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Dietary Factors and Cognitive Health: A Critical Review of the Evidence.

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Abstract

As reported in 2019 by the Lancet Commission, our society is facing the Global Syndemic of obesity, undernutrition, and climate change. This critical situation is causing an increase in many different health complications, among which are neurodegenerative disorders and dementia. Over the last thirty years, the number of people with dementia almost tripled, and it is expected to triple once more by 2050, reaching 152,8 million. This will come with very high socioeconomic costs. This master thesis aims to thoroughly and critically review the current evidence about nutrition's impact on cognitive functions and their preservation through aging. Nutrition is intended in its most comprehensive range: from the single nutrients in foods to the complexity of entire dietary patterns. Whole, plant-based foods such as but not limited to berries and fruits, green leafy vegetables and other vegetables, nuts, and fatty fish appear to be the most promising for dementia prevention due to the many brain activity-supporting nutrients present in them. Finally, using the best evidence, this master thesis provides scientific dietary guidelines for optimal cognitive health and dementia prevention.

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1. Introduction

Malnutrition, intended as obesity and undernutrition, is the global leading cause of poor health. In addition, climate change is exacerbating the health problems related to malnutrition because of its direct effects on human health and indirect impact on the natural systems we depend on as humans (Swinburn et al., 2019). The Lancet Commission has defined this current situation as a Global Syndemic, and among its health consequences is a rapidly increasing incidence of neurodegenerative disorders and dementias. Between 1990 and 2019, the number of people who have dementia rose from 20,2 million to 57,4 million, with a 13,6 million increase from 2016 to 2019 ("Estimation of the Global Prevalence of Dementia in 2019 and Forecasted Prevalence in 2050: An Analysis for the Global Burden of Disease Study 2019," 2022). The Lancet Commission also reports that by 2050 the number of people with dementia is expected to reach 152,8 million, almost three times what it is today. This can be better visualized from the figures below, extracted from the abovementioned report (Figure 1).

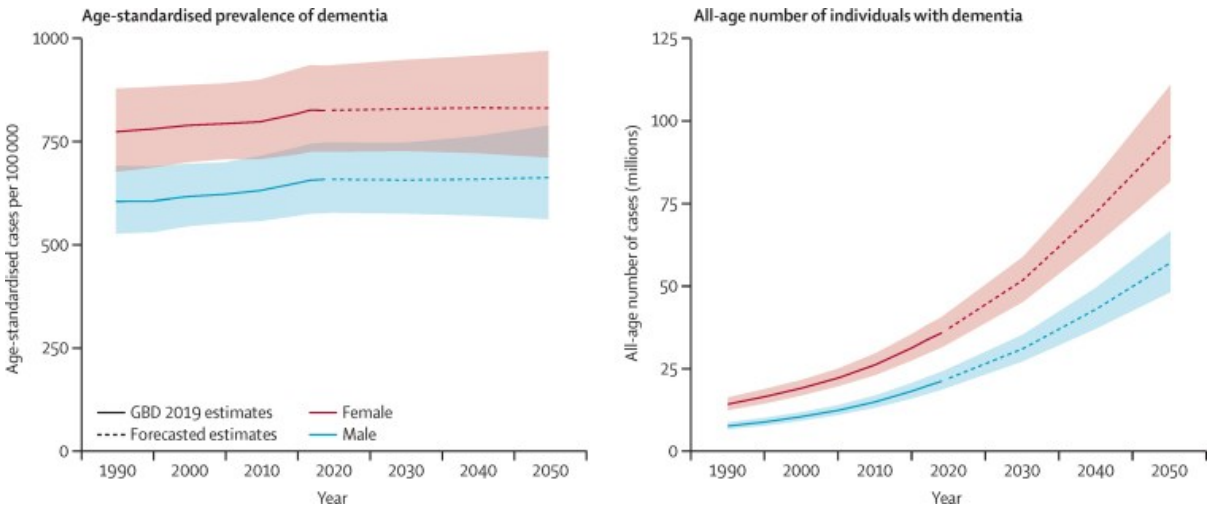

Figure 1: Estimated trends in the global age-standardized dementia prevalence (A) and all-age number of cases (B), with 95% uncertainty intervals, 2019–50 ("Estimation of the Global Prevalence of Dementia in 2019 and Forecasted Prevalence in 2050: An Analysis for the Global Burden of Disease Study 2019," 2022).

An increase in longevity can partly explain this, but this is far from the whole picture. With the growing body of scientific literature available on the subject, it is evident that age is just one of many risk factors. Genetics, lifestyle (nutrition, physical activity, cognitive activity), and other environmental factors also play a determinant role (Armstrong, 2019). The belief that

severe mental decline is a natural part of aging, referred to as "senility" or "senile dementia," is inaccurate (Irwin et al., 2018). Healthy aging does not include severe cognitive impairment, just like it does not include severe physical impairment.

The social cost of dementia was comparable to that of tumors, heart disease, and stroke in the 2010 World Report on Alzheimer's Disease (AD) (Alzheimer's Disease International, 2010). The World Health Organization (WHO) reports that dementia is now the seventh leading cause of death globally ("2022 Alzheimer's Disease Facts and Figures," 2022). As stated above, with the current population growth and aging population, the incidence of dementia will rise, with social and economic costs. AD and other forms of dementia pose significant challenges to the health and well-being of millions of people worldwide, and the burden on caregivers and healthcare systems is immense. Ongoing research into the causes and potential treatments for these diseases is critical, as it may lead to breakthroughs in early detection, prevention, and management. Scientists are exploring various approaches, including drug therapies and lifestyle interventions, to combat AD and other forms of dementia, but a cure has yet to be found (Breijyeh & Karaman, 2020; Krauss et al., 2021). It's also essential to better understand the risk factors for AD and other dementias, such as genetics, lifestyle factors, and environmental exposures. This knowledge can help identify those at higher risk of developing these diseases and inform public health efforts to reduce the incidence and prevalence of dementia. Overall, the need for continued research and investment in AD and dementia is crucial for improving the lives of millions of people affected by these devastating conditions.

This master thesis comprehensively and critically examines the scientific literature on nutrition's impact on cognitive function, cognitive decline, and dementia. Following a concise overview of the primary forms of dementia, their associated risk factors, and their underlying physiological pathways, the main body of the thesis is devoted entirely to the exploration of nutrition as a powerful tool in addressing the growing prevalence of dementia cases. Lastly, evidence-based dietary guidelines are offered, laying the ground for a comprehensive nutritional approach to prevent cognitive decline, optimize mental performance, and enhance overall well-being. This thesis also acknowledges the interconnections between cognitive decline and widespread psychiatric conditions such as depression, suggesting that preventive measures against cognitive decline may also mitigate the risk of psychiatric illnesses.

2. Overview of Alzheimer's Disease and other dementias

Dementia encompasses a range of medical conditions that cause abnormal brain changes, leading to a decline in cognitive abilities and impacting daily life, behavior, emotions, and relationships. Alzheimer's disease (AD) and vascular dementia (VaD) are the two predominant forms of neurodegenerative disorders in our society, and together they account for 60-80% of all cases (Ashraf et al., 2016).

2.1. Causes and risk factors

The pathogenesis of AD and other forms of dementia is very complex: it involves multiple factors such as genetics, age, lifestyle, and environmental factors (Armstrong, 2019). The risk of developing AD and other forms of dementia begins to increase with age at around 65; other risk factors typically associated with a higher dementia risk include diabetes, depression, hypercholesterolemia, hypertension, hyperhomocysteinemia, smoking and little social contact (Livingston et al., 2017). More recently, new risk factors have been added to the list: excessive alcohol intake, brain damage, and air pollution (Livingston et al., 2020). Because of its strong correlation to other pathologies, such as type 2 diabetes, obesity is also considered a risk factor for dementia (Selman et al., 2022).

The only genetic risk factors seemingly meaningful are those correlated with the early-onset form of AD: the genetic factors linked to all the remaining AD and dementia cases are not good predictors of developing the disease. (Institute for Quality and Efficiency in Health Care (IQWiG), 2017).

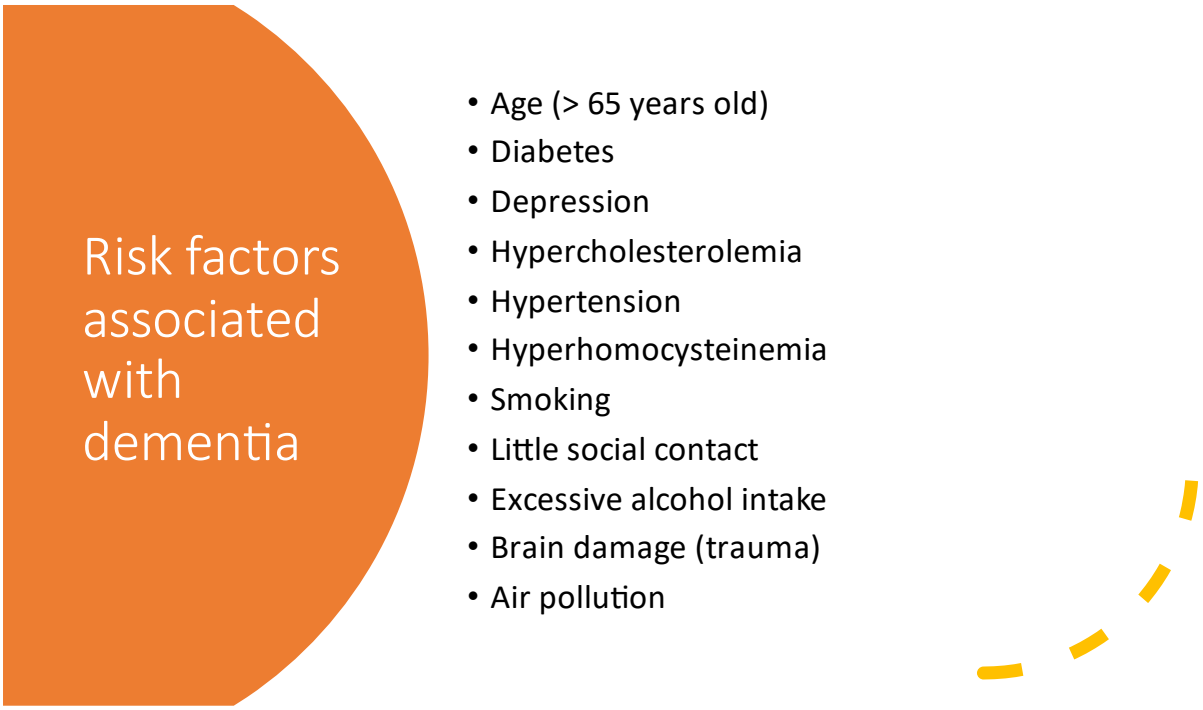

Figure 2: Summary of the risk factors associated with dementia.

