective factor against AD [34]. People following a MeDi showed a decrease in the

risk of cognitive disorders in several epidemiological studies. While higher adherence to a MeDi was linked to a reduced risk of incident cognitive impairment [35], lower adherence was associated with an increase in the incidence of AD and mild cognitive impairment [36]. In a prospective cohort of 2,258 community-based non-demented people, higher adherence to the MeDi was associated with a significant reduction in the risk for AD [37]. However, no association of MeDi with cognitive decline was found in a sub-study of the Women's Health Study [38]. A systematic review of available literature reported an association between adherence to a MeDi diet and a decrease in cognitive decline, including onset of AD, in 9 of 12 studies [39]. Despite methodological heterogeneity and limited statistical power in some studies, a reasonably consistent pattern of associations was found. However, the findings for mild cognitive impairment were inconsistent [39]. The benefits of MeDi adherence were particularly evident in studies with mean baseline ages of participants above 75 years, possibly because differences between MeDi adherence and non-adherence were easier to detect due to the higher risk of incident cognitive problems in this age group. A short-term randomized trial on MeDi and cognitive performance had several limitations, such as a small sample size and a follow-up period of 10 days [40]. A long-term randomized clinical trial comprising 334 participants with high cardiovascular risk (mean age 67 years) found that a MeDi supplemented with either olive oil or nuts was associated with better cognitive functions at 4-year follow-up than a control diet [41]. The randomization of this study provides a stronger level of scientific evidence than findings based on observational studies [42].

A review of 11 cross-sectional and prospective studies concluded that there is robust scientific evidence in support of a relationship between slower cognitive decline and adherence to a MeDi [43]. A systematic review and meta-analysis of five studies found a 33% reduction in onset and development of both mild cognitive impairment and AD in participants strictly following a MeDi [44]. However, some studies found no correlation between adherence to a MeDi and a delay or reduction in cognitive decline [45,46]. Possible explanations for the discrepant findings include the use of varying methods to assess diet adherence, the poor reliability of food questionnaires, and heterogeneity of the samples investigated [39].

In a more recent prospective study from Greece, with 401 participants aged >65 years, a mini-mental state examination [47] was performed twice over a period of 7 years [48]. This study reported a significant inverse association between MeDi adherence and both mild and substantial cognitive decline, in particular in older people [48].

Adherence to a Mediterranean diet was examined in relation to brain volume and cognitive functioning, which were assessed in participants at age 75 using magnetic resonance imaging and a short screening test, respectively [49]. While no association was found between MeDi score and cognitive function or brain volume, low consumption of meat and meat products correlated with healthier cognitive aging [49]. Adherence to the MeDi and DASH (Dietary Approaches to Stop Hypertension) diet has been shown to be associated with a reduced risk of incident dementia and global cognitive decline in 6- and 11-year follow-up studies [50,51]. In addition, single components of the MeDi, such as fish oil, have been linked to slower cognitive decline and a reduced risk of AD [52].

In a 3-year brain imaging study, the effects of higher versus lower adherence to a Mediterranean-style diet on changes of AD biomarkers in midlife were examined [53]. The biomarkers were brain β-amyloid load, as assessed using ^{11}C-Pittsburgh compound B PET, and neuro-degeneration, as assessed using ^{18}F-fluorodeoxyglucose PET and structural MRI. In 70 cognitively unimpaired participants aged 30−60 years (34 people with higher (MeDi+) and 36 with lower (MeDi−) MeDi adherence), clinical, neuropsychological, and dietary examinations were performed and neuroimaging biomarkers were measured twice, with at least 2 years between the measurements. Clinical and neuropsychological measures were comparable for both MeDi groups. At baseline, participants of the MeDi− group showed a statistically significant decrease in glucose metabolism and increase in Aβ deposition in AD-affected brain regions compared to the MeDi+ group [53]. Longitudinally, the MeDi− group showed further reductions in glucose metabolism and increases in Aβ deposition, which were significantly greater than those in the MeDi+ group. Effects on structural MRI were not found. Higher MeDi adherence was estimated to provide 1.5 to 3.5 years of protection against AD [53]. Further studies using larger samples and longer follow-up periods should be conducted in community-based samples in order allow the generalizability of these findings and to justify clinical application. In summary, lower adherence

to a MeDi was associated with the emergence and longitudinal progression of abnormalities of AD biomarkers in middle-aged adults compared to higher adherence, i.e. glucose hypometabolism and Aβ deposition progressed at higher rates in MeDi− than MeDi+ participants [53]. However, the question of whether changes in AD biomarkers predict future AD in relation to MeDi adherence needs to be investigated.

