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Review

A Narrative Review of Dietary, Lifestyle, and Other Complementary and Alternative Approaches in Alzheimer's Disease and Related Dementias

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Abstract

As age progresses and the population increases, the prevalence of dementia also increases. Pharmacological interventions are used to treat cognitive decline. Alternative approaches to traditional pharmacology, such as dietary interventions, may help combat cognitive decline in aging populations. This review summarizes existing investigations using complementary and alternative approaches as mitigating interventions. We also briefly note other important modifiable factors to decrease the risk of cognitive decline, and Alzheimer's disease and related dementias. Such approaches include nutrition and dietary interventions that show promising results for mitigating cognitive decline, as well as additional lifestyle modifying factors that are important to note (e.g., sleep, cardiovascular diseases, environmental factors, physical, social and leisure activities, cognitive stimulation, psychosocial factors, and sensory functioning) for their impact on cognition in aging. Despite the limited findings and support for complementary and alternative approaches in combating existing cognitive decline, findings suggest that such approaches may be most beneficial prior to the onset of cognitive impairment. Specific nutrition components, including flavonoids and omega fatty acids, may mitigate cognitive decline, and emerging evidence suggests that these nutrients may promote a healthy gut microbiota. Of the complementary and alternative approaches, adhering to specific diets, generally, has the most consistent support to combat cognitive decline. It is important to note that other non-nutritional or non-dietary modifiable lifestyle factors also show promising benefits in mitigating further cognitive decline. Future investigations and clinical trials with replication studies are needed to elucidate these complementary and alternative approaches as effective treatment options for clinicians.

Keywords: Alzheimer's disease; dementia; mild cognitive impairment; dietary interventions; complementary and alternative approaches; preventative medicine

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1. Introduction

Dementia—including Alzheimer's disease—impacts the quality of life for patients, family members, and care takers [1], and poses one of the largest challenges for health care systems globally [1,2]. In 2019, an epidemiology report showed that dementia affects approximately 57.4 million individuals among the global population with approximately 5.3 million cases in the United States of America [3]. In fact, Alzheimer's dementia was

listed the sixth leading cause of death in the United States in 2019 [4]. It has been estimated that the population of individuals with dementia will double every 20 years with 81.1 million individuals experiencing dementia by 2040 [1,5]. However, currently approved treatment interventions for these patients provide limited help for cognitive and behavioral related symptoms. Interventions and therapy options for these patients can include AD treatments, such as cholinesterase inhibitors, immunotherapies (e.g., lecanemab and donanemab), and n-methyl-D-aspartate (NMDA) antagonists [6]. Despite these interventions and therapy options, findings have shown some impact on functional ability within these patient populations [7], but the impact of these medications is modest. The long-term impact of immunotherapies in this population remains unclear, but the other classes of agents do not impact the trajectory of the disease.

Age-related changes in cognitive functioning are well documented [8–10]. As age increases, cognitive domains for executive functioning [9,10], processing speed [10,11], divided attention [12], episodic memory [9,13,14] working memory [15], source memory and prospective memory [16] generally decline. Conversely, cognitive domains for semantic memory [9], spatial attention [17,18], and sustained attention [19] tend to be preserved. Cognitively impaired populations, including mild cognitive impairment (MCI)—characterized as a transitional stage between normal cognitive aging and dementia onset [20]—and Alzheimer's dementia, experience worse cognitive functioning that exceeds normative age-related cognitive decline [9,21]. Specifically, patients with amnestic MCI tend to experience memory impairments while other cognitive domains are preserved [22]. In contrast, AD is characterized by progressive cognitive decline affecting multiple cognitive domains [23]—including executive functioning [24], episodic memory [25], word-finding abilities, and visuospatial abilities [26]—along with impaired daily living activities (e.g., personal hygiene, finances, mobility, etc.; [23]). The trajectory from MCI advancing through mild, moderate, and severe AD dementia is marked by early memory decline in MCI, then progressing with further cognitive decline in memory, executive functioning, language, and visuospatial abilities, all of which are cognitive domains that are accompanied with impaired daily living abilities [27]. AD dementia is clinically distinguished from other major forms of dementia—including vascular dementia, frontotemporal dementia, and Lewy body dementia—by the presence of specific pathology and the progression of cognitive decline in specific cognitive domains, in addition to motor features for Lewy body dementia [26,28].

