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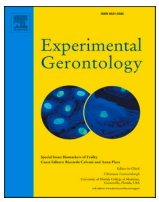

Review

The role of nutrition and the Mediterranean diet on the trajectories of cognitive decline

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ABSTRACT

The worldwide burden of dementia is immense, and set to increase to unprecedented levels in the coming decades, due to population aging. In the absence of disease-modifying treatment, there is therefore a strong rationale to support the assumption that acting on modifiable risk factors, especially in midlife, is a good strategy for reducing the burden of dementia. Among these risk factors, nutrition is key, as it is fundamental to healthy aging, and has interrelated benefits on a number of organ systems, metabolic processes and health states that can all contribute to modifying the risk of dementia. In this paper, we review the methodological challenges of comparing studies of dietary interventions. We then discuss the effect of genetics and the environment on brain health, and review in particular the literature data on the effect of nutrition on cognition. We summarize the body of data reporting the largely beneficial effects of the Mediterranean diet on brain health, and the possible mechanisms that mediate these effects. Finally, we discuss future perspectives for further research in the field, notably the "gut-brain axis", thought to be a key mediator of the effect of nutrition on brain health.

1. Introduction

It is estimated that around 50 million people currently live with dementia around the world, and this number is projected to double every 20 years, to affect up to 130 million individuals by the year 2050 (Alzheimer's Disease International, 2015), or even 150 million according to some estimates (Livingston et al., 2020). The burden of dementia is disproportionately borne by low- and middle-income countries, where it is reported that 58 % to 66 % of those with dementia live (Livingston et al., 2020). Minority populations are also disproportionately affected, with African-Americans shown to have a 65 % higher risk of dementia than Asian-Americans (Mayeda et al., 2016). In addition, minority groups may have less opportunity to receive appropriate care, thereby compounding this inequality (Barnes and Bennett, 2014). Alzheimer's disease (AD) accounts for 60 % to 80 % of all dementias, and is a leading cause of disability worldwide, although "pure" forms are quite rare, and cognitive disorders of mixed etiology are the most frequent, particularly with a vascular contribution (Livingston et al., 2020; Qiu and Fratiglioni, 2015). Currently, there is no known cure for AD, but several risk factors have been identified. Age is a major determinant of AD, and at age 80, there is a four-fold greater incidence of AD compared to 70 years of age, and a nine-fold greater incidence compared to 65 years age (Mayeux and Stern, 2012). Other genetic and environmental factors contribute to the risk of AD, including educational level, hypertension, alcohol consumption, obesity, smoking, physical inactivity, diabetes or depression (Livingston et al., 2020). Experts estimate that taken together, 12 modifiable risk factors account for 40 % of worldwide dementia (Livingston et al., 2020). A reduction of 10 % to 25 % in 7 of these risk factors has the potential to prevent up to 3 million AD cases worldwide (Barnes and Yaffe, 2011). Although nutrition is not specifically listed among the risk factors, lifestyle and dietary habits underpin several of the known risk factors, such as hypertension, obesity and physical (in)activity. Indeed, the most prominent risk factors identified in a study of 378,615 individuals, from the nationally representative US Behavioral Risk Factor Surveillance Survey data were midlife obesity and physical inactivity (Nianogo et al., 2022). A healthy lifestyle can help to reduce the incidence of hypertension, diabetes or overweight, which in turn could contribute to reducing the risk of AD. Furthermore, healthy lifestyle habits could offset some of the genetic risk for AD, except in cases where the genetic burden is too high to be modified by lifestyle alone (Lourida et al., 2019; Licher et al., 2019; Yassine et al., 2022). In the absence of disease-modifying treatment, there is therefore

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a strong rationale to believe that the best hope for reducing the burden of AD is by acting on modifiable risk factors, especially in midlife. Among these risk factors, nutrition is key, as it is fundamental to healthy aging, and has interrelated benefits on a number of organ systems, metabolic processes and health states that can all contribute to modifying the risk of dementia.

We review here the role of nutrition in dementia and brain health. In particular, we examine the effects of isolated eating habits compared to overall dietary patterns, specifically the Mediterranean diet. Finally, we discuss future perspectives for research into open questions, with a view to mitigating the burden of dementia in the coming decades.