Physical activity is critically important: it constitutes a very relevant protective factor for AD and other dementia forms (Iso-Markku et al., 2022), and it can even improve cognition in older adults affected by AD (Jia et al., 2019). Other relevant modifiable risk factors linked to environment and lifestyle are education, cognitive activity, active social life, and sleep (Yu et al., 2020). A balanced diet with lots of fruit and vegetables, legumes and whole grains, nuts, extra virgin olive oil, and fish while consuming little meat and drinking as little alcohol as possible is also associated with a remarkable risk reduction for developing dementia (Guzmán-Martínez et al., 2021).

Recent research has also focused on the role of the gut microbiome in Alzheimer's disease (Jiang et al., 2017). Studies have shown that gut microbiome dysbiosis may cause the release into the blood of neurotoxic substances able to pass the blood-brain barrier, thus contributing to the development of the disease (Sochocka et al., 2019). Furthermore, researchers have found that the gut-brain axis, the bidirectional communication pathway between the gut and the brain, may be disrupted in Alzheimer's disease, worsening cognitive and behavioral symptoms (Kesika et al., 2021).

Today it is well understood that inflammation plays a role in the development and progression of Alzheimer's disease (Akiyama et al., 2000). For example, studies have found that levels of inflammatory markers, such as cytokines and chemokines, are elevated in the brains of individuals with Alzheimer's disease (Domingues & Da Cruz E Silva, 2017). Furthermore, chronic inflammation can lead to oxidative stress, which can damage brain cells and contribute to the development of the disease (Ionescu-Tucker & Cotman, 2021).

The whole picture becomes clearer when we consider that AD is an inflammatory disease at its very core. This is also true for VaD and MxD (Wang et al., 2020). It is clear that dementia risk factors are associated with higher inflammation levels: this is the case of diabetes, depression, hypercholesterolemia, smoking, obesity, and excessive alcohol intake (Rohm et al., 2022; Beurel et al., 2020; Tall & Yvan-Charvet, 2015; Ambrose & Barua, 2004; Bishehsari, 2017). On the other hand, it is not surprising that protective factors correlate with lower inflammation levels: physical activity, a diet full of plant-based foods, and unsaturated fatty acids (Dominguez et al., 2021).

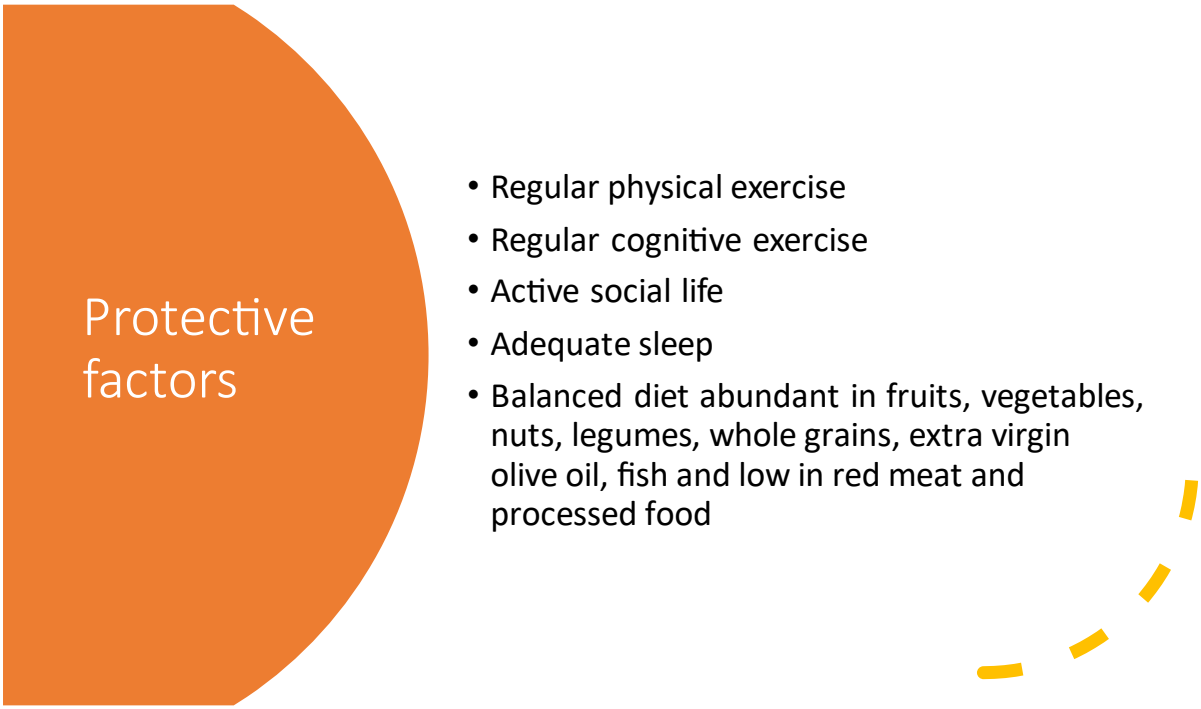

Figure 3: Summary of the protective factors against dementia.

2.2. Pathophysiology

The principal pathophysiological manifestation of AD is the accumulation of amyloid-beta (Aβ) plaques and tau tangles in the brain's extracellular space (Tiwari et al., 2019). Aβ plaques are a product of the aggregation of Aβ peptides. These peptides are produced from the cleavage of the amyloid precursor protein (APP) catalyzed by two enzymes: beta-secretase and gamma-secretase (Gouras et al., 2015). Tau tangles are a product of the hyperphosphorylation and subsequent aggregation of tau proteins. By destabilizing microtubules, tau tangles impair axonal transport (Gao et al., 2018). These abnormal protein aggregates cause neuroinflammation, triggering a process that involves the release of pro-inflammatory cytokines and chemokines and the recruitment of microglia and other immune cells, leading to progressive brain cell death and neurodegeneration (Lane et al., 2017). This affects multiple brain regions but is especially apparent at the level of the hippocampus, which is the center in which new memories are formed and old memories are retrieved (Fjell et al., 2014).

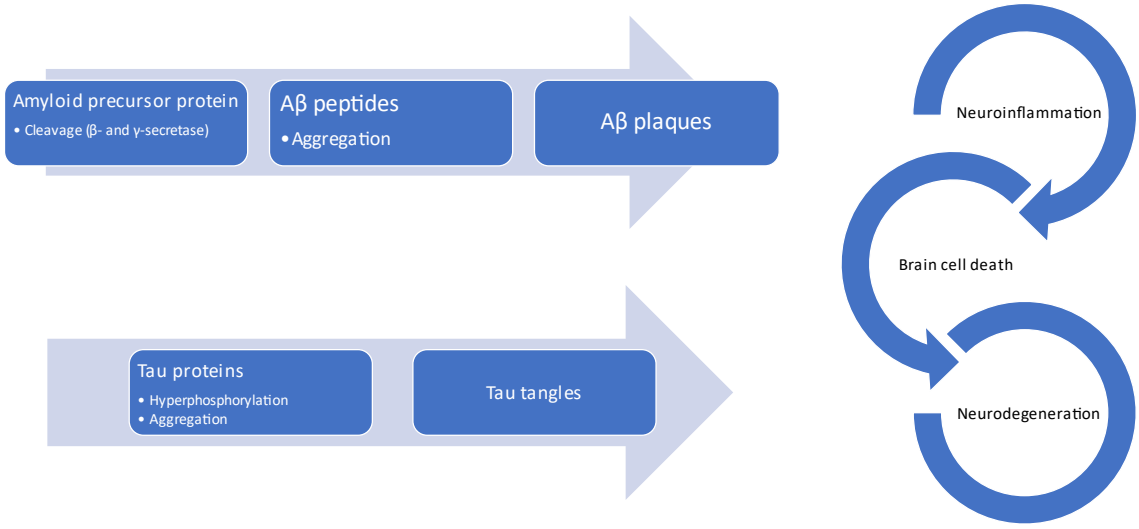

Figure 4: Pathophysiology of Alzheimer's disease.

VaD, conversely, is a consequence of cerebrovascular disease resulting in impaired blood flow to the brain. Diabetes, dyslipidemia, atherosclerosis, and hypertension are all conditions that can lead to vascular damage and blood flow impairment. Whereas proper blood flow is not

restored quickly, neurons are deprived of oxygen and nutrients; thus ischemia occurs (Kalaria et al., 2016). This results in the formation of infarcts or small areas of dead tissue in the brain, affecting cognitive function and ultimately leading to dementia (O'Brien & Thomas, 2015). Another pathophysiological pathway leading to VaD is white matter disease, characterized by the damage and loss of myelin. This condition disrupts the connection between different brain regions, impairing cognitive function and dementia (Rost et al., 2022). In both cases and similar to AD, inflammatory processes exacerbate neuronal damage by releasing pro-inflammatory mediators, activating microglia, and recruiting immune cells. The oxidative stress during inflammatory processes contributes significantly to neuronal damage by attacking crucial structures such as proteins, lipids, and DNA—the sustained neuronal damage results in the apoptosis of the neurons (Wang et al., 2020).

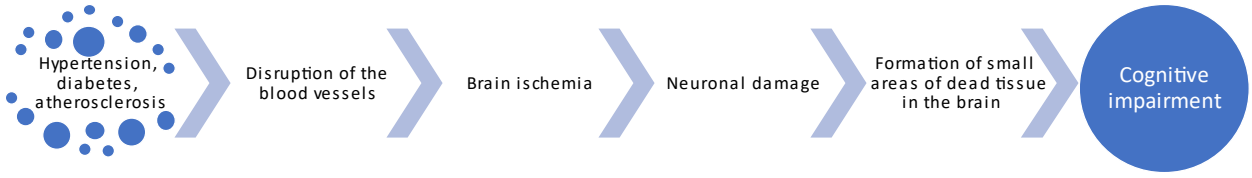

Figure 5: Pathophysiology of vascular dementia.

Mixed dementia (MxD) is defined as the coexistence of AD and VaD, which is anything but rare (Fierini, 2020). In fact, on the one hand, both signs of cerebral microangiopathy and large infarcts can often be observed in AD patients (Jellinger & Attems, 2005); on the other hand, VaD patients often present hippocampal atrophy and hyperphosphorylated tau-protein aggregates (Allan et al., 2011).