3. MeDi components and AD

Both epidemiological studies (e.g. references 37,54,55) and clinical trials [41,56] have linked higher adherence to a Mediterranean-style diet to a reduced risk of cognitive decline and dementia. The potential of a MeDi to prevent neurodegeneration has been attributed primarily to its high content of vegetables, fruits, and olive oil, which contain a wide range of bioactive phytochemicals, such as polyphenols, phytosterols, carotenoids, and sulfur compounds (e.g. references 37,54,57−61). However, whether the reported benefits of the MeDi in regard to AD derive from the diet as a whole or through the action of its individual components is unclear. The hypothesis that some dietary components may be more important than others is supported by findings showing that a MeDi enriched with extra-virgin olive oil had a stronger positive effect on cognitive function, and was the only dietary pattern that slowed the onset of mild cognitive impairment, in comparison with a MeDi enriched with nuts or a low-fat control diet [56,62].

The MeDi comprises a complex array of components and, thus, the observed health effects may derive from a multitude of single components [63,64]. It has been reported that the consumption of non-refined cereal correlated positively with cognitive performance, and fish consumption was inversely associated with dementia [65]. Numerous studies assessing the impact of individual components of the MeDi on cognitive functions as the brain ages suggest that the intake of diet-derived or supplementary omega-3 fatty acids and plant polyphenols such as flavonols and resveratrol exerts positive effects on brain health and cognition in older people [66]. The effects of these two MeDi components are discussed below. Furthermore, wine has been claimed to contribute to the neuroprotective effects of the MeDi.

3.1. Omega-3 PUFAs and AD

The easy availability of processed food in Western societies has led to an increase in the consumption of saturated fatty acids and trans fats, with a reduced intake of omega-3 fatty acids. This could contribute to the elevated incidence of mental disorders [67]. The consumption of unsaturated fatty acids, including the omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6), is a characteristic of the MeDi. Omega-3 PUFAs are important components of neuronal membranes and are essential for the growth and development of the infant brain during pregnancy and following birth [68]. They are involved in neuronal differentiation, modulation of membrane fluidity, synaptogenesis, synaptic function, and neurotransmission [69,70]. DHA is abundantly present in the brain and may play a role in the maintenance of cognitive functions in old age [71]. Findings of animal studies regarding DHA supplementation include, for example, beneficial effects on learning and memory performance [72] and a substantial decrease in amyloid-β [73]. These results suggest neuroprotective effects of DHA in AD [72,74].

Low plasma concentrations of omega-3 fatty acids, including DHA, appear to indicate an increased risk of cognitive deficits and dementia [75]. In epidemiological studies, associations have been shown between the consumption of fish [76,77] or fish oil [71,78] and improved cognitive functioning and a decreased risk of dementia (for review see reference 79). In France, the consumption of fish has been reported to have protective effects against dementia, while meat intake was associated, although poorly, with an increase in dementia risk [80]. Fish consumption at least once a week was associated with a reduction by 34% of the development of any form of dementia and by 31% for AD [80]. In Chicago, the consumption of fish was associated with a decrease in age-related cognitive decline, as assessed using a global cognitive score [77], in a prospective community-based cohort study with 6,158 participants aged 65 years or older [77]. AD was 60% less common in individuals with an intake of approximately 60 mg DHA daily, i.e. at least one fish meal a week, than in people consuming very little fish [81]. Similar results were found in Japan [82], where more fish is consumed than in the West.

3.2. Polyphenols and AD

Polyphenols are secondary plant metabolites, and thousands of molecules have been shown to have a polyphenolic character [83]. Polyphenols are found in abundance in the MeDi and are believed to contribute to its beneficial effects on brain health.