2. Methodological issues in studies of nutritional interventions

The body of evidence investigating the role of nutrition in preventing or slowing cognitive decline provides a firm basis in support of an overall neuro-protective effect of nutrition. Nevertheless, it is very difficult to establish direct, statistically significant and clinically meaningful associations between nutrition and cognitive function, for numerous reasons. First and foremost, nutrition is an umbrella term encompassing an extremely wide spectrum of behaviours in terms of the foods eaten, the portion sizes, the timing of meals, how the foods are cooked and combined etc. It has previously been reported that there are non-linear relationships between foods, whereby patients with dementia had significantly different food combinations compared to those without dementia, despite the absence of any difference in the quantity of foods consumed between groups (Samieri et al., 2020). The nutritional intake also includes potential consumption of unhealthy products as well, even among those who consume the recommended amounts of "healthy" nutrients. Diet is multifactorial, and includes an element of environmental exposure, through the origins and quality of the products consumed. The effect of diet may also be mediated, promoted or exacerbated by other conditions (such as level of education, socio-economic status, or disease) or behaviours (e.g. exercise, smoking, alcohol consumption), or genetic inheritance (e.g. sex, and factors known to affect cognitive status, such as *APOE4*). Therefore, studies investigating nutrition suffer from the heterogeneity of nutritional patterns, and the complexity of the relationships between nutrition and health outcomes. Many studies of the effect of nutrition on cognitive health have failed to show any positive effect, but this does not mean that there is no such effect. It just means that it may be occulted by the various other factors that contribute to aging and cognitive status.

There is thus a paucity of studies showing a large effect size of diet/nutrition on cognitive status. This can likely be explained by methodological differences between studies, which render comparisons across studies hazardous, at best. Methodological issues include the study population for example –the population may be too old for a temporary change in nutrition to counteract the cumulated effects of a lifetime spent engaging in different habits; the cognitive reserve of the population may be too high to show any benefit of nutrition interventions, or the risk of dementia may be too low. Compliance in nutrition studies is another issue, as adherence can be suboptimal, or hard to measure, or the intervention may not be sufficiently intense to show any effect alone, especially if administered in subjects whose baseline nutrition is already of high quality and close to (or above) recommended standards. In many studies of nutritional interventions, it may be difficult to demonstrate a significant effect if the endpoint used is not sensitive to change, or at least, to change directly resulting from the intervention. Indeed, as outlined above, cognitive health is dependent on numerous factors, and the contribution of one specific nutrient to overall risk may be insufficient to affect the cognitive outcome. Lastly, studies that have examined the benefits of dietary patterns, rather than the effects of single nutrients, might have a greater chance of showing a positive effect, but it is then difficult to identify which specific component of the dietary pattern is responsible for the effect. In addition, "control" diets can be hard to establish and measure when testing overall dietary patterns. There is also potential for reporting bias and social-desirability bias when subjects self-report their eating habits. Finally, the effects of lifestyle changes can take many years to become apparent, so it is therefore understandable that short-term interventions (ranging from several weeks to several months) would fail to produce a visible benefit.

3. Effect of the environment and genetics

Epidemiologists have debated the limitations of dominant causal models of disease that emphasize a linear and sequential view of causality, with focus on proximate and individual-level risk factors. A focus on how social, environmental and biological factors combine to jointly influence health, in a lifelong approach, may be more appropriate. In this regard, an ecological approach to health issues, with ecological models of intervention, have become distinctive features of disease prevention and health promotion in public health. Indeed, brain function is the result of a lifetime of interaction between the genes and the environment. It has been postulated that the modulating effects of diet on cognition may begin as early as during embryonic development (Polverino et al., 2021). The biological processes that affect late-life cognitive decline, including synaptic plasticity, oxidative stress, or neurogenesis, can be modulated starting in utero and right through adulthood, underlining the life-long cumulative effects that culminate (or not) in cognitive decline (Polverino et al., 2021). Several lines of evidence converge to indicate that epigenetic mechanisms acting during the peri-conceptional period, pregnancy and the first 2 years of life can have lifelong effects on neurodevelopment; such processes include DNA methylation, histone modification and regulation of intestinal permeability involving the gut-brain axis (Polverino et al., 2021). These findings have led to the emergence of the "First Thousand Days of Life" concept, whereby the period from conception to the child's second birthday plays a key role in determining health later in life, not only in terms of cognition and brain health, but also mental and emotional well-being, nutrition and body-weight (Darling et al., 2020; Koletzko et al., 2014).