Various other conditions can result in dementia symptoms, some of which can be reversible, such as vitamin deficiencies and thyroid problems (Gibson et al., 2016; Przybylak et al., 2021), but they are far from the aim of this thesis.

3. Nutrition and cognitive functions

Several studies have explored the effect of nutrition on AD risk and severity, identifying different dietary patterns impacting the disease's onset and development. For instance, the notorious Mediterranean diet (rich in fruits, vegetables, whole grains, legumes, nuts, and fish) has been associated with a lower risk of cognitive decline and AD compared to a traditional Western diet (Lourida et al., 2013; Scarmeas et al., 2006). Similarly, the DASH (Dietary Approaches to Stop Hypertension) diet (emphasizing fruits, vegetables, low-fat dairy, and lean protein) has been linked to not only lower risk of dementia but better cognitive performance as well, compared to the Western diet (Morris et al., 2015).

This is not only limited to cognitive decline and dementia. As discussed in this chapter, nutrients and foods can profoundly impact the brain at a molecular level (neuronal transmission, neurogenesis, neuronal inflammation) and a macroscopic level (optimal cognitive functioning, cognitive decline, and other illnesses). Inflammatory processes at the level of the brain are correlated with cognitive impairment and dementia, as explained in the previous chapter. However, there is more to this picture. As highlighted by recent studies, high neuronal inflammation and impaired hippocampal neurogenesis also correlate with depression, another illness impacting more and more human beings (Troubat et al., 2021). Since depression is outside of the scope of this master thesis, this aspect is not going to be adequately discussed and eviscerated. However, the part that dementia and depression have in common in their respective pathophysiologies is interesting and could be essential for better understanding these two seemingly separate phenomena. Neuronal inflammation does not only imply cognitive decline: this should be kept in mind while reading the rest of this master thesis.

This section will analyze the evidence regarding nutrition's effects on cognitive functions while speculating on possible mechanisms and pathways. The discussion starts from different nutrients, progressively zooming out to single foods, and finally flowing into whole dietary patterns.

3.1. Role of single nutrients

3.1.1. Antioxidants

As previously illustrated, oxidative stress is a crucial part of the pathogenesis of dementia: it causes damage to neurons, thus impairing brain function. By preventing oxidative stress at the central nervous system level, many different antioxidant compounds can be beneficial in preventing neuroinflammation and, with it, neurodegeneration, cognitive decline, and dementia. There are a myriad of classified antioxidant compounds, such as flavonoids (among which quercetin, kaempferol, and many others), anthocyanins, ascorbic acid, and many more others (Orhan et al., 2015; Suresh et al., 2022; Monacelli et al., 2017). Despite this, the performed clinical trials are far from enough for most of the studied antioxidants. Scientific evidence still needs to be improved, especially when considering the supplementation of isolated substances rather than their intake through food, and to an even greater degree when evaluating their efficacy on the central nervous system. Because of these limitations, we have considered only two antioxidant molecules – the two most investigated as well as promising antioxidants for their effects on AD and dementia risk: vitamin E and resveratrol. We hope that more clinical trials investigating the efficacy of the many other antioxidant compounds will be available in the future.

Vitamin E is present in nuts, seeds, and minimally processed vegetable oils. One observational study found that higher vitamin E intake reduces the risk of cognitive decline and AD (Basambombo et al., 2017). Despite this, clinical trials of vitamin E supplementation have yielded mixed results. Some reported benefits, others reported no effects, and others reported adverse side effects such as an increase in all-cause mortality (Boothby & Doering, 2005). For this reason, more research is needed to investigate the effects of vitamin E supplementation on dementia before it can be safely recommended for prevention or treatment of the disease.

Resveratrol is found in red wine, grapes, and berries. In animal models of AD, resveratrol has been demonstrated to be able to cross the blood-brain barrier, thus reducing oxidative stress and inflammation induced by Aβ peptide, promoting neuronal survival and plasticity, improving brain blood flow, and rescuing the reduction in the expression of SIRT1 (Gomes et

al., 2018). The few human clinical trials available today provide promising results (Moussa et al., 2017; Lee et al., 2017). A single study found increased brain volume loss, but it was not associated with a cognitive or functional decline (Turner et al., 2015). More research is needed to determine the effectiveness of resveratrol supplementation and an optimal, safe dosage and duration for reducing dementia risk.

3.1.2. Omega-3 fatty acids

The physiological role of omega-3 fatty acids is to maintain the structure and function of cell membranes in the brain and regulate inflammation and oxidative stress (Shahidi & Ambigaipalan, 2018). They are found in fatty fish, nuts, and seeds and have also demonstrated anti-inflammatory and neuroprotective effects (McGrattan et al., 2019). Many observational studies and several randomized controlled trials found an association between higher omega-3 intake and reduced risk of cognitive decline and dementia, highlighting a reduction in markers of inflammation and oxidative stress (Del Moral & Fortique, 2019). Omega-3 may be especially beneficial for reducing VaD risk as they improve blood flow and reduce inflammation at the level of the blood vessels (Carracedo et al., 2019). More randomized controlled trials are welcome; however, today's evidence is extremely promising.

3.1.3. Vitamin D

Vitamin D receptors are found in many areas of the brain, and it seems to have a role in the regulation of inflammatory processes as well as protection against neurodegeneration (Calvello et al., 2017). This is well-demonstrated in animal models, but a proper clinical trial has yet to be performed to our knowledge. More research is needed, as vitamin D's role in calcium homeostasis may be very relevant in the brain: a disruption in calcium homeostasis due to a vitamin D deficiency may expose neurons to neurodegenerative processes (Gezen-Ak & Dursun, 2019).

3.1.4. B vitamins

B vitamins such as folate, B6, and B12 are involved in synthesizing neurotransmitters essential for neuron signaling and, thus, neuroplasticity (Jadavji et al., 2017; Pourié et al., 2022). B vitamins supplementation is, in fact, associated with slower cognitive decline in individuals

with dementia. However, only folate supplementation (not B6 and B12 vitamins) has a clear protective role in the non-dementia, aged population (Z. Wang et al., 2022). This can be partly explained by a reduction in homocysteine levels, which, as mentioned earlier in the thesis, is another risk factor for dementia (Yuan et al., 2021). However, more research is needed to determine the optimal levels and forms of B vitamin supplementation for dementia prevention.

3.1.5. Magnesium

Magnesium has a role in many biological processes, including neuron signaling and neuroplasticity (Billard, 2006). The mineral is also involved in the regulation of inflammation and oxidative stress, two processes tightly linked to dementia (Maier et al., 2021). Studies have shown lower magnesium levels in AD patients (Veronese et al., 2016). Moreover, serum magnesium is a good predictor of AD progression (Çilliler et al., 2007). Despite this, clinical trials show conflicting results, and further evidence is needed before magnesium supplementation can be safely recommended for dementia prevention and possibly even treatment.

The following table summarizes the findings about the effectiveness of the nutrients examined on preserving cognitive functions and preventing dementia (Table 1).

It is important to note that nutrients do not act in isolation. Often, a combination of different nutrients produces results substantially different from the sum of the effects of the single nutrients in isolation. For this reason, the impact of whole foods will be critically evaluated in the next part.

Table 1: Summary of the role of single nutrients.

Substance	Effects	Evidence
Vitamin E	Risk reduction for cognitive decline and dementia	Few conflicting clinical trials
Resveratrol	Antioxidant and anti-inflammatory activity, promotes neuronal survival and plasticity, increases SIRT1 expression	Animal studies, few promising clinical trials
Omega-3 fatty acids	Anti-inflammatory and neuroprotective effects, blood flow improvement, risk reduction for cognitive decline and dementia	Randomized controlled trials
Vitamin D	Anti-inflammatory, anti-neurodegenerative effect, its deficiency may expose neurons to neurodegenerative processes	Animal studies
B vitamins	Slower dementia progression (B vitamins), protection towards dementia in healthy population (only folate), reduction of homocysteine levels	Animal studies, few clinical trials
Magnesium	Antioxidant and anti-inflammatory activity, lower levels correlate with further Alzheimer's disease progression	Few conflicting clinical trials

3.2. Role of single foods

3.2.1. Berries

Berries are rich in polyphenolic compounds such as resveratrol, flavonoids, anthocyanins, and proanthocyanidins. As such, these antioxidant compounds have shown potent neuroprotective effects through a reduction in oxidative stress and inflammation, which, as stated various times in this thesis, are two central phenomena in both AD and VaD.

Animal studies provide evidence for the neuroprotective effects of berries. A 7-day blueberry-supplemented diet significantly improved learning and memory in rodents through improvements in brain antioxidant properties (reduction in lipid peroxidation products) and acetylcholinesterase inhibition (Papandreou et al., 2009). Another study on rats found enhanced motor performance, improved cognition, and increased hippocampal neurogenesis and insulin-like growth factor 1 expression with a blueberry-supplemented diet administered for eight weeks (Shukitt-Hale et al., 2015).

Results from human studies have also reported promising results. A randomized control trial on overweight, insulin-resistant men and women aged 50-65 observed improved lexical access and memory interference by administering powdered freeze-dried blueberries (Krikorian et al., 2022). Interestingly, along with the cognitive benefits, the same study found improvements in markers of insulin resistance and metabolic syndrome. Another randomized control trial witnessed enhanced neural activation during working memory tasks in older adults with cognitive decline (Boespflug et al., 2017). A longitudinal study conducted on 16,010 older women found that women consuming two or more servings of strawberries or blueberries each week had a significantly slower rate of cognitive decline than women eating berries less frequently (Devore et al., 2012). Lastly, a systematic review highlights how berry-based supplements can improve resting brain perfusion, cognitive functions, memory performance, executive functioning, processing speed, and attention indices (Bonyadi et al., 2022).

In addition to scavenging free radicals, thus reducing oxidative stress, polyphenols such as those present in berries can modulate signaling pathways involved in inflammation, such as nuclear factor-kappa B and mitogen-activated protein kinase leading to an overall reduction

in inflammation (Yahfoufi et al., 2018). Moreover, berries, especially blueberries, seem to have a remarkable protective effect against atherosclerosis and cardiovascular disease even in individuals suffering from metabolic syndrome, thus reducing the risk for cardiovascular disease complications, such as VaD (Basu et al., 2010; Paixão et al., 2011).