A study comprising 447 people aged 55–80 years at high risk of cardiovascular disease investigated urinary polyphenols as markers of food consumption and their association with cognitive scores, as assessed using neuropsychological tests [84]. This study found a positive correlation between urinary polyphenol levels and verbal memory scores, suggesting that increased intake of polyphenolic compounds contained in the MeDi may be able to ameliorate age-related cognitive decline. A cross-sectional study with 2,031 participants aged 70–74 years reported that a diet rich in flavonol-containing foods over one year was dose-dependently associated with improved cognitive performance compared to a control condition [85]. A significant increase in processing speed was observed in a double-blind clinical trial of a nutraceutical formulation containing blueberry, green tea, carnosine, vitamin D3, and biovin [86]. Blueberry supplementation was shown to improve test performance in regard to learning and memory in a small sample of older adults compared to matched placebo controls [87]. In comparison to placebo, a significant enhancement of memory performance was found in healthy overweight older adults following a daily intake of 200 mg resveratrol for 26 weeks [88]. Furthermore, in healthy adults aged 50−69 years, a diet high in cocoa-flavonol for 3 months was compared in a randomized study with a diet low in this compound and was found to improve both memory function and related activation in the dentate gyrus, as assessed using MRI [89].

3.3. Wine and AD

Intake of moderate amounts of alcohol (especially wine consumed for the most part during meals) is a component of the MeDi [3] and has been suggested to contribute to its beneficial health effects, including a reduction in the risk of cognitive decline and AD (e.g. references 90−93). The potential cognitive benefits are attributed to the polyphenolic compounds abundantly present in wine. Of these, the stilbenoid resveratrol (trans-3,5,4'-trihydroxystilbene) has been proposed as a major constituent responsible for the beneficial effects [88,94,95].

Studies in rodent models of AD have shown neuroprotective effects of resveratrol on central features of AD, including decreased amyloid deposition and tau-hyperphosphorylation, enhanced hippocampal neurogenesis, and improved memory functions [96]. However, the results of published intervention trials of resveratrol in individuals with mild cognitive impairment [97] or mild to moderate AD [98] do not provide evidence of neuroprotective or therapeutic effects in humans.

The impact of alcohol consumption on age-related cognitive decline is unclear. While alcohol was shown to be independently related to a reduced risk of AD [54], an increased alcohol intake was associated with an elevated risk of mild cognitive impairment [46]. Better health in moderate drinkers compared to those who abstain from alcohol has frequently been reported (e.g. reference 99). A J-shaped curve has been posited to describe the relationship between alcohol consumption and the risk of various diseases, including AD. This indicates that the risk of disease is reduced for moderate drinkers compared to non-drinkers, while the risk is increased for heavy drinkers. In a comprehensive meta-analysis, the average ratio of risk for cognitive risk (cognitive impairment or dementia) associated with moderate "social" drinking of alcohol was 0.77, with non-drinkers as a reference group [100]. A dose-response meta-analysis of prospective studies found that modest alcohol consumption (≤12.5 g/day) was associated with a reduced risk of dementia, with 6 g/day of alcohol conferring a lower risk than other levels, while excessive drinking (≥38 g/day) may elevate the risk [101]. A weakness of this study is that "current non-drinkers", or the lowest category of intake in each study, were used as a reference group, and no distinction was made between ex-drinkers and lifetime abstainers. If the reference group is defined as "current non-drinkers" (without knowledge of previous drinking), this group will include a variable number of former heavy drinkers, who tend to have a higher risk of many disease outcomes ("sick quitters") than lifetime abstainers. If a large percentage of ex-drinkers consist of former heavy drinkers, an apparently protective effect observed in moderate drinkers may be misleading. The findings of other studies did not support the hypothesis that low-to-moderate alcohol consumption prevents cognitive decline [102].

A meta-analysis based on a small number of studies indicated that wine consumed in moderate quantities provided a significant reduction in cognitive risk, while beer and spirits did not [100]. The beneficial effect of wine could be due to specific favorable biological effects but could also be related to confounding variables, such as socioeconomic status and healthier dietary or other lifestyle habits [103].