While treatment and therapies for dementia [29] and Alzheimer's disease [6] have documented modest effects, thus far, no randomized clinical trials have been conducted to determine if interventions can prevent dementia [30]. However, substantial emerging evidence supports strategies that may potentially prevent dementia. For instance, a recent meta-analysis found that single- and multi-domain lifestyle interventions—including diet, physical exercise, social activity engagement, and cognitive training—provided global cognitive functioning benefits in those without extant cognitive impairment and showed the strongest effect with a combined physical exercise and cognitive training intervention [31]. Reducing risk factors (e.g., hypertension, obesity) has also been suggested to decrease the risk of developing dementia [32]. In a recent report, a 12-factor life-course model was proposed that consisted of modifiable factors that have the potential to impact dementia outcomes [33]. Findings showed that an approximately 40% risk for dementia was associated with lower education, smoking, depression, hypertension, excessive alcohol consumption, head injury, diabetes, lack of social contact, and air pollution. To assist in combating cognitive decline, "successful cognitive aging" (i.e., healthy cognitive aging)—referred to as maintaining cognitive reserve and information processing, and minimizing cognitive decline [34,35]—strategies have been documented including reducing cardiovascular risks

(e.g., hypertension, obesity, diabetes), engaging in regular physical activity, maintaining social engagement, participating in cognitively stimulating activities, adhering to diets that are heart healthy, managing stress and depression, avoiding smoking, limiting alcohol consumption, achieving adequate sleep, and addressing sensory deficits, along with avoiding activities that can lead to brain damage [34]. In fact, a recent study in patients aged 60+ years with type 2 diabetes showed that greater adherence to "Healthy Lifestyle Factors," such as not currently smoking, less sedentary lifestyle, a healthy diet, and more frequent social contact, were associated with a reduced incidence of dementia [36]. In the instance when AD dementia is established, findings suggest that clinical outcomes are more impacted by a narrower set of risk factors, including baseline cognitive abilities, presence of neuropsychiatric symptoms, altered gene regulation, genetic variants, malnutrition, and extrapyramidal signs [37]. Given previous work proposing risk factors for dementia, it is possible that the implementation of complementary and alternative approaches may play a preventative role for neurocognitive impairment rather than providing treatment after dementia onset.

Although previous work has proposed risk factors for dementia, there have been limited reviews of complementary and alternative approaches in cognitively impaired populations. Evidence discussed in previous reviews regarding complementary and alternative approaches in cognitively impaired populations primarily focused on supplements (e.g., vitamins C, E and B, and omega-3 fatty acids), mind-body therapies/practices (e.g., yoga, tai chi), and physical activity, along with some information on dietary interventions (primarily the Mediterranean diet) and acupuncture [38–41]. Notably, specific nutritional components—such as unsaturated fatty acids—play a role by supporting neuronal membrane integrity, cellular metabolism and immunological signaling, which are implicated in the pathophysiology of Alzheimer's disease and related dementias (ADRD; [42,43]). This is of particular importance given that the link between inflammation contributing to AD pathogenesis [44], and the potential anti-inflammatory benefits from omega-3 fatty acids [45]. However, there are several other potential interventions that should be noted, such as flavonoids, non-Mediterranean related diets, specific components found in foods [39], altering the gut microbiome [46,47], and other modifiable lifestyle factors [48].

The narrative review summarizes evidence on complementary and alternative approaches for AD and other causes of cognitive impairment, with a focus on their potential role for preventing neurocognitive decline among those with or without extant cognitive impairment. Given the extensive nature of proposed risk factors and treatment approaches for AD and other forms of dementia populations [29,49], we primarily focused on recent complementary and alternative approaches published within the past decade relating to dietary and nutritional interventions, individual food dietary components, and recent evidence for gut microbiome as a potential treatment option for preventing neurocognitive impairment.