To our knowledge, no human study has investigated the efficacy of blueberry and other berries for treating AD and VaD yet. However, two animal studies found an increase in neuronal autophagy with subsequent reduction of neuronal damage and improvements in learning and memory following a period of blueberry extract supplementation (Tan et al., 2017) (Li et al., 2022). More research and evidence are needed to determine the optimal dose and form of berry consumption for dementia prevention and possibly even treatment. At the present moment, what can be stated for sure is that incorporating berries into a balanced diet may be a simple yet effective dietary intervention for promoting healthy brain aging.

3.2.2. Fish

Fish and fatty fish especially is a source of omega-3 polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). As previously stated, omega-3 fatty acids have shown potential neuroprotective effects against cognitive decline and dementia.

Two distinct meta-analyses produced the same result: both clearly show an inverse correlation between fish consumption and dementia risk (Bakre et al., 2018, Kim & Je, 2022). Interestingly, a third meta-analysis found that the protection offered by fish intake against cognitive decline levels off with more than two servings of fish per week (Kosti et al., 2022). A randomized controlled trial measured significantly higher cognitive functions in older but cognitively intact adults following 12 weeks of additional fish intake consisting of canned pilchards and fish spread, accounting for roughly 2.2g omega-3 PUFA per day (Kühn et al., 2022). A prominent 215,803 participants prospective study linked fish oil supplement consumption to a lower all-cause dementia incidence in a population aged 60-73 years old (Liu et al., 2022). Although scientific evidence seems to agree with the fact that higher fish and fish oil intake can improve cognition and prevent dementia, a systematic review found no convincing evidence for the efficacy of omega-3 PUFA supplements in the treatment of AD

(Burckhardt et al., 2016), meaning that although the role of fatty fish in dementia prevention is clear, its efficacy after the onset of the disease requires further investigation. However, in a mouse model experiment, DHA did grant protection against Aβ plaque formation, accumulation, and thus toxicity (Lim et al., 2005).

In addition to reducing inflammation and oxidative stress, omega-3 PUFAs can modulate neurotransmitter systems, such as the dopaminergic and serotonergic, which are involved in cognition and mood regulation (Hibbeln et al., 2006). Moreover, omega-3 PUFAs are also well-known to improve blood flow, particularly brain blood flow. This leads to enhanced neuroplasticity, which is essential for healthy brain function (Cutuli, 2017).

Summarizing what has been found, at the moment, evidence suggests that regularly including fish in the diet can significantly help to prevent cognitive decline and dementia. Still, it is probably not that effective after the disease's onset.

3.2.3. Extra virgin olive oil

Extra virgin olive oil (EVOO) is rich in phenolic compounds, vitamin E, and other potent antioxidant compounds. It is considered a vital component of the Mediterranean diet, but at this point in the thesis, we will consider the effects of EVOO alone.

In animal models of AD, EVOO intake resulted in a significant reduction in tau oligomers, increased basal synaptic activity and neuroplasticity, and improved memory and cognition (Lauretti et al., 2020). Another animal study also found improved memory, motor coordination, and reduced lipid peroxidation in the brain (Pitozzi et al., 2012).

A recent randomized controlled trial examined the effects of EVOO intake on 25 subjects suffering from mild cognitive impairment (MCI), comparing the outcomes with those of refined olive oil intake. As could be hypothesized, only EVOO enhanced brain connectivity and reduced blood-brain barrier (BBB) permeability, although both EVOO and refined olive oil intake did result in improved Aβ clearance and lower clinical dementia rating (Kaddoumi et al., 2022). Another recent randomized controlled trial found similar results: better cognitive improvements with the consumption of EVOO with higher phenolic compounds concentrations (Tsolaki et al., 2020).

Aside from the antioxidant and anti-inflammatory properties of EVOO's bioactive compounds, EVOO might play a role in downregulating the production and improving the clearance of both Aβ plaques and tau tangles, especially when EVOO is consumed before Aβ and tau accumulation begins (Qosa et al., 2015).

All of this evidence suggests that the consumption of EVOO itself plays a central role in preserving cognitive function during aging processes, thus helping to prevent and possibly even to treat MCI and dementia. The evidence also suggests that EVOOs with higher phenolic compounds concentrations are preferred in these regards. Nevertheless, more research is needed to determine the optimal dose and duration of EVOO consumption and further explore EVOO's efficacy for AD and VaD treatment in human patients.

3.2.4. Nuts

Nuts like walnuts, Brazil nuts, and peanuts are rich in polyunsaturated fats, protein, fiber, vitamins, and minerals. They are also an essential part of the Mediterranean diet. However, the effects of the whole dietary pattern will be considered in the next section.

A study on mouse models of AD found improved memory, learning ability, and motor development with a walnut-supplemented diet (Muthaiyah et al., 2014). Another animal study reported ameliorated scopolamine-induced oxidative stress and memory dysfunction with a pre-treatment consisting of almond administration, suggesting that almond consumption may protect from oxidative stress-induced memory loss and age-related memory impairment (Batool et al., 2018).

A randomized controlled trial on 636 older adults found that consuming 30-60g of walnuts daily might delay cognitive decline in higher-risk subgroups, although no direct cognitive improvement was reported (Sala-Vila et al., 2020). Another randomized controlled trial reported improvements in verbal fluency after six months of daily consumption of Brazil nuts among older adults suffering from MCI. The researchers hypothesized that the improvements are due to the restoration of selenium deficiency, a nutrient present in remarkable amounts in Brazil nuts (Cardoso et al., 2016). Neuroinflammation is not only correlated with dementia but also with depression (Troubat et al., 2021). A randomized controlled trial reported improvements in memory and lower anxiety and depression scores in young adults following

a six months-long intervention consisting of daily consumption of peanuts. The results correlate with the higher intake of polyphenols from the peanuts and increased fecal short-chain fatty acids concentration (Parilli-Moser et al., 2021).

Nuts contain a range of bioactive compounds, and their beneficial effects on cognition are probably due to the synergistic effects of various nutrients, including vitamin E, folate, and polyphenols. Nuts have also been shown to improve vascular function, which is essential for healthy brain function and VaD prevention (Morgillo et al., 2019). Nuts may also act positively on the gut microbiota's composition and diversity, granting protection against neuroinflammation and dementia (Creedon et al., 2020; Chen et al., 2022).

Incorporating nuts into a balanced diet may help preserve cognitive function, reduce the risk, and possibly even slow the progression of cognitive decline and dementia in older adults, regardless of the type of nut consumed. In the younger population, nuts can still be helpful and should still be consumed as they also help prevent severe psychiatric disorders involving neuroinflammation, such as depression.

3.2.5. Leafy Greens

Leafy greens like spinach, kale, collard, and broccoli are rich in vitamins, minerals, and other antioxidant compounds. They are also a central part of the Mediterranean diet.

Sulforaphane (a bioactive compound contained in *Cruciferae*, such as broccoli or kale) administration improved cognition in animal models of AD, seldom without inhibiting Aβ aggregation. Leafy greens have also shown the capacity to inhibit acetylcholinesterase and butyrylcholinesterase activities, two key enzymes in AD pathophysiology, and prevent lipid peroxidation. Interestingly, the effect was not as significant when using blanched vegetables (Oboh et al., 2014).

A prospective study of 960 participants found an association between higher intakes of green leafy vegetables rich in phylloquinone, lutein, nitrate, folate, α-tocopherol, and kaempferol and slower cognitive decline (Morris et al., 2018). Another prospective study of over 10,000 women measured slower cognitive decline rates in those consuming the most cruciferous vegetables (Kang et al., 2005). Moreover, a prospective study of 245 older adults found lower

AD risk in those consuming plenty of foods rich in vitamin C, pelargonidin, anthocyanins, and flavonoids, such as leafy greens.

Although still unclear, the mechanisms are related to antioxidant compounds such as vitamin C, vitamin E, and flavonoids, which protect the brain from oxidative damage. Leafy greens are also a source of B vitamins, which, as discussed earlier, play an essential role in cognition. Often leafy greens contain relevant amounts of nitrates, which can improve cognition by increasing cerebral blood flow (Wightman et al., 2015).

The evidence suggests that adding leafy greens to a balanced diet is a low-risk strategy for preserving the cognitive function of older adults, potentially decreasing the risk of dementia. However, randomized controlled trials are required to state this claim with more certainty.

3.2.6. Coffee

Coffee is one of the most consumed beverages in the world, and recent research has brought to light some of its attractive benefits. Among the many bioactive compounds present in coffee are caffeine, chlorogenic acid, and other phenolic compounds.

In mouse AD models, caffeine administration reduced the accumulation of Aβ plaques and improved cognitive function (Arendash et al., 2006). Another study on animal models of AD reported a reduction in hippocampal Aβ deposition and even Aβ fibrils degradation, in addition to preventing cognitive dysfunction, with the administration of coffee polyphenols (Ishida et al., 2020).

Two different meta-analyses found a significant risk reduction for cognitive decline and even dementia with higher consumption of coffee (Qingping et al., 2016; Ran et al., 2021). However, another meta-analysis found no correlation between coffee consumption and dementia incidence (Larsson & Orsini, 2018). In a 114,551 participants cohort study, moderate self-reported coffee consumption was associated with lower dementia (both AD and non-AD) incidence (Nordestgaard et al., 2022). However, too much coffee probably increases the risk of dementia. A prospective analysis found higher dementia rates and smaller total brain volume in the population slice consuming more than 6 cups of coffee daily

(Pham et al., 2021). To our knowledge, no randomized controlled trial on the effects of caffeine on dementia risk has been performed yet.

The mechanisms through which moderate coffee consumption decreases dementia risk are manifold. Caffeine and antioxidant compounds play an essential role. Chlorogenic acid especially seems to have a remarkable antioxidant and anti-inflammatory action and a high bioavailability in humans (Farah et al., 2008). As it could be hypothesized, the beneficial effects of coffee are not due to the sum of the isolated actions of the different compounds included in the beverage but rather to their synergistic effect. An *in-vivo* study reported increased plasma levels of granulocyte-colony stimulating factor (GCSF), IL-6, and IL-10 only with the administration of caffeinated coffee and not with caffeine alone or decaffeinated coffee. Those plasma factors are responsible for better microglia recruitment, synaptogenesis, and neurogenesis, translating into better cognitive performance (Cao et al., 2011).

Excessive coffee consumption is proven to cause adverse effects on health, such as increased anxiety, sleep disturbance, and GI problems. As discussed above, it may also lead to higher dementia risk. However, moderate coffee consumption is likely to benefit brain health and cognition and may also help prevent cognitive decline and dementia. However, more research, primarily randomized controlled trials, is needed to understand coffee's action better and determine the ideal amount of consumption to optimize its neuroprotective effects.