Even if potentially positive effects of alcohol intake on cognitive risk could be proven, these effects are likely to be outweighed by the general health hazards of alcohol. For example, an increase in all causes of death was

observed among nearly 600,000 people with no history of cardiovascular disease when more than 100 g of alcohol (e.g. five 175 ml glasses of wine) was consumed every week [104]. A higher alcohol intake was also associated with a greater likelihood of stroke, heart failure, and fatal aneurysm [104]. Furthermore, an observational cohort study assessing weekly alcohol intake and cognitive performance over 30 years showed that even moderate levels of alcohol consumption were associated with adverse brain outcomes, including dose-dependent hippocampal atrophy [105]. In addition, no protective effect of light drinking compared to abstinence was found.

In conclusion, evidence of a neuroprotective or therapeutic efficacy of the polyphenolic resveratrol contained in wine is lacking. Moreover, wine is not an appropriate source of potentially neuroprotective compounds, since even moderate alcohol consumption poses various health risks, including pathological changes in the brain. Moderate alcohol intake cannot be recommended as a means to promote brain health and to decrease the risk of developing AD, and any claims regarding an efficacy of wine in the prevention of AD are unsubstantiated [106].

4. Potential mechanisms underlying MeDi effects in AD

Multiple biological mechanisms have been suggested to play a role in regard to the effects of MeDi on cognitive health. Adherence to the MeDi has been linked to a reduced risk of coronary heart disease, hypertension, type 2 diabetes, dyslipidemia, and metabolic syndrome [7,107−111], all of which have been associated with mild cognitive impairment, dementia, or AD. Higher adherence to the MeDi has also been linked to improved insulin sensitivity and glucose metabolism and may thereby facilitate metabolic control [112]. Chronically increased levels of blood glucose have been associated with a greater AD risk in older people, even in the absence of manifest type 2 diabetes [113,114]. Oxidative stress and damage in the brain are found in AD [115], and the decrease in oxidative stress in individuals adhering to a MeDi containing a wide variety of antioxidants may also contribute to the reduced risk of dementia [116−119]. Furthermore, the MeDi may increase plasma levels of brain-derived neurotrophic factor, which protects neurons against oxidative stress [120]. In addition, neurotransmitter synthesis, synaptic plasticity, and cell metabolism are influenced by the intake of vitamins C and B [121]. Neuroinflammation in the central nervous system, a pathological feature of AD, is characterized by the activation of microglia, which is the first line of immune defense. Microglia-mediated neuroinflammation has been demonstrated in vitro to be mitigated by dietary polyphenolics and their derivatives (see reference 122). Increased levels of C-reactive protein, a nonspecific marker of inflammation, have been shown to be associated with an increased risk of cognitive decline and AD [123], while reduced levels of C-reactive protein and other inflammation markers appear to be related to adherence to the MeDi [124]. Food components of the MeDi such as omega-3 fatty acids from fish and monounsaturated fatty acids from olive oil reduce or prevent inflammation [125]. However, strict adherence to a MeDi was shown to be associated with a reduction in AD by 34%, although indicators of inflammation, such as C-reactive protein, as well as metabolic markers of diabetes and obesity, such as fasting insulin and adiponectin, were either modestly reduced or unchanged [126].

Omega-3 PUFAs may exert beneficial effects on cognition through a reduction of cardiovascular risk factors, such as improving cerebral blood flow and decreasing triacylglycerol levels [79,127,128]. Other effects of omega-3 fatty acids include stimulation of neurogenesis and neurite outgrowth [129], enhancement of synaptic membrane fluidity [130], elevation of the expression of myelin-related proteins [131], and the upregulation of genes involved in maintaining synaptic function and plasticity [132]. In addition, omega-3 PUFAs appear to play a role in reducing inflammatory processes [133−135]. They may downregulate genes associated with the production of reactive oxygen species and upregulate the expression of antioxidant enzymes [133,136].

Various mechanisms have been proposed to mediate the effects of polyphenols on the brain. For example, resveratrol has beneficial effects on cerebral blood flow [137] and glucose control [138−140]. Neuroprotective mechanisms of polyphenols include reduction of mitochondrial dysfunction, glucose toxicity, and oxidative damage, as well as activation of longevity genes (e.g. sirtuins) (see references 88,141,142).