The perinatal and infancy period of life has also been recently recognized as extremely important in shaping the structure of the gut microbiota (Bokulich et al., 2016; Vandenplas et al., 2020), and several lines of experimental evidence increasingly indicate this period as being involved in the pathophysiology of age-related cognitive impairment and dementia, in the "microbiota-gut-brain axis" framework (Cryan et al., 2019). In mice, birth by Caesarean section, which can dramatically influence the gut microbiota composition in the early phases of life, has been associated with the later development of cognitive deficits (Morais et al., 2020). Although these findings were not confirmed by a recent large cohort study in humans (Blake et al., 2022), the perinatal period remains a critical window in which perturbations of the labile equilibrium of gut microbial communities can influence later onset of behavioural disturbances (Otten et al., 2022).

Genetic inheritance also plays a role in shaping the risk of dementia, and genome wide association studies have greatly advanced our understanding of dementia and Alzheimer's disease in particular. For example, it has been shown that the ε4 allele of the apolipoprotein E gene (*APOE4*) is associated with an increased risk of Alzheimer's disease (Lambert et al., 2013; Verghese et al., 2011). In a retrospective cohort study of almost 200,000 individuals aged over 60 years, of European ancestry, and free of cognitive impairment or dementia at baseline, Lourida et al. calculated a polygenic risk score for dementia, and reported that participants with a high genetic risk had an almost two-fold increase in the risk of dementia compared to those with a low genetic risk (adjusted hazard ratio 1.91, 95 % confidence interval (CI) 1.64–2.23, $p < 0.001$) (Lourida et al., 2019). Furthermore, using long-term data on genetic risk and modifiable risk factors among 6352 individuals aged 55 years and older from the population-based Rotterdam Study, Licher et al. reported that a favorable modifiable-risk profile was associated with a lower risk of dementia compared to those with an

unfavorable profile of modifiable lifestyle behaviours (Licher et al., 2019). Conversely, in those at high genetic risk (i.e. carriers of ε2ε4, ε3ε4 or ε4ε4 APOE genotypes), the protective effects of modifiable risk profile was not observed, indicating that the high risk of developing dementia based on APOE carrier status could not be offset by modifiable lifestyle factors in midlife (Licher et al., 2019). The authors put forward several hypotheses to explain this finding, including the fact that the harmful effects of *APOE- ε4* may gain traction over the whole life course, with cumulative effects in later life; the potential for *APOE- ε4* to cause irreversible neuronal damage; and the potential for *APOE- ε4* to trigger other pathways that can influence dementia risk, such as inflammation (Licher et al., 2019).

4. Nutrition and brain health

Despite the conflicting evidence regarding the ability of lifestyle modifications to offset genetic risk for dementia, the fact remains that AD is neither reversible nor curable, and therefore, the sole means at our disposal to avert or delay the onset of dementia is through potentially modifiable risk factors. In particular, a focus on midlife exposures is warranted, before subclinical diseases processes begin, and before clinical disease becomes apparent. Indeed, many of the prominent risk factors for dementia, such as obesity or hypertension, become apparent in midlife and can efficiently be targeted, with a view to indirectly influencing dementia risk (Nianogo et al., 2022). Nutrition is one of life's most basic and central behaviours, and therefore, is a prime target for interventions, which in turn may propagate beneficial effects into other conditions affected by diet, such as body weight, hypertension, metabolic disturbances etc. It should be noted that trials of nutritional interventions may be hampered by this complex interplay between nutrition and health, and between nutrients themselves. Indeed, certain nutrients may have opposite effects on the risk of AD, and their simultaneous consumption may result in positive and negative effects weighing each other out, giving the false impression of an absence of relation with the outcome (Gu et al., 2010). A recent student of >28,000 individuals from Sweden reported a median of 19.8 years of follow-up of dietary habits, and failed to observe any significant association between adherence to conventional dietary recommendations or to a modified Mediterranean diet, and the risk of all-cause dementia, AD, or vascular dementia (Glans et al., 2023). In that study, 6.9 % were diagnosed with dementia during follow-up, but it should be noted that no systematic cognitive testing was performed, and dementia diagnosis information was retrieved from a national registry. The proportion with dementia may thus have been underestimated. Furthermore, the group with incident dementia had higher rates of cardiovascular risk factors at baseline (e.g. history of coronary event, stroke, diabetes, hypertension), which may have occulted the effect of diet on the development of dementia.