3.2.7. Cocoa

Cocoa, the key ingredient of chocolate, contains several bioactive compounds associated with cognitive benefits. First, above all, are flavanols, which have been studied for their antioxidant and anti-inflammatory properties and can also improve the blood flow to the brain (Martin & Ramos, 2021).

An *in-vitro* study found that cocoa extract effectively reduced Aβ polymerization in mouse hippocampal tissue (J. Wang et al., 2014). Another study witnessed the activation of the brain-derived neurotropic factor survival pathway with the administration of the cocoa extract to an *in-vitro* human brain model of AD (Cimini et al., 2013).

A few human studies on the subject are also present. A double-blind clinical trial on 90 older adults with MCI found significantly improved cognitive function and reduced insulin resistance after an 8-week administration of cocoa flavanols (Desideri et al., 2012). A study on young adults found that cocoa flavanols can counteract mental stress-induced endothelial dysfunction (Baynham et al., 2021). While this last finding is not inherently relevant to dementia, it indicates cocoa's beneficial effect on cardiovascular health, resulting in better dementia prevention. Another study observed an increase in cerebral blood flow after an acute administration of cocoa flavanols, confirming these molecules' potential for treating cardiovascular impairments associated with dementia, such as hypertension and stroke (Francis et al., 2006).

It is worth noting that the bioavailability of cocoa flavanols is influenced by several factors (processing, storage, and interindividual differences in metabolism). Also, the effects of the same amount of bioactive flavanols may be affected by other individual factors. Evidence suggests that cocoa flavanols and cocoa itself probably play a beneficial role in preventing cognitive impairment and dementia. However, more research is needed to understand this correlation better and possibly find the ideal dose and form of cocoa administration for the highest degree of neuroprotection. For now, all that can be said is that incorporating moderate amounts of dark chocolate (70% cocoa and above) into our diet might lower the risk of developing all-cause dementia.

3.2.8. Turmeric

Turmeric is a spice commonly used in Southeast Asian cuisine. Its main active ingredient is a polyphenol called curcumin. Curcumin has been shown to have antioxidant, anti-inflammatory, and neuroprotective effects.

A rat study observed increased antioxidant enzyme activity and anti-inflammatory cytokines, decreased apoptotic cells in the hippocampus of animal models for AD, and improved behavioral profile, following a period of curcumin administration (ELBini-Dhouib et al., 2021). This is in line with the findings from many other animal studies: curcumin exerts both preventive and therapeutic effects on molecular and behavioral levels in animal models of AD (Voulgaropoulou et al., 2019).

Unfortunately, to our knowledge, many clinical trials have not been performed on the efficacy of turmeric in dementia prevention and treatment. However, the little human evidence available suggests that turmeric and curcumin in particular, are better than a placebo in improving memory and cognitive functions in older humans (Zhu et al., 2019). A randomized controlled trial also witnessed an improvement in insulin sensitivity and type 2 diabetes following 12 weeks of turmeric supplementation (Thota et al., 2020). As discussed earlier, there is a very close link between insulin resistance/type 2 diabetes and dementias, both AD and VaD. Thus any substance effective in improving insulin sensitivity is probably also effective in reducing the risk of developing cognitive impairment and dementia. However, evidence is somewhat conflicting, and one of the many reasons is the low bioavailability of curcumin. This problem can be solved by a concomitant administration of black pepper, which is very effective in increasing the availability of curcumin (Hewlings & Kalman, 2017).

As for the mechanisms of action, as witnessed by the above-mentioned animal studies, curcumin can lower oxidative stress by increasing the activity of antioxidant enzymes. It also increases anti-inflammatory cytokines, preventing neuron cells from dying. There is also some interesting early evidence that curcumin may prevent AD even by modulating genomic pathways in human macrophages in a complex interaction with vitamin D metabolites (Masoumi et al., 2009; Alamro et al., 2020).

Although clinical trials provide conflicting evidence, their evidence combined with animal studies is promising. The weight of turmeric supplementation as a preventive factor for dementia appears to be relatively low. Nevertheless, the safety of this spice makes turmeric supplementation a low-risk intervention that could lower the odds of developing dementia, especially if combined with black pepper.

3.2.9. Green tea

Green tea contains various bioactive compounds, mainly caffeine, theanine, and epigallocatechin gallate (EGCG). These compounds are being studied for their potential effects on cognitive function and preventing cognitive decline.

A prospective cohort study on 365,682 50-74 years old participants found a significantly lower risk of dementia in those regularly consuming coffee and green tea (Zhang et al., 2021).

Another cohort study found a significant dementia risk reduction with the regular consumption of green tea, although only for adults 60-69 years old (Matsushita et al., 2021). A third cohort study of 377,592 participants reported a significantly lowered risk for tea drinkers, up to 6 cups per day, with the highest benefits for men. The same study showed diminishing returns for over 3 cups of tea daily (H. Hu et al., 2022).

The benefits appear related to caffeine, which, as discussed for coffee, can slow cognitive decline (Driscoll et al., 2016). However, EGCG showed potent antioxidant, anti-inflammatory, and even anti-atherogenic activity; thus, this molecule most likely also plays a significant role in preserving cognitive function during aging (Cascella et al., 2017).

Similarly to the other foods and beverages discussed earlier in the thesis, the evidence for the cognitive benefits of regular green tea consumption still needs to be expanded. It is also essential to notice that green tea, more than the other items mentioned, can be subject to healthy user bias. As this beverage is commonly perceived as "healthy", those consuming it most likely engage in many other beneficial tasks, such as regular physical activity and a healthier diet overall. This bias could flaw the results from the extensive epidemiological studies cited above. Nevertheless, green tea is known for its many benefits on overall health. Its regular consumption remains a low-risk habit that can lower the risk of dementia and other illnesses (Musial et al., 2020).

3.2.10. Red wine

Red wine is a popular alcoholic beverage. Alcohol is classified as a group 1 carcinogen (World Health Organization: WHO, 2023). However, many studies link moderate alcohol, especially red wine consumption, with a lower risk of cognitive decline. Is this benefit worth the risk?

Many meta-analyses suggest that low-to-moderate alcohol consumption, generally defined as 10g or one drink per day, is, at worst unrelated to dementia incidence (Mewton et al., 2022). Most meta-analyses even show a link between this degree of alcohol consumption and a lower incidence of all-cause dementia (Ran et al., 2021b; Xie & Feng, 2022). In particular, the highest benefit in terms of dementia risk reduction appears to come with 6g of alcohol per day, which is approximately half of a regular alcohol serving size (Xu et al., 2017). An umbrella review and meta-analysis clearly shows that low alcohol consumption (up to one

serving per day) is associated with a significant risk reduction for many illnesses, among which dementia and all the conditions related to it (AD, type 2 diabetes, stroke, hypertension) (Zhong et al., 2022). However, as the same review reports, the same amount of alcohol consumption significantly increases the risk of upper digestive tract and breast cancers and subarachnoid hemorrhage. This can be seen distinctly from the figure below, extracted from said review (Figure 6). As found by another systematic review and meta-analysis, the ideal alcohol form consumption in terms of health benefits seems to be red wine, and the ideal amount is probably between 1 and 4 glasses per week, even less than what the previous umbrella review regards as “low alcohol consumption” (Krittanawong et al., 2022).

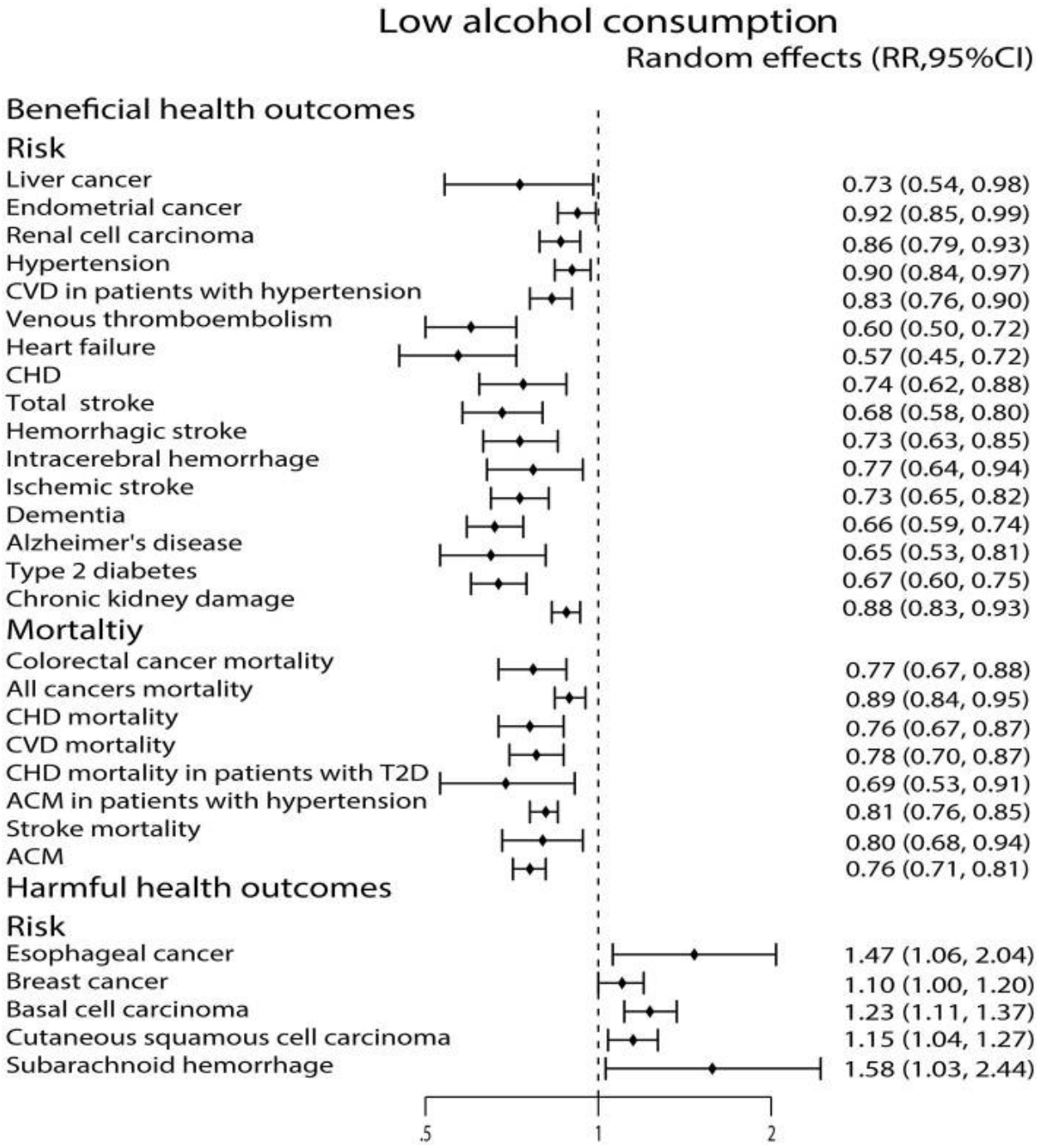

Figure 6: recalculated effects estimates of meta-analyses reporting significant associations of low alcohol consumption with health outcomes (Zhong et al., 2022).