Gut dysbiosis, i.e. alterations in the composition and/or density of gut microbiota, has been linked to a wide range of diseases, including AD [143]. It has been suggested that the gut-brain axis might contribute to age-related dementias [144,145], and gut microbiota may thus play a role in diet-induced increase or decrease of AD risk [143]. While the high-fat diet common in Western cultures seems to be a factor contributing to gut

dysbiosis [146,147], the MeDi may be capable of balancing the gut microbiome [148−150]. However, the mechanisms underlying the effects of gut microbiota in the control of AD require further investigation.

In summary, the beneficial effects of the MeDi on risk for AD could be mediated through reduced vascular risk factors and benefits for glucose and lipid metabolism. In addition, findings of animal studies suggest that specific nutrients might have direct protective effects on the brain regarding, for example, amyloid-β metabolism (e.g. references 96,151).

5. Conclusions and future directions

On the basis of findings from prospective studies demonstrating that greater adherence to a MeDi may be associated with reduced cognitive decline and risk of AD [152−154], it has been suggested that adherence to MeDi may be a preventive measure able to delay the onset of dementia. A suggestive, but inconclusive, protective effect of the Mediterranean diet on outcomes related to cognition in AD and mild cognitive impairment was demonstrated by several prospective cohort studies, the majority of which found significant positive relationships between adherence to the Mediterranean diet and cognitive health (for review see reference 155). A meta-analysis including five prospective studies showed that, in individuals adhering to the Mediterranean diet, the risk of AD or mild cognitive impairment was reduced by 33% in those in the highest tertile compared to those in the lowest tertile [44]. In addition, greater adherence to the Mediterranean diet was protective against the progression from mild cognitive impairment to AD [44]. In a brain imaging study of individuals with higher versus lower adherence to a Mediterranean-style diet, lower adherence was shown to be associated with progressive abnormalities of AD biomarkers in middle-aged adults [53].

Current evidence suggests that the MeDi may protect against cognitive decline and dementia [30]. However, the majority of available studies are observational, and a causational link has, as yet, not been established. While the associations observed are commonly interpreted as a preventive influence of the MeDi on cognitive outcomes, the reverse could also be true, i.e. people may experience changes in appetite, eating habits, and food preferences both prior to the diagnosis or as an aspect of AD [156,157]. In addressing this issue, some studies excluded people with dementia or AD from the dietary analyses, and multiple dietary assessments were used to investigate the stability of MeDi adherence over time [37,54,158,159]. The processes underlying cognitive decline and AD are likely to commence many years prior to the onset of symptoms. Studies including middle-aged adults with long-term MeDi adherence may provide a better understanding of the relationship with cognition and dementia and may suggest a time window for the greatest benefits regarding disease-modifying effects of the MeDi [160]. Furthermore, one should consider that depressive symptoms are related to cognitive impairment and dementia [161], and adherence to the MeDi pattern has been associated with a reduced risk of depression [162].

Large epidemiological studies and randomized controlled studies need to be performed in order to provide further empirical evidence for the significance of the MeDi in cognitive decline and AD. Possible confounding factors, such as sex, comorbidities, ethnicity and other lifestyle habits, should be considered. In addition, individual and synergistic effects of MeDi components should be evaluated. The question of whether brain volume and function, as examined using neuroimaging and neurophysiological techniques, are affected by dietary intervention is also of interest [163].

5.1. External validity

The external validity of most findings demonstrating cognitive benefits in people on a MeDi remains problematic, since many overlaps and interactions exist between diet and other lifestyle factors, such as physical exercise (e.g. references 23,164). Older people following a Mediterranean-type diet may have a healthier lifestyle, which could protect them from dementia. For example, a randomized controlled trial, using a robust design and showing cognitive benefits in participants on a MeDi, was conducted in a highly active population in a Mediterranean culture [41]. Health benefits of the MeDi have also been shown to be relevant for non-Mediterranean populations [165]. However, substantial differences in dietary composition exist between countries, especially regarding fatty acids [37,46,166]. In comparison with refined oil, virgin olive oil has additional anti-inflammatory and antioxidant properties, which are beneficial to cellular function and cardiovascular health [167]. In addition, differences in cooking style (e.g. frying versus baking) may play a role [46,168]. Food processing is seldom taken into consideration when assessing health effects of the MeDi, although this factor can influence phytochemicals in certain MeDi food groups, such as vegetables, olives, olive oil, and nuts, and may therefore

alter the composition and nutritional value of these foods [169].