2. Nutrition and Dietary Interventions

No medications have been shown to significantly slow or reverse cognitive decline in aging adults, except for anti-amyloid treatments which show some effects in earlier stages of AD [50]. Thus, it is important to examine other potential modifying factors to help mitigate cognitive decline. Diet is a potential modifiable factor that may be a potential treatment avenue for preventing cognitive decline [51] and a potential intervention avenue to support healthy cognitive aging [52]. Here, we describe various dietary interventions for cognitive functioning, and their potential benefits in cognitively impaired populations (see Table 1).

2.1. Mediterranean Diet and Related Diets

Among complementary and alternative approaches for dementia, the Mediterranean diet is one of the most consistently supported interventions. Adherence to this dietary plan is associated with a decreased risk for AD dementia or neurocognitive decline [53–57]. The Mediterranean diet involves a greater consumption of legumes, vegetables, fruits, cereals, nuts, and unsaturated fatty acids (primarily from olive oil), and moderate-to-high intake of fish, as well as a low consumption of meat, saturated fatty acids (e.g., dairy products), supplemented by limited regular alcohol consumption [56]. Interestingly, those who follow a Mediterranean diet have less accumulation of amyloid beta (Aβ; [58,59]), a neuropathological species associated with Alzheimer disease, along with attenuated total brain volume decline over 3 years [60] and reduced white matter hyperintensities in community based older adults [61]. Similarly, in middle-aged women at risk for ADRD with APOE ε4 genotype, adherence to the Mediterranean diet was found to modulate APOE ε 4 homozygote metabolites, reducing the risk of ADRD onset [62].

Further, when the Dietary Approaches to Stop Hypertension (DASH) diet—emphasizing the consumption of berries, vegetables, whole grains, limited saturated and trans fats, low-fat dairy consumption, and reduced sodium intake—is combined with the Mediterranean diet, referred to as the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND [63]), work has shown that the MIND diet is associated with a lower emergence of dementia [64,65], reduced dementia burden at time of death [66], and better overall cognitive function [67]. Other work has suggested that the MIND diet may mitigate cognitive decline compared to the Mediterranean diet [63], and may reduce the risk of hippocampal sclerosis (mid-hippocampus cornu ammonis 1 or subiculum neuronal loss and astrogliosis; OR = 0.78) in older adults (from the Rush Memory and Aging Project cohort study), particularly among those with limbic-predominant age-related TDP-43 encephalopathy (OR = 0.79; [66]).

However, investigations examining Mediterranean or MIND diets in patient populations with existing cognitive decline are limited. In the work that exists, a pilot study consisting of the Mediterranean diet enriched with coconut oil in patients with AD showed cognitive benefits for episodic, semantic memory and temporal orientation abilities [68]. On the other hand, a Swedish population-based study did not observe protective effects for cognitive functioning in mid-to-late adults with dementia who adhered to a modified Mediterranean diet [69]. It is possible that the duration of diet adherence, lack of standardized cognitive testing, and olive oil vs. vegetable oil consumption may have contributed to the contradictory findings. Specifically, the benefits of the greater proportion of monounsaturated fatty acids relative to polyunsaturated fatty acids in olive oil compared to vegetable oil may contribute cognitive benefits in those with neurocognitive impairment (see Section 3.2. Other Fatty Acids discussed later in this paper).

Taken together, the Mediterranean or MIND diets show promising benefits for healthy cognitive aging and reducing the risk of neurocognitive impairment, reliably shown in recent reviews [57,70,71] and a meta-analysis [72]. Nevertheless, further work is warranted to delineate the therapeutic effect of these diets in those with extant cognitive impairment.

Table 1. *Summary of Dietary Intervention Findings Across Cognitive Stages and Neuropathological Outcomes.* Summary of specific dietary interventions for the Mediterranean, MIND, ketogenic, and other dietary pattern adherence across cognitive stages and associated changes with neuropathology. "Yes" indicates studies with findings in support of each category presented. "Mixed" indicated studies that have findings in support or null findings for each category. "Limited" indicates findings from previous single studies, pilot trials, or early-phase evidence. The dashes indicate insufficient research in that category. (MCI = mild cognitive impairment; AD = Alzheimer's disease; MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay).