Along with alcohol, as it could be hypothesized, the mixture of bioactive compounds contained in grapes also exerts a neuroprotective role (Lee et al., 2017). In addition, the resveratrol contained in red wine is known for its many benefits, such as cardiovascular disease risk reduction, type 2 diabetes risk reduction, and an overall anti-inflammatory effect (Weaver et al., 2021; Sahebkar, 2013; Hausenblas et al., 2015; Moore et al., 2018). As

discussed, resveratrol promotes neuroprotection and neurogenesis by increasing anti-inflammatory cytokines and SIRT1 expression. For these reasons, the best form of alcohol consumption for the maximization of its health benefits is red wine.

In conclusion, light-to-moderate alcohol consumption may be worth the risk if the goal is to reduce the risk of all-cause dementia. However, the choice has to be taken in the awareness that by drinking alcohol, the patient is exposed to higher risks of upper digestive tract and breast tumors and subarachnoid hemorrhage. Based on the current evidence, the optimal form appears to be resveratrol-rich red wine, and the optimal amount is half a serving per day.

The following table summarizes the findings about the foods' effectiveness in preserving cognitive functions and preventing dementia (Table 2).

Table 2: Summary of the role of single foods.

Food	Effects	Evidence
Berries	Improved cognitive functions and markers of metabolic syndrome	Randomized controlled trials, prospective studies
Fish	Lower all-cause dementia risk, improved cognitive functions	Meta-analyses, randomized controlled trials, prospective studies
Extra virgin olive oil	BBB permeability reduction, improved Aβ clearance, lower dementia scores	Randomized controlled trials
Nuts	Delayed cognitive decline (walnuts), improved verbal fluency in older adults with MCI (Brazil nuts)	Randomized controlled trials
Leafy greens	Slower cognitive decline, lower AD risk	Prospective studies
Coffee (moderate consumption)	Lower cognitive decline and dementia risk	Meta-analyses, prospective studies
Cocoa	Improved cognitive functions and brain blood flow, reduced insulin resistance	Randomized controlled trials
Turmeric	Improved cognitive functions and insulin sensitivity	Meta-analyses, randomized controlled trials
Green tea	Lower dementia risk	Prospective studies
Red wine (moderate consumption)	Lower dementia and metabolic syndrome risks	Meta-analyses

3.3. Dietary patterns and cognitive health

3.3.1. The Western diet and obesity

Before we can discuss the optimal dietary pattern for the prevention of cognitive decline and dementia, we must thoroughly understand the Western diet and all the pathways through which it increases not only the risk for AD, VaD, and other forms of dementia but also the risk for many other non-communicable diseases.

Although the Western diet is not as defined as other evidence-based dietary patterns, it is generally intended as a diet rich in processed food and poor in unprocessed or minimally processed food. This results in a high amount of refined sugar, sodium, trans and saturated fatty acids, and a low amount of fiber, unsaturated fatty acids, vitamins, minerals, and other beneficial compounds typically present in fruits, vegetables, and other whole, plant-based foods. Another critical point of the typical Western diet is the excess calories consumed. This dietary pattern is tightly linked to obesity, especially visceral obesity, and all its complications, often summarized using the umbrella term “metabolic syndrome”. Metabolic syndrome comprehends dyslipidemia, hyperglycemia, hypertension, and some underlying and consecutive pathologies (Engin, 2017). The underlying pathologies are low-grade chronic inflammation, insulin resistance, and atherosclerosis. The consecutive pathologies include but are not limited to cardiovascular disease, steatohepatitis, type 2 diabetes, cancer, cognitive decline, and dementia (Mottillo et al., 2010; Younossi et al., 2019; Esposito et al., 2012; Davie et al., 2018). Not all of these pathologies are present in a subject suffering from metabolic syndrome, but the subject is exposed to a significantly increased risk of developing such diseases.

When examining the link between obesity and cognitive decline, the most significant factor is probably insulin resistance. In fact, AD is also sometimes referred to as “type 3 diabetes” (Kandimalla et al., 2017). Insulin resistance can cause dysregulation of glucose metabolism and impaired glucose uptake in the brain. This significantly adds up to the neuroinflammatory context that contributes to AD development. Moreover, insulin resistance can even cause increased Aβ protein levels in the brain (Nguyen et al., 2020).

Another potential mechanism involves chronic low-grade inflammation, typical of visceral obesity and metabolic syndrome. The pro-inflammatory cytokines produced by dysfunctional adipose tissue can overcome the compromised blood-brain barrier, which is significantly correlated with metabolic syndrome, thus entering the brain and supporting the inflammatory processes at that specific site (Bowman et al., 2018). As previously stated, inflammation is critical in AD, VaD, and other dementias.

Moreover, hypertension, dyslipidemia, and atherosclerosis, associated with obesity and cardiovascular disease, can also contribute to VaD. The increased adiposity can also lead to compromised cerebral blood flow and oxygenation, thus aggravating the situation (Littleton & Tulaimat, 2017).

Obesity also leads to the accumulation of advanced glycation end products (AGEs) that cause oxidative stress. AGEs are tightly linked to the physiopathological process leading to dementia and AD especially (A. Singh et al., 2023).

Although the mechanisms linking obesity and dementia are complex and multifactorial, involving a range of metabolic and inflammatory pathways, rapidly growing evidence suggests that obesity is a significant risk factor for all-cause dementia. Consequently, any hypocaloric dietary regimen will play a protective role in cognitive decline in a person suffering from obesity, as the reduction in weight will lead to an amelioration in parameters linked to metabolic syndrome and dementia risk. In this sense, all dietary patterns analyzed in this master thesis indeed protect from cognitive decline when compared to a traditional Western diet.

3.3.2. Ketogenic diet

The ketogenic diet is a high-fat, low-carbohydrate dietary pattern that has gained attention for its potential therapeutic effects in various health conditions, especially neurological diseases (Pietrzak et al., 2022). Although evidence is still lacking, the results available at the present moment are promising. Two systematic reviews, one of which considering only randomized controlled trials, report a beneficial effect of the ketogenic diet in terms of slower cognitive decline (both in cases of mild cognitive impairment and AD) and amelioration of the cognitive symptomatology (Grammatikopoulou et al., 2020; Pavón et al., 2020). A third

systematic review of randomized controlled trials shows a beneficial effect also towards diabetes, providing some insight into the possible mechanisms of action (Devranis et al., 2023).

One of the most relevant possible mechanisms through which this dietary pattern can benefit cognitive decline involves ketone bodies. Reduced cerebral glucose uptake and impaired glucose metabolism have been observed in AD (Hohman et al., 2018). This metabolic impairment contributes to aggravating the clinical picture. However, by reducing carbohydrate intake, the ketogenic diet increases the concentration of ketone bodies in the blood. In this way, ketones may serve as an alternative energy substrate for the brain, bypassing the metabolic abnormalities associated with AD, thus sustaining neuron activity and mitigating cognitive decline. Hopefully, future studies will confirm this speculation.

The ketogenic diet has also been suggested to modulate neuroinflammation through various pathways (Z. Jiang et al., 2022). Neuroinflammation is a central feature in all forms of cognitive decline and dementia; therefore, this anti-inflammatory effect probably also plays a role in preserving cognitive function.

The ketogenic diet also seems capable of balancing pro- and anti-oxidant processes in the brain, thus protecting against neuronal damage and contributing to the maintenance of cognitive function (Pietrzak et al., 2022).

Animal studies suggest that good quality of dietary polyunsaturated fatty acids leads to beneficial gut microbiota alteration, which in turn protects against metabolic syndrome and its complications (Bidu et al., 2018). Despite this, there is human evidence that a high-fat diet could cause gut microbiome dysbiosis, altering the composition of the microbiota and leading to a decrease in the production of beneficial short-chain fatty acids (Wan et al., 2019). These results could be explained by the poor nutritional quality of dietary fatty acids, as the researchers utilized soybean oil as the primary fat source. Nevertheless, this aspect needs to be clarified by future studies.

In conclusion, the ketogenic diet seems promising overall for its effects on cognitive function and preventing cognitive decline and dementia. Despite this, further research, especially well-designed clinical trials, is needed to fully elucidate this dietary pattern's benefits and long-

term effects and mitigate or confirm our doubts about its dysregulation of the gut microbiome.

3.3.3. Intermittent fasting

Intermittent fasting (IF) is an eating pattern that shifts the focus from food and food groups to the time of the day food is consumed. It involves a restriction of the feeding time window so that the fasting time window becomes wider. This eating pattern has gained remarkable attention in recent decades for its various health benefits. Unfortunately, to the best of our knowledge, no well-designed clinical trials are exploring the application of IF to prevent cognitive decline. However, we provide educated speculations about the mechanisms through which IF might be effective in enhancing cognitive functions and delaying their decline. Hopefully, soon clinical trials will be available.

The first mechanism is, of course, calorie restriction. As IF limits the feeding window, it usually creates a caloric deficit. A meta-analysis of eleven randomized controlled trials demonstrated that caloric restriction generally enhances cognitive function even in subjects with moderate cognitive impairment (Lü et al., 2022). A randomized controlled trial tried to compare intermittent energy restriction with continuous energy restriction in a population with central obesity (C. Kim et al., 2020). Both groups witnessed cognitive improvement and improved pattern separation, although the intermittent energy restriction group significantly lost recognition memory. This outcome could be due to a flaw in the study design, but it needs further investigation. In any case, energy restriction promotes many positive metabolic adaptations at the macroscopic and molecular levels (reduced visceral adiposity, improved insulin sensitivity, enhanced mitochondrial function). Such adaptations explain the evidence mentioned earlier.