Several nutrients, examined individually, have been shown to have a positive effect on cognitive outcomes. In a longitudinal analysis of 49,493 women from the Nurses' Health Study and 27,842 men from the Health Professionals Follow-up Study, Yeh et al. examined the associations between dietary protein, amino acids, and various protein food sources with subsequent subjective cognitive decline, using regular assessments via food frequency questionnaires (Yeh et al., 2022). They reported that higher intake of total protein, animal protein, and plant protein was significantly associated with a lower risk of subjective cognitive decline in both men and women (Yeh et al., 2022). Although the subjective assessment of cognitive decline is not ideal from a methodological point of view, the large number of study participants, the long follow-up period, and the repeated measurements give sufficient strength to these findings to support the conclusion that compared to the same number of calories obtained from carbohydrates, intake of protein has a significant role in maintaining cognitive function. A study specifically addressing the role of protein is currently ongoing and will investigate the effect of a protein-enriched Mediterranean diet on nutritional and cognitive status in older people at risk of undernutrition and cognitive decline (O'Neill et al., 2022).

Fruits rich in polyphenols have also been investigated for their potential to counteract the age-related decline in cognition. In a 12-week randomized trial testing the effect of freeze-dried cranberry powder supplementation in 60 participants aged 50 to 80 years on cognition, Flanagan et al. reported that cranberry supplementation was associated with improvements in visual episodic memory compared to the control group, with evidence from magnetic resonance imaging of increased perfusion in key brain regions supporting cognitive function (Flanagan et al., 2022). Interestingly, these authors also noted a significant decrease in low-density lipoprotein (LDL) cholesterol concentrations in the cranberry supplementation group, showing how the collateral effects of nutrition interventions may indirectly act on other risk factors. Indeed, the causative role of LDL cholesterol in atherosclerotic cardiovascular disease has been definitively established (Ference et al., 2017). Elsewhere, Krikorian et al. tested the effects of daily blueberry supplementation on cognitive decline in a randomized, controlled trial among overweight individuals aged 50 to 65 years, with insulin resistance and an elevated risk of future dementia (Krikorian et al., 2022). In the group receiving blueberry supplementation, the authors observed improved performances on domains of cognitive function such as lexical access, memory interference and memory encoding, together indicating improved executive function. These results open interesting perspectives for targeted interventions in overweight individuals in midlife, as it has been reported that the natural decline in executive function with increasing age is exacerbated by overweight and metabolic disturbances (Favieri et al., 2019), once again highlighting the importance of considering nutrition along with other risk factors such as metabolic disease or overweight in shaping the risk of dementia across the life course.

The role of the intestinal microbiota as mediator of the effects of dietary polyphenols on cognition should be also considered (Ticinesi et al., 2022). Many polyphenolic compounds contained in foods of vegetal origin do not have any biological effect per se, but need transformation into bioactive compounds by specific metabolic functionalities expressed by gut bacteria. For example, ellagitannins, a subclass of polyphenolic compounds contained in pomegranates and nuts, can be alternatively transformed by certain gut microbiota metabotypes into the bioactive compounds urolithin A or B (D'Amico et al., 2021). Increasing evidence from animal models indicates that urolithin A is able to slow down brain aging, reduce neuroinflammation and amyloid deposition, and improve cognitive tests (Chen et al., 2019; Gong et al., 2019; Fang et al., 2019). Interestingly, the administration of pomegranate extracts or polyphenol supplements was associated with significant clinical improvements of memory function in human studies (Bookheimer et al., 2013; Kaplan et al., 2022), underlining the importance of the interaction between food and microbiota in the pathophysiology of dementia.