A further major limitation and threat to external generalizability of studies on associations between the MeDi and cognitive functions is that there are no *a priori* determinations of cut-off points or recommendations regarding the exact composition of the MeDi. Research studies normally compare participants within a given sample, who follow the MeDi to a greater or lesser extent. In a recent cross-sectional study using *a priori* determined cut-off points for MeDi adherence, greater adherence was associated with improved cognition and a decreased risk of dementia [65]. Among 1,865 individuals (mean age 73±6 years), 90 were diagnosed with dementia and 223 with mild cognitive impairment. An *a priori* MeDi score was derived from a food frequency questionnaire [65]. Each unit increase in the MeDi score was associated with a 10% decrease in the risk of dementia. Adherence to the MeDi was also linked to better performance in memory, language, and visuospatial perception as well as the composite cognitive score. The strongest associations were found for memory [65].

5.2. Lifestyle

Certain lifestyle activities, including physical exercise, have the potential to contribute to cognitive reserve capacity and thereby to reduce the incidence of dementia in older adults [170]. Some evidence suggests that exercise may help improve memory function in individuals with mild cognitive impairment [171]. However, evidence from randomized controlled trials regarding a role of exercise training in preventing mild cognitive impairment or dementia is sparse and does not support the premise that exercise reduces the risk of developing clinically relevant cognitive outcomes [172]. Trends toward significant improvement in executive functions following exercise in older people with AD have been reported in a systematic review of (a small number of) available studies [173]. Exercise has been demonstrated to preserve white and gray matter, induce changes in the hippocampus, including neurogenesis, and improve cognitive function [174]. Most animal and human studies have suggested that physical activity attenuates neuropathological changes and beneficially affects cognitive function in AD [175]. In summary, the available evidence suggests that the incorporation of regular physical activity into daily routines may mitigate AD-related symptoms, especially in early stages of the disease. Further studies are needed to confirm this.

Future research should examine synergistic effects of food, including the MeDi, with other lifestyle patterns that may help maintain cognitive functions in old age. In the so-called "Blue Zones" (e.g. Sardinia/Italy, Ikaria/Greece, Okinawa/Japan, Nicoya Peninsula/Costa Rica) dietary patterns similar to the MeDi are associated with exceptional longevity and a relatively high number of nonagenerians and centenarians [176]. Moreover, older Blue Zone Sardinians showed fewer cognitive impairments compared to people in another Italian region (Lombardy). This was related to superior performance in working memory and reduced levels of depressive symptoms [177−179]. However, apart from diet, other lifestyle factors, including long-term low levels of stress and a high level of regular physical activity as well as strong familial and social ties and a spiritual life [180], are characteristic of the Blue Zones.

5.3. Outcome assessment

Since a variety of tools for the assessment of cognitive function have been used in different studies, comparing outcomes of the studies is a challenging task. Dietary approaches to the modification of age-related cognitive decline, including the MeDi, require a valid and reliable assessment of various outcomes in early phases of the disease process. A consensus concerning the optimal approach to outcome assessment in dementia research does not exist. A comprehensive representation of the impact of interventions requires outcome measures to reflect not only cognitive functioning but also the personal experiences and patient-centered aspects of functional performance and quality of life [181]. A standardized approach to these problems is needed. In view of the heterogeneity of AD phenotypes, the development of valid and reliable as well as clinically and ecologically meaningful outcome measures is a major challenge [182].

The insufficiency of psychometric properties of functional and quality of life outcome measures used to demonstrate changes in AD drug trials is an important problem [183]. Most of the scales are impaired by serious limitations, such as incomplete assessment of validity and reliability for the intended purposes. A further major problem is the lack of data on responsiveness to change [183]. New assessment tools are therefore needed in regard to functional ability and quality of life. In addition to studies attempting to enhance cognition and function in individuals with AD, the focus of research has shifted towards prevention trials in early disease stages, when treatment responses

may be subtle and difficult to detect. This requires new cognitive and functional outcome measures that will be of value in clinical trials assessing the gradual progression to cognitive and functional impairment [184]. An evidence-based consensus on core outcome measures for trials of disease modifying interventions in mild-to-moderate dementia has recently been provided [185].