Dietary Intervention	Delays MCI Onset [References]	Reduces Risk for AD Dementia/ Neurocognitive Decline [References]	Reduces MCI-to-Dementia Conversion [References]	Improves Cognitive Functioning in Dementia Populations [References]	Improves Age-Related Normal Cognitive Functioning [References]	Reduces AD-Related Pathology/ Neurophysiology [References]
Mediterranean Diet	Yes [63,67]	Yes [53–56,65]	Mixed (limited) [68,69]	Yes (limited) [68]	Yes (limited) [60,73]	Yes (limited) [58,59,61,62]
MIND	Yes [63,67]	Yes [64–66,74]	--	--	--	Yes (limited) [66]
Ketogenic Diet	Mixed (limited) [75–77]	Mixed (limited) [76,78]	Yes (limited) [76,77,79]	Yes (limited) [76,79,80]	[76]	Yes (limited) [75,76]
Japanese Diet	--	Yes (limited) [81,82]	--	--	Yes (limited) [81]	--
General Healthy Diets	Yes (limited) [83]	Yes (limited) [84]	--	--	Yes (limited) [83]	--
Vegetable-Rich Diets	Yes (limited) [85]	Yes (limited) [86]	--	--	Yes (limited) [87,88]	Yes (limited) [89]
Fruit-Rich Diets (excluding juices, citrus emphasis)	Yes (limited) [86,90]	Yes (limited) [82,86]	--	--	Yes (limited) [88]	--

2.2. Ketogenic Diet

Recent dietary interventions show increasing support for the ketogenic diet for cognitive functioning and health [78]. The ketogenic diet involves a high consumption of healthy fats (e.g., avocados, nuts, olive oil), moderate consumption of protein, and low consumption of carbohydrates. This diet permits the use of ketones in the brain rather than using the more typical use of glucose for energy [91]. Findings from a randomized trials showed improved daily functioning abilities and improved quality of life in AD patients [80], along with improved brain ketone (not glucose) metabolism, as assessed by positron emission tomography (PET) imaging, and improved cognitive performance in mid-to-late life patients with mild cognitive impairment (MCI; [75]). These findings are further supported by a recent meta-analysis in healthy adults, MCI and AD populations [76]. Other work has also shown memory benefits in patients with early AD-dementia and MCI with adherence to a modified Atkins diet (MAD; [77])—characterized as <20 g of net carbohydrates, moderate consumption of protein, high fat consumption to satiety, and adequate hydration, which can induce ketogenesis—and a medium-chain triglyceride (MCT) based ketogenic diet in patients with mild-to-moderate AD [79]. These findings suggest that using ketones as alternative energy sources in the brain from adhering ketogenic-related diets may provide memory benefits in those with extant cognitive impairment; however, further work is needed to determine potential neural underlying mechanisms that may contribute to mitigating neurocognitive decline with the adherence to ketogenic-related diets.

Despite the promising neurocognitive effects associated with adherence to ketogenic-related diets in AD and MCI populations, emerging evidence suggests that variations to this diet—particularly those high in saturated or long-chain fatty acids—may have adverse effects in cognitively impaired populations [92–94]. Specifically, the high-fat intake of the ketogenic diet may increase oxidative stress (increasing the inflammatory response) and, therefore, exacerbate memory impairments in these populations. Moreover, the chain length and the degree of unsaturated fatty acids may impact metabolic and cognitive outcomes in cognitively impaired populations [95,96]. Importantly, the long-term safety and efficacy of the ketogenic diet in cognitively impaired populations is unclear [92]. The limited, small sample sizes, and short-term ketogenetic interventions contribute to the inconclusive understanding of the impact of this diet in such populations [93].