The evidence regarding the effects of vitamin supplementation remains controversial. There are many forms of over-the-counter vitamin supplements available on the market. Products that do not seek approval as prescription drugs may not be subject to the same strict rules regarding the scientific evidence of efficacy. Therefore, over-the-counter products may claim to be beneficial on a variety of outcomes, but actual scientific proof of efficacy, e.g. via randomized trials, may be lacking. This said, vitamin supplements lend themselves well to testing in a research environment, because it is easier to quantify consumption compared to trials testing food patterns. A systematic review of the effect of vitamin supplementation on dementia examined 14 studies testing B-complex vitamins, 10 studies of vitamin D supplementation, and 3 studies of vitamin E (Gil Martinez et al., 2022). In the studies of B-complex vitamins (folic acid, vitamin B1, vitamin B12 and a B-complex combination), subjects with folic acid supplementation were found to perform better than controls on cognitive tests. It is noteworthy that B vitamins are required for the elimination of homocysteine, known as a

risk factor for cognitive decline. There is therefore a rationale for hypothesizing that individuals with high baseline homocysteine concentrations and low baseline vitamin B concentrations may yield a benefit from vitamin B supplementation (Scarmeas et al., 2018). The brain also has a high concentration of lipids and is sensitive to oxidative stress. There is thus also a rationale for hypothesizing that supplementation with antioxidant substances, such as vitamin C or E, could affect cognitive function. However, the results observed in studies testing the impact of vitamin D or E supplementation on cognitive function have been less encouraging, and are not sufficient to recommend the