In summary, the use of different methods may explain the discrepancies in findings regarding the effectiveness of the MeDi in the prevention of cognitive decline. The variability in methods of cognitive assessment used in the available studies does not allow meta-analysis; a standardization of assessment tools is therefore needed. In particular, standardized neuropsychological scales for the assessment of cognitive function and impairment with proven sensitivity, specificity, and ecological validity should be developed and used across different studies [186,187]. This would allow the comparison of findings from different studies in meta-analyses.

5.4. Individual MeDi components

Some studies have addressed the health effects and neuroprotective properties of individual components of the MeDi, such as omega-3 fatty acids [188] and olive oil as the main source of monounsaturated fats [189]. Analyses for certain food groups showed that high vegetable intake and a high ratio of monounsaturated fat plus polyunsaturated fat in relation to saturated fat were associated with a reduced risk for mild cognitive impairment [190]. In a review, the influence of two MeDi components (omega-3 fatty acids, derived from fish consumption or supplementation, and diet-derived or supplementary polyphenols, such as resveratrol) on cognitive performance and brain health in aging was evaluated [66]. The findings of a majority of available studies suggested that consumption of omega-3 fatty acids with fish or fish oil supplements has positive effects on brain health and cognition in older humans. In regard to polyphenols, only a small number of controlled studies were available and the evidence was inconclusive [66].

When considering potential health effects of nutrients, the type of intake needs to be taken into account. For example, in the case of omega-3 PUFAs, both the consumption of fish and the intake of supplements could be problematic. While fish may be contaminated by organic chemicals and mercury, fish oil supplements may contain oxidation products of omega-3 fats and added antioxidants, both of which may have adverse effects. Omega-3 PUFAs are highly prone to oxidative degradation. A substantial proportion of omega-3 fish oils sold in retail stores in several countries worldwide have been shown to markedly exceed voluntary limits for at least one measure of oxidation or the international voluntary safety recommendations for total oxidation (see reference 191). It is possible that omega-3 PUFA supplements administered in previous clinical trials were oxidized and that the findings reported were confounded by the use of oxidized oils. Differences in omega-3 oxidation levels may explain the protective effects of fish consumption but not for omega-3 supplementation, as reported in a meta-analysis of available findings [192]. Furthermore, the effects of oxidized oils on human health and safe limits of oxidation for human consumption need to be investigated. In addition, possible adverse effects of long-term administration of vitamin E added as an antioxidant to fish oil supplements should be taken into consideration. While cancer preventive activity of vitamin E has been suggested by some epidemiological studies, large-scale human trials have shown increased rates of prostate cancer incidence in men taking α-tocopherol supplementation, the most commonly used form of vitamin E (e.g. reference 193).

5.5 Summary

The potential of a MeDi to prevent neurodegeneration has been attributed primarily to its high content of vegetables, fruits, and olive oil, which contain a wide range of bioactive phytochemicals, such as polyphenols, phytosterols, carotenoids, and sulfur compounds (e.g. references 37,54,57–61). The available findings suggest differential effects of individual food components of the MeDi on age-related cognitive decline. While the consumption of vegetables showed a significant inverse association with cognitive decline, a high ratio of monosaturated to saturated fatty acids showed only a weak inverse association [48]. Further research is needed to provide a better understanding of the significance of individual components of the MeDi. Furthermore, potentially synergistic effects of different MeDi components, as yet unknown, may exert specific effects in regard to cognitive function in aging.

The evidence for a protective effect of the MeDi on AD risk is suggestive but far from conclusive. The prescription of the MeDi as a preventive or therapeutic measure in AD is hindered by the lack of established levels of individual dietary components, especially of biologically active chemicals whose content, chemical structure, and efficacy are well characterized. Further

investigations are needed to elucidate the mechanisms by which MeDi or its components exert their potential cognition-enhancing effects on the nervous system.

6. The bottom line

Current evidence would suggest the adoption of the MeDi as an element of public health measures seeking to reduce the risk of AD. However, long-term randomized controlled trials are needed to establish a causal relationship between MeDi and the prevention or improvement of cognitive decline in AD. At present, it is not possible to prescribe the MeDi as a preventive measure in AD, since knowledge of the type and quantity of individual food components and bioactives required for effective neuroprotection is insufficient.

Conflict of interest

The author declares no conflict of interest**.**

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