Moreover, according to animal studies, both IF and continuous energy restriction may stimulate the production of brain-derived neurotrophic factor (BDNF) (Elesawy et al., 2021) (Kishi et al., 2015). This protein promotes the growth and survival of neurons, thus playing an essential role in learning and memory. Increased BDNF levels may improve cognitive function and protect against cognitive decline (Brocchi et al., 2022).

Furthermore, IF is well-known for modulating cellular stress response pathways, primarily autophagy and antioxidant defenses. There is abundant animal model evidence that IF may facilitate the clearance of abnormal proteins in the brain due to the upregulation of autophagic pathways (Ntsapi & Loos, 2021). Nevertheless, to our knowledge, human trials have yet to be performed to confirm this.

In animal studies, IF has also been shown to modulate inflammation and oxidative stress, which are central to neurodegenerative processes (Dai et al., 2022). There is decisive human evidence that calorie restriction is beneficial in terms of lower inflammation levels and improved biomarkers of healthy aging (Lettieri-Barbato et al., 2016; Kemalasari et al., 2022). Therefore, it is consequent that these benefits apply to IF as well, whereas this eating pattern is executed in an energy-restrictive manner. In this sense, IF may protect from neuronal injury and improve cognitive outcomes by attenuating inflammation and preventing oxidative damage.

To summarize, IF seems a promising eating pattern for promoting cognitive health and preventing dementia. Its potential mechanisms of action include the stimulation of neuronal plasticity, modulation of cellular stress response pathways, metabolic adaptations, and reduction of neuroinflammation. However, most of these pathways appear to be linked to caloric restriction in general, regardless of the eating pattern. Human evidence is severely lacking in this field: well-designed clinical trials are required to fully understand the efficacy of IF, especially in comparison with traditional caloric restriction, its optimal protocols, and its long-term effects on cognitive function and dementia prevention.

3.3.4. Mediterranean diet

The Mediterranean diet is characterized by high consumption of fruits and vegetables, whole grains, legumes, fish, and olive oil, and moderate consumption of red wine (Davis et al., 2015). This dietary pattern has been repeatedly associated with lower cognitive decline rates and lower dementia risk (Psaltopoulou et al., 2013; Singh et al., 2014).

As discussed earlier, chronic inflammation is tightly linked to all dementia forms. On the other hand, the Mediterranean diet has demonstrated in many different studies strong anti-inflammatory effects, which results in better glucose metabolism (better insulin sensitivity

and lower type 2 diabetes risk) and improved antioxidant activity (Antoniazzi et al., 2021; Papadaki et al., 2020). This is primarily due to the emphasis on the consumption of whole foods rich in bioactive compounds, such as fruits, vegetables, and extra virgin olive oil, which is the real protagonist of the Mediterranean diet.

Another pathway that has to be taken into account is the gut microbiome. Recent research highlighted that the gut-brain axis is intimately linked to cognition and its decline (Escobar et al., 2022). The Mediterranean diet is affluent in fiber, especially compared to a traditional Western diet, and fibers are well-known to impact gut microbiota positively (Ojo et al., 2021). Healthy gut bacteria produce, among other substances, short-chain fatty acids (SCFAs) that, in turn, protect the host with their anti-inflammatory and neuroprotective effects (Marizzoni et al., 2020).

The Mediterranean diet is also abundant in nutrients, as shown in the earlier sections, linked to lower inflammation and improved brain health. In particular, omega-3 fatty acids are found in fatty fish and EVOO, B vitamins in vegetables and legumes, and E vitamin in EVOO.

The high amount of monounsaturated and polyunsaturated fatty acids in this dietary pattern, plus the simultaneously low amount of saturated and trans fatty acids, has been shown to have significant cardioprotective effects (Y. Zhu et al., 2019). As it protects from cardiovascular disease, it also has a protective impact on VaD.

Summarizing, the beneficial effects of a Mediterranean diet on AD and VaD prevention and treatment are mainly mediated by its anti-inflammatory properties, positive influence on gut microbiota, and antioxidant-rich nutrient profile. This dietary pattern is auspicious for dementia prevention, treatment, and general optimization of cognitive performance and well-being.

3.3.5. DASH diet

The Dietary Approaches to Stop Hypertension (DASH) diet emphasizes fruits, vegetables, low-fat dairy, whole grains, poultry, fish, and nuts while limiting red meat, sugar-sweetened beverages, and sodium. This dietary pattern's anti-inflammatory and antioxidant effects are well-proven (Juraschek et al., 2021). There also seems to be a correlation between adherence

to the DASH diet and lower rates of cognitive decline (Tangney et al., 2014; Berendsen et al., 2017). However, the evidence is still conflicting (Daniel et al., 2021).

As the name suggests, this dietary pattern is known firstly for its effectiveness in lowering blood pressure. The DASH diet is rich in foods high in potassium and low in sodium, such as fruits and vegetables, whole grains, and legumes. These foods are also rich in magnesium and calcium. An adequate supply of magnesium and calcium and a lower sodium/potassium ratio is a proven way to lower blood pressure (Iqbal et al., 2019). As pointed out earlier in this thesis, hypertension is a significant risk factor for AD and VaD, as it can damage the blood vessels in the brain, thus lowering blood flow and contributing to neuronal damage and cognitive decline. Therefore, by lowering blood pressure, the DASH diet also takes care of a significant risk factor for dementia.

The DASH diet is rich in fruits, vegetables, whole grains, nuts, and fatty fish, all abundant in bioactive antioxidant and anti-inflammatory compounds. Indeed, this dietary pattern is also very effective in lowering inflammation (Juraschek et al., 2021). As mentioned earlier, chronic inflammation is tightly linked to the pathogenesis of AD and VaD: by reducing inflammation levels, the DASH diet could also effectively slow down cognitive decline.

Because of its emphasis on whole foods, the DASH diet is rich in monounsaturated and polyunsaturated fatty acids and low in saturated and trans fatty acids. Similarly to the Mediterranean diet, this benefits cardiovascular health (Y. Zhu et al., 2019). Since cardiovascular disease in all of its facets is an ulterior risk factor for dementia, the DASH diet appears protective towards dementia also in this aspect.

Furthermore, the DASH diet (like the Mediterranean diet) is rich in nutrients and foods linked to improved brain health. This is the case with omega-3 fatty acids, B vitamins, E vitamin, fatty fish, and nuts. As discussed earlier, these nutrients and foods protect and improve cognitive function, reduce inflammation levels, and protect against oxidative stress in the brain.

Finally, the DASH diet is often a hypocaloric diet. A hypocaloric diet and subsequent weight loss effectively improve insulin sensitivity and glucose metabolism (So¨Nnichsen et al., 1992). It is clear by now that insulin resistance, even when not severe enough to fall into the “type 2 diabetes” label, is a very relevant risk factor for all kinds of dementia. Thus, this is another

possible pathway through which the DASH diet can effectively reduce cognitive decline and the risk of dementia.

The DASH diet may be beneficial in preventing AD and VaD as it benefits blood pressure, chronic inflammation, cardiovascular health, and insulin sensitivity. Even though this speculative reasoning seems promising, the clinical evidence remains uncertain, and more research is needed to understand better the positive effects of this dietary pattern on cognitive health.

3.3.6. MIND diet

The MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet is a hybrid of the Mediterranean and DASH diets. This dietary pattern is being utilized in an ongoing randomized controlled trial. It is characterized by an emphasis on the daily consumption of brain-healthy foods and a limit on the consumption of less healthy foods. The encouraged foods are green leafy vegetables and other vegetables, nuts, berries and fruit, legumes, whole grains, fish, poultry, and EVOO. The limited foods are red and processed meat, butter and margarine, full-fat cheese, pastries, candy bars and other sweets, fried and fast food. This study is being conducted on 604 65-84 years old men and women with familiarity with dementia for three years. The subjects will undergo many cognitive tests for different domains and magnetic resonance imaging scans to check for changes in brain structure and functioning (Liu et al., 2021). This study is unique in its thoughtful selection of the subjects, the definition of an auspicious evidence-based dietary pattern for dementia prevention, and the choice of specific measured outcomes.

Although the study is still ongoing and the results will not come out before the beginning of next year (2024), in our opinion, it could be an interesting exercise to make an educated speculation about the results that said study will yield based on the influence that thanks to preliminary evidence we know these foods have on brain health.

Before we dive into this speculation, it is essential to note that although the said study is the first clinical trial on this dietary pattern, previously the MIND diet had already been tested through an epidemiological study of 960 participants for the duration of almost five years (Morris, Tangney, Wang, Sacks, Barnes, et al., 2015). This study yielded excellent results in

terms of slower cognitive decline. However, it was based on annual food-frequency questionnaires and did not look for structural changes in the brain. For this reason, we are looking forward to the final results of the first-mentioned study. What are the MIND diet's core features and benefits, and why is it so promising?

Firstly, a diet poor in refined sugar and processed fats and simultaneously rich in fruits, vegetables, legumes, and grains is proven to have strong anti-inflammatory properties (Galland, 2010). Chronic inflammation can lead to AD and VaD through many pathways. Reducing inflammation through a diet rich in anti-inflammatory foods helps prevent or at least delay the onset of these conditions. Additionally, fruits, vegetables, nuts, whole grains, and legumes, emphasized in the MIND diet, are also high in antioxidants. By protecting against oxidative stress, these compounds can effectively reduce the risk of developing dementia.

The high consumption of plant-based whole foods in this dietary pattern also contributes to a functional microbiome, which, as mentioned earlier, is critical in preserving healthy brain functions and maintaining an overall health condition.

Generally, the MIND diet includes foods that, based on the current evidence, appear to be very important for brain health. For instance, leafy greens and legumes are rich in folate, which, as explained earlier, is vital for brain functioning and supporting the maintenance of brain functions throughout aging. To make another example, fish, nuts, and EVOO are rich in omega-3 fatty acids, which play a central role in the correct functioning of the brain, and their consumption has been shown to have a protective effect on cognitive decline and dementia. Berry consumption also seems especially relevant in protecting the brain from cognitive decline based on the evidence examined earlier, but despite this, they are not being particularly emphasized in the Mediterranean diet; thus, it will be interesting to compare the results of this intervention to those of other interventions based on a traditional Mediterranean diet.

Overall, the MIND diet’s emphasis on nutrient-rich foods and its focus on antioxidant and anti-inflammatory nutrients make it one of the most promising dietary approaches for preventing cognitive decline and dementia. We will patiently wait until next year for the results of the study. Still, based on the current evidence, there are solid reasons to think that this dietary

pattern will prove to be more effective than both a traditional Mediterranean diet and a DASH diet in preventing all dementia forms.