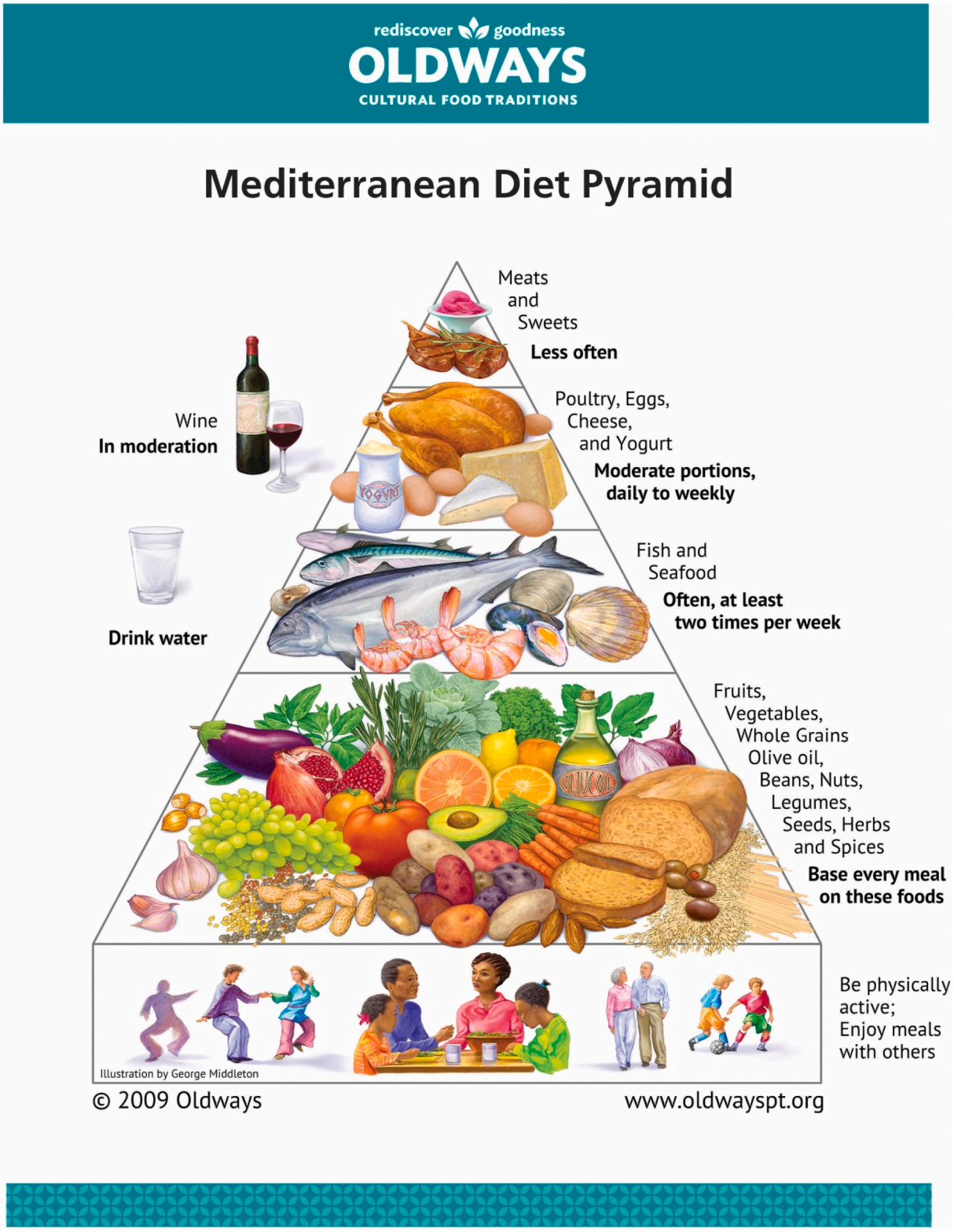

Fig. 1. Defining features of the Mediterranean dietary pattern.
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systematic use of vitamin supplementation for the prevention, delay or slowing of cognitive decline (Gil Martinez et al., 2022; Scarmeas et al., 2018). A recent meta-analysis of 884 randomized controlled intervention trials evaluating 27 types of micronutrients among 883,627 participants (4,895,544 person-years) found that some, but not all micronutrients were associated with positive effects on cardiometabolic health (An et al., 2022). The authors concluded that above all, what matter is a diversified diet, choosing whole-food based dietary patterns that promote cardiovascular health. In this regard, there is evidence suggesting differences between dietary and supplemental vitamin intake, whereby the context in which vitamins are ingested can effectively influence their absorption and therefore their effects in the body (Liu, 2003; Burton et al., 1998).

5. Mediterranean dietary pattern and brain health

People do not eat individual foods in isolation, and nutrients are, by definition, essential and therefore never completely absent from the diet of control groups. It therefore makes more sense to study composite dietary patterns, which are likely a better reflection of an individual's overall eating habits. They also show effects that are the combination of the individual effects of the different foods in the overall dietary pattern, since foods are biologically interactive, making it more likely that an effect will be visible on a given outcome in a research setting. A range of dietary patterns have been studied in the literature for their effects on cognitive function or dementia. The most widely studied is the Mediterranean diet, and a substantial body of evidence from observational studies and randomized trials concurs that greater adherence to the Mediterranean diet is associated with a slower rate of cognitive decline, and a reduced risk of dementia, or progression to dementia (Scarmeas et al., 2018). The Mediterranean dietary pattern is among the oldest eating patterns ever described, and encompasses not only a wide range of foods, but also socio-cultural aspects, such as the enjoyment of meals surrounded by friends and family, the consumption of locally produced, seasonal foods, with the possibility of moderate alcohol consumption. The defining features of the Mediterranean dietary pattern are displayed in Fig. 1.

One of the first studies to document a benefit of adherence to the Mediterranean diet in terms of incidence AD used data from the Washington Heights-Inwood Columbia Aging Project (WHICAP) to prospectively evaluate cognitive function every 1.5 years among 2258 community-dwelling, non-demented individuals in New York (Scarmeas et al., 2006). In this study, Scarmeas et al. reported that adherence to the Mediterranean diet was associated with a significantly lower risk of incident AD. In the Chicago Health and Aging Project, a longitudinal study of adults aged over 65 years, Tangney et al. found that among 3790 participants, greater adherence to the Mediterranean diet, as measured by MedDiet scores, was associated with slower rates of cognitive decline after adjustment for age, sex, race, education, participation in cognitive activities, and energy (Tangney et al., 2011). Another of the key studies to have demonstrated a positive effect of the Mediterranean diet on brain health is the randomized PREDIMED-NAVARA study, which examined cognitive performance, assessed by the Mini-Mental State Examination (MMSE) and Clock Drawing Test (CDT) among 522 participants at high vascular risk with a mean age of 74.6 years (Martinez-Lapiscina et al., 2013). After 6.5 years of nutritional intervention, they observed higher mean MMSE and CDT scores in those who adhered to the Mediterranean dietary interventions, versus the control group. A currently ongoing project is investigating the specific role of a protein-enriched Mediterranean diet combined with exercise, on nutritional status and cognitive performance in older adults (the PROMED-EX trial) (O'Neill et al., 2022).