2.3. Other Important Healthy Diets

Similar to the Mediterranean and MIND diets, other diets have shown potential benefits for cognitive performance in older adults. For instance, older adults with greater adherence with the Japanese diet—characterized by a high consumption of fish, seaweed, soybean products, vegetables, and green tea—had reduced risk of the incidence of dementia, while those with less adherence to this diet had elevated risk for the incidence of dementia [81]. Findings from assessment of adherence to a healthy diet showed that aging adults with the healthiest diet (based on the Alternative Healthy Eating Index) had less cognitive decline [84], and cognitive benefits for global cognition and executive functioning were found in healthy older adults with an elevated risk for dementia (from the Study to Prevent Cognitive Impairment and Disability (FINGER) [83]).

Adherence to other diets emphasizing consumption of specific types of food has also demonstrated benefits for cognitive abilities. For example, a greater consumption of green leafy vegetables was associated with a decrease in cognitive decline (from the Rush Memory and Aging Project [97]) and a decreased risk for the development of all-cause MCI (from the Chinese Longitudinal Aging Study [85]). Additionally, diets rich in citrus have been linked with reduced risk for all-cause dementia in Japanese older adults [82], and with a ~20% reduction in the risk of cognitive impairment and dementia in adults

aged 65+ years [86]. Diets rich in both fruits and vegetables have been associated with better memory abilities in European older adults (from the Survey of Health, Ageing and Retirement in Europe study [87]), better verbal memory and executive functioning in a 25-year longitudinal study with aging American adults [88], and reduced odds of subjective cognitive decline among older adult men [90]. Many of these benefits may be attributed to bioactive compounds in such diets—such as polyphenols, flavonoids, carotenoids, and methylation-supporting nutrients—that have been associated with reducing oxidative stress, modulating the inflammatory response, and promoting synaptic plasticity [98,99]. Additionally, plant-based diets rich in methylation-supporting compounds have been linked to reductions in epigenetic age (i.e., deoxyribonucleic acid (DNA) methylation clock), which may provide mechanistic support for cognitive resilience in older adults [98]. Further, a green-Mediterranean diet—rich in polyphenol dense plants, including Mankai, green tea, and walnuts—attenuated brain age trajectories in mid-to-late life adults [89].

Dietary fiber from fruit and vegetable consumption may exert neuroprotective effects by mitigating inflammation and alternative macrophage activation [88]. Findings from diets that include a specific dietary fiber supplement (polydextrose, a soluble fiber that promotes beneficial gut bacteria and modulates neuroinflammatory pathways) that targets the gut microbiome have shown a link between a dietary fiber supplement and improved cognitive performance in healthy older adults (see Section 5.1. Modifiable Factors for Microbiome-Gut-Brain Axis discussed later in this paper for further details) [100]. Overall, higher fiber diets (from the US National Health and Nutritional Examination Survey) were associated with improved executive functioning abilities in older adults [101]. A recent review suggests that increased fiber intake, especially in Western diets where fiber intake is typically low, may provide benefits for cognitive functioning [102]. However, it is unclear whether soluble or insoluble fiber may have differing effects relating to cognitive functioning.

Taken together, adherence to healthy diets—including the Mediterranean diet, MIND, Japanese diet, and diets rich fruits and vegetables—appears to support healthy cognitive aging and the potential for therapeutic intervention for those with neurocognitive impairment. Yet, heterogeneity in diet composition, population risk profiles, and cognitive assessments among such investigations highlight the importance of further exploration in precision dietary strategies tailored to cognitive status (e.g., MCI, early onset dementia, mild AD, etc.) and biological aging trajectories. Additionally, adherence to the ketogenic diet has shown some promising cognitive benefits, as well as some adverse effects with the high fat diet nutritional component in this diet. The change in energy metabolism (glucose to ketones) may provide cognitive benefits, but such benefits in cognitively impaired populations are inconclusive. Further work is needed to understand the long-term effects of the ketogenic diet, optimization of the dietary components of this diet, and potential risks.