The following table summarizes the findings about the dietary patterns' effectiveness in preserving cognitive functions and preventing dementia (Table 3).

Table 3: Summary of the effect of different dietary patterns on cognitive health

Dietary pattern	Effects	Evidence
Western diet (rich in processed foods, refined sugar, sodium, trans and saturated fatty acids, poor in minimally processed foods, fiber, unsaturated fatty acids)	Obesity and metabolic syndrome, including insulin resistance, chronic low-grade inflammation, cardiovascular disease, AGEs accumulation, higher cognitive decline and dementia risk	Meta-analyses, randomized controlled trials
Ketogenic diet (low carbohydrates, high fat)	Slower cognitive decline, amelioration of cognitive symptomatology, lower insulin resistance	Randomized controlled trials
Intermittent fasting (time-restricted feeding)	Possibly improved cognitive health	Animal trials
Mediterranean diet (rich in fruits, vegetables, whole grains, legumes, fish, EVOO, nuts, moderate red wine consumption)	Anti-inflammatory and antioxidant effect, promotion of a functional gut microbiome, lower cardiovascular risk, lower insulin resistance, improved cognitive health, lower cognitive decline and dementia risk	Meta-analyses, randomized controlled trials
DASH diet (rich in fruits, vegetables, low-fat dairy, whole grains, poultry, fish, and nuts, poor in red meat, sweets, and sodium)	Lower blood pressure, anti-inflammatory and antioxidant effect, lower cardiovascular risk, lower insulin resistance, improved cognitive health, lower cognitive decline and dementia risk	Meta-analyses, randomized controlled trials
MIND diet (rich in green leafy vegetables, nuts, berries, legumes, whole grains, fish, poultry, EVOO, poor in red and processed meat, sweets, fried and fast food)	Anti-inflammatory and antioxidant effects, promotion of a functional gut microbiome, lower insulin resistance, improved cognitive health, lower cognitive decline and dementia risk	Ongoing randomized controlled trial (no result yet), prospective studies

4. Evidence-based dietary guidelines for optimal cognitive health

At this point of this master thesis, using all the evidence gathered about the benefits on cognitive health of different nutrients, foods, and dietary patterns; we will provide a set of nutritional guidelines aimed at optimizing cognitive health. Indeed, as previously discussed, the same nutritional (and not only) interventions for slowing cognitive decline and preventing dementia, Alzheimer's disease, and vascular dementia can also significantly enhance brain health and, with it, cognitive functions and cognitive well-being, as they contribute to lower oxidative stress and inflammation levels, and optimal overall functioning of the molecular and macroscopic mechanisms that result in cognition. Although the guidelines provided are projected using the best of our knowledge and the best of the current evidence, they could be disproven in the future. For this reason, we encourage their critical reading and use.

In planning these dietary guidelines, foods and beverages were divided into three categories: foods to eat daily (Table 4), foods to eat weekly (Table 5), and foods to limit (Table 6). We also included the ideal amount of each food or beverage that, according to the evidence presented earlier in this thesis, will yield the most significant benefit for most of the population. Because it is based on statistical calculations, there may be a need to change this amount for some particular cases.

Finally, these guidelines were outlined using as a basis not only all the evidence collected so far for this master thesis but also considering the most recent report of the EAT-Lancet Commission on Food, Planet, Health (*The EAT-Lancet Commission on Food, Planet, Health - EAT Knowledge*, 2023). To overcome the current Global Syndemic, it is of critical importance that any dietary guidelines proposed for any purposes, including the prevention of chronic diseases such as Alzheimer's disease and vascular dementia, respect the health of our planet, in addition to that of the individual.

Table 4: foods to eat daily

Food, food category, or beverage	Recommended amount per day
Blueberries	150g (1 cup)
Other fruits	1 serving
Leafy greens	75g (1 cup) raw
Other vegetables	2-3 servings
Whole grains	1-2 servings
Legumes	1 serving
Nuts	30g
Extra virgin olive oil	30ml (2 tablespoons)
Dark chocolate (at least 70% cocoa)	15g
Coffee	1-2 cup
Green tea	2-3 cups
Turmeric	1.5g (½ teaspoon)

Table 5: foods to eat weekly (no more than one serving of the same item per day)

Food, food category, or beverage	Recommended amount per week
Fatty fish	2-3 servings (100-150g each)
Low-fat dairy	2-3 servings (100-150g each)
Poultry	1-2 servings (100-150g each)
Red wine	2-4 servings (1 glass each)

Table 6: foods to limit

Food, food category, or beverage	Recommended amount
Red meat	≤ 1 serving (100-150g) per week
Processed meat	As low as possible, ideally none
Whole-fat dairy	≤ 30g per week
Fried food	As low as possible, ideally none
Fast food	As low as possible, ideally none
Processed sweets	≤ 2 servings per week

As a final note, we want to remind that these are general guidelines, and as such, they apply to the average population. They are calibrated on the average individual's daily caloric, macro-, and micronutrient requirements. Therefore, adjustments must be made or at least considered when applying these guidelines to a singular individual.

Moreover, for the thorough prevention of dementia, lifestyle interventions are equally important, if not more important. As explained in the early part of this thesis, regular physical exercise, regular cognitive exercise, and an active social life play a huge role in preserving brain functions through aging and maximizing mental well-being.

There is consistent research behind these guidelines. We hope that, together with the rest of this thesis, they may aid scientists and policymakers in perfectioning dietary guidelines and political interventions to prevent Alzheimer's disease, vascular dementia, and other forms of dementia and cognitive decline. Moreover, we wish to stress that these guidelines have the potential not only to be a powerful tool for the prevention of cognitive decline but also to contribute to helping with the prevention and treatment of the devastating widespread psychiatric illness that is depression. As explained in the previous chapters, cognitive decline and depression have interesting overlapping features, especially at the molecular level. Thus a dietary approach aimed at reducing the risk of dementia could also effectively reduce the risk of depression.

5. Conclusion

The quickly increasing prevalence of dementia correlated with the Global Syndemic of obesity, undernutrition, and climate change, highlights the urgent need for effective prevention strategies. This master thesis underscores the importance of a healthy diet as a critical component of such strategies while reminding the importance of comprehensive prevention that includes lifestyle and environmental factors. Although nutrition is a very influential modifiable risk factor, the others cannot be disregarded in the process of achieving a properly comprehensive prevention protocol for dementia. For instance, geographic location may also play a preponderant role in the progression of such diseases, as it can affect not only many urban, cultural, social, and economic aspects but also lifestyle factors such as food choices and other behaviors that are proven to affect the risk for cognitive decline, namely sleep, physical activity, and social life. More often than not, seemingly isolated risk factors are correlated with each other; thus, an effective prevention protocol must consider global lifestyle changes.

This master thesis provides a comprehensive review of the current evidence on the impact of nutrition on cognitive health and dementia prevention, starting from the molecular level (single nutrients) up to the complexity of entire dietary patterns. The findings suggest that dietary patterns in which whole, plant-based foods are predominant are likely to be the most protective ones against cognitive decline. In particular, berries and other fruits, leafy greens and other vegetables, nuts, but also fatty fish, coffee, chocolate, and green tea seem to be able to protect and enhance cognitive functions thanks to a wide range of vitamins, minerals, and other nutrients present in them that are very important for a correct functioning of the brain.

A critical limitation of this thesis is that some of the claims are based on speculations due to a need for more evidence in some of the fields explored. We highlighted the uncertainty of the current evidence in the most speculative passages. We hope to motivate and inspire other scientists and researchers to test our speculations with proper clinical trials. The topic of this master thesis is exceptionally new and still relatively unexplored, although its recent interest

is directing a promisingly increasing research effort toward its investigation. In the following table, we report a few of the most interesting ongoing clinical trials on the subject (Table 7).

Table 7: ClinicalTrials.gov Search Results 05/25/2023

Title	Conditions	Interventions
Clinical Trial of a Low Protein Diet in Patients With Cognitive Impairment	Mild Cognitive Impairment; Mild Dementia; Fasting-Mimicking Diet	Dietary Supplement: Fasting-Mimicking Diet ProlonADTM
Enhancing Health and Quality of Life for Individuals With Dementia Through Transitional-State Snacks	Dementia; Poor Nutrition	Dietary Supplement: Transitionalstate food therapeutic nutrition supplement
Electronic-Nutrition-Optimizer for Personalized Prevention	Diabetes; Hypertension; Frailty; Dementia; Cardiovascular Diseases	Device: eNutrition Optimizer
Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diet in Stroke Patients	Cognitive Decline; Dementia, Vascular; Alzheimer Disease; Dementia; Stroke	Behavioral Dietary intervention (MIND Diet); Behavioral Usual Care Diet Intervention
Nutrition Interventions for Cognitive Enhancement	Alzheimer Disease	Mediterranean Diet; Study Supplement; Low-fat Diet
Dietary Treatments for Cognitive Impairment in Older Adults	Mild Cognitive Impairment; Probable Alzheimer's Disease	Modified Atkins Diet; NIA Diet for Seniors
Intermittent Calorie Restriction, Insulin Resistance, and Biomarkers of Brain Function	Alzheimer's Disease; Obesity; Diabetes Mellitus	Boost (R) 5-2 diet; Healthy Living Diet
Chocolate and Physical Exercise to Reduce Malnutrition in Pre-dementia Aged People	Dementia; Mild Dementia; Moderate Dementia; Senile Dementia; Malnutrition; Nutritional Deficiency; Deficiency Diseases	Combination of High Protein Diet and Physical Exercise Protocol; Dietary Supplement: HPP Choko; Dietary Supplement: HPP/VE Choko

We anticipate the outcomes of randomized clinical trials that employ PET analyses, aiming to enhance our comprehension of macroscopic morphological alterations and microscopic cellular and metabolic changes occurring in the brain as a result of a specific dietary regimen or targeted nutrient supplementation. As delineated in the main body of this master thesis, numerous nutrients, foods, and dietary patterns have demonstrated the potential to diminish neuroinflammation and enhance neuroplasticity. Therefore, conducting a study employing advanced brain imaging technologies to provide definitive human evidence of these effects would be immensely significant in advancing our understanding in this domain.

Finally, the proposed dietary guidelines offer practical and evidence-based recommendations for individuals, healthcare providers, researchers, and policymakers to promote optimal cognitive health. In addition to reducing the risk of cognitive decline, the proposed healthy eating habits may also help prevent a range of other chronic diseases burdening our current society, such as cardiovascular disease, type 2 diabetes, and some form of cancer.

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