More recently, a randomized controlled trial among 284 obese or dyslipidemic participants reported that a high-polyphenol diet, rich in Mankai, green tea, and walnuts and low in red or processed meat, was potentially neuroprotective for age-related brain atrophy (Kaplan et al., 2022). Another study among 183 cognitively intact adults aged 20 to 80 years showed that greater adherence to the Mediterranean diet was associated with a reduced increase in white matter hyperintensity over time, providing further support for the hypothesis that a healthy diet, especially if begun at an early age, may contribute to long-term brain health (Song et al., 2022). Finally, an exploratory study among 87 middle-aged adults in the USA compared the effects of the western-type and Mediterranean diets on metabolic parameters, cerebrospinal fluid biomarkers of AD, cerebral perfusion assessed by magnetic resonance imaging (MRI), and cognition (Hoscheidt et al., 2022). The authors observed striking differences of the dietary intervention between those with mild cognitive impairment and those with normal cognition, whereby the Mediterranean-type diet had beneficial effects on cerebrospinal fluid AD biomarkers, cerebral blood flow, and memory among cognitively normal adults, while the Western-type diet had negative effects (Hoscheidt et al., 2022). Taken together, these findings collectively show that the effects of diet may cumulate over the lifetime, and may be mediated by cognitive status. Furthermore, the emphasis on social interaction and physical exercise in the overall Mediterranean dietary pattern may also enhance successful aging (Lisko et al., 2021).

In relation to the cardiovascular risk factors of dementia, the Dietary Approaches to Stop Hypertension (DASH) diet has been shown to reduce blood pressure, low-density lipoprotein cholesterol, body weight and inflammation (Morris, 2016). Adherence to this dietary pattern has also been shown to improve cognitive function (Tangney et al., 2014; Wengreen et al., 2013). A new diet combining the most advantageous components of both the Mediterranean and DASH diets was devised by a team of American researchers to protect against neurodegeneration; and called the "MIND" diet (Mediterranean-DASH Intervention for Neurodegenerative Delay). The ability of the MIND diet to prevent cognitive decline and AD was tested in 960 participants with an average of 4.7 years of follow-up (Morris et al., 2015). The authors reported that the MIND score was positively associated with slower decline both in global cognitive score, and in each of five individual cognitive domains. The difference in the rate of decline between the highest tertile of MIND diet score compared to the lowest tertile was approximately equivalent to being 7.5 years younger in age (Morris et al., 2015). A recent study from the UK biobank study examined self-reported intake of food groups considered to be part of the Mediterranean diet among 249,511 participants aged at least 55 years old, and free of dementia at baseline (Dobreva et al., 2022). The authors found that the consumption of fish and fruit was associated with a significantly reduced risk of all-cause dementia, providing insights into the possible mechanisms of the Mediterranean diet's neuroprotective effects.

More recently, several systematic reviews and meta-analyses of existing studies have underlined the positive impact of the Mediterranean diet on cognitive decline and AD (Garcia-Casares et al., 2021; Fu et al., 2022; Loughrey et al., 2017; Wu and Sun, 2017; Petersson and Philippou, 2016; Singh et al., 2014; Limongi et al., 2020; Gauci et al., 2022). A meta-analysis including 11 studies totalling 12,458 participants found that higher adherence to the Mediterranean diet was associated with a significantly lower risk of mild cognitive impairment (relative risk (RR) 0.91, 95 % confidence interval (CI) 0.85–0.97) and AD (RR = 0.89, 95 % CI = 0.84–0.93) (Garcia-Casares et al., 2021). Another meta-analysis recently performed by Fu et al. included 26 cohort studies and two randomized clinical trials (RCTs) (Fu et al., 2022). They reported that in cohort studies, higher adherence to the Mediterranean diet was associated with a 25 % lower risk of mild cognitive impairment, and a 29 % lower risk of AD. In the RCTs, high adherence to the Mediterranean diet was associated with better episodic and working memory (Fu et al., 2022). Moreover, a recent systematic review summarized reported associations between dietary patterns and neuroimaging markers from nine prospective studies (7 testing the Mediterranean diet, 1 evaluating the Alternative Healthy Eating Index-2010, and 1 examining a posteriori derived dietary patterns) (Townsend et al., 2022). The parameters investigated included for example

grey matter volume, total brain volume, cortical thickness, white matter volume, white matter integrity or white matter hyperintensity. Overall, there was evidence of an association between healthy dietary patterns and changes in neuroimaging markers over time, suggesting the plausibility of a neuroprotective effect of adherence to healthy dietary patterns.

Overall, the collective body of evidence from these meta-analyses converges towards a significant relationship between adherence to the Mediterranean diet and the rate of cognitive decline, impairment and dementia. Based on the existing evidence, the Mediterranean diet is recommended by the US Department of Health and Human Services (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2020), and was identified by the World Health Organization (WHO) as an effective dietary strategy to prevent and control non-communicable diseases (Renzella et al., 2018). The WHO recommendations for risk reduction for cognitive decline and dementia state that the Mediterranean-like diet may be recommended to adults with normal cognition and mild cognitive impairment to reduce the risk of cognitive decline and/or dementia (World Health Organization, 2019).

The Mediterranean and DASH-style diets can also induce favorable modulation of the gut microbiota, which can reinforce their neuroprotective effect through the microbiota-gut-brain axis (Merra et al., 2020). A high level of adherence to the Mediterranean dietary pattern was also associated with increased biodiversity of the gut microbiota, with enhanced representation of bacterial taxa and functionalities involved in modulation of inflammation and regulation of cognitive function (De Filippis et al., 2016). In the aforementioned Nu-AGE study, positive modulation of the gut microbiota composition and function was matched by improved performance in cognitive tests after a 1-year intervention (Ghosh et al., 2020). In the PREDIMED-Plus Study, a group of subjects aged 55 to 75 years old were randomized to receive a 1-year intervention with traditional Mediterranean diet versus an energy-restricted Mediterranean diet plus regular exercise programs. All participants experienced a shift of their gut microbiota composition towards increased representation of taxa with purported health-promoting functionalities at the end of the intervention period, but the changes were more pronounced in the diet plus exercise arm, highlighting the synergistic effects of combining two lifestyle interventions (Muralidharan et al., 2021).

6. Future research directions

One of the most promising avenues for future research is the elucidation of the gut-brain axis, whose involvement in neurodegeneration is becoming increasingly documented and well described. Adherence to the Mediterranean diet could have neuroprotective effects by modulating the gut microbiota, and these alterations in turn affect cognitive function. The full range of pathways by which the gut microbiota environment affects the brain remains to be elucidated, but they are numerous, largely overlapping and intricately related. Exploring these pathways further could shed light on novel parameters that could be leveraged to interrupt deleterious pathways and/or promote beneficial pathways, with a view to optimizing neurocognitive outcomes. One of the major challenges lies in performing well-designed, microbiome-centred studies in human beings, and to decipher the exact role of individual foods, or overall dietary patterns in the microbiome. A further perspective is to bridge the gap being experimental evidence relating to the gut-brain axis coming from animal models, and the results from human studies, which are sometimes disappointing, in view of the expectations raised by experimental models. Finally, the role of probiotics in modulating the microbiota is also the subject of ongoing debate. Translating the intestinal effects observed with individual strains into the development of drugs or nutriceuticals that show proven efficacy for clinical use is the focus of intense ongoing research.

7. Conclusion

There is a considerable burden of dementia in the world, and this burden is set to increase in the coming years. Addressing the possible causes of dementia, and Alzheimer's disease in particular, is paramount to tackling the immensity of the oncoming "silver tsunami". As a major contributor to mid-life risk factors for cardiovascular, metabolic and neurodegenerative diseases, diet warrants specific attention and targeted interventions, as a means to leverage the potential risk of obesity, hypertension, diabetes, frailty, sarcopenia and/or dementia. Genetic and environmental factors may also shape the risk of late-life dementia, but in the hypothesis that brain health is the long-term result of a lifetime's worth of interaction between genes and the environment, diet should be targeted as a modifiable factor that can be used to offset, as far as possible, the negative effects of other variables. Given that AD is neither reversible nor curable, the sole means at our disposal to avert or delay the onset of dementia is through potentially modifiable risk factors, such as diet. Despite methodological issues hampering the comparison of dietary intervention studies, there is a large body of evidence that consistently shows the neuroprotective benefits of adherence to a Mediterranean-type diet. Adherence to a Mediterranean-type dietary pattern, starting early in life, should therefore be promoted as an accessible and effective means to contribute to maintaining brain health and cognitive function across the life course.

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CRediT authorship contribution statement

Stefania Maggi: Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Andrea Ticinesi:** Methodology, Writing – review & editing. **Federica Limongi:** Data curation, Writing – review & editing. **Marianna Noale:** Data curation, Writing – review & editing. **Fiona Ecarnot:** Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

Competing interest

No author has any competing interests to declare.

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