3. Specific Dietary Components

In addition to interventions based on diets, and their impact on cognitive functioning and in cognitively impaired populations, it is important to discuss how specific nutrients (i.e., docosahexaenoic acid, creatine), bioactive compounds (i.e., fatty acids, flavonoids), and vitamin supplements may contribute to mitigating cognitive decline. Further understanding the contribution of such dietary components may be important for tailoring treatment aimed at preventing cognitive impairment and reducing further cognitive decline in those with extant cognitive impairment. Here, we describe various dietary components with cognitive functioning, and their potential benefits for prevention of cognitive decline as well as effects in cognitively impaired populations, as shown in Table 2.

Table 2. *Summary of Specific Dietary Component Findings Across Cognitive Stages and Neuropathological Outcomes.* Summary of specific dietary components across cognitive stages and associated changes with neuropathology. "Yes" indicates studies with findings in support of each category presented. "Mixed" indicates that studies that have findings in support or null findings for each category. "Limited" indicates that previous studies are single studies, pilot trials, or early-phase evidence. The dashes indicate insufficient research in that category. (MCI = mild cognitive impairment; AD = Alzheimer's disease; DHA = docosahexaenoic acid.).

Dietary Individual Component	Delays MCI Onset [References]	Reduces Risk for AD Dementia/Neurocognitive Decline [References]	Reduces MCI-to-Dementia Conversion [References]	Improves Cognitive Functioning in Dementia Populations [References]	Improves Age-Related Normal Cognitive Functioning [References]	Reduces AD-Related Pathology/ Neurophysiology [References]
DHA and Omega-3 Fatty Acids	Mixed [103–105]	Yes [103,104,106–108]	--	Mixed [109–111]	Yes [112,113]	Yes [114–118]
Olive Oil	Yes (limited) [119]	Yes [120,121]	--	Yes (limited) [73,119]	--	--
Avocados	Yes (limited) [122,123]	Yes (limited) [122,124]	--	Yes (limited) [123,124]	Yes [124]	Mixed [125–127]
Coconut Oil	--	--	Mixed (limited) [68,128]	Yes (limited) [68,128,129]	--	--
Creatine	Yes (limited) [130,131]	Yes (limited) [132,133]	Mixed [131]	Yes (limited) [134–136]	Yes (limited) [137,138]	Yes [136,139]
Anthocyanin Flavonoids	Mixed [140–144]	Mixed [145–148]	Yes (limited) [140,149,150]	Yes (limited) [140,142,149–152]	Yes (limited) [152–154]	Yes [141,145,146,148]
Coffee Flavonoids	Yes (limited) [155,156]	Yes (limited) [155,157]	Yes (limited) [158]	--	Yes (limited) [158]	Yes (limited) [158]
Tea Flavonoids	Yes (limited) [159–161]	Yes [155,159]	--	--	Yes (limited) [160]	Yes (limited) [162,163]
Vitamin B	Yes (limited) [164–167]	Mixed [168,169]	Yes (limited) [167,170,171]	Yes (limited) [167,171]	Mixed [164,165,172,173]	Yes [166,169,170,173–177]
Vitamin D	Mixed (limited) [178,179]	Yes [180–184]	Mixed (limited) [178]	Yes (limited) [183,185]	Yes (limited) [180,181]	Mixed (limited) [185,186]
Vitamin C	--	--	--	--	Yes [187]	--
Vitamin E	--	Mixed [188,189]	--	Yes (limited) [190,191]	--	Mixed [189,191]
Multivitamin Supplements	Mixed [192,193]	Mixed [194,195]	Yes (limited) [196]	Yes (limited) [196]	Yes (limited) [194,197,198]	Mixed (limited) [199]
Cocoa/Chocolate	Mixed (limited) [200,201]	Mixed (limited) [201,202]	--	Yes (limited) [203,204]	Yes (limited) [201,204]	Mixed (limited) [202,205]

Table 2. *Cont.*

Dietary Individual Component	Delays MCI Onset [References]	Reduces Risk for AD Dementia/Neurocognitive Decline [References]	Reduces MCI-to-Dementia Conversion [References]	Improves Cognitive Functioning in Dementia Populations [References]	Improves Age-Related Normal Cognitive Functioning [References]	Reduces AD-Related Pathology/ Neurophysiology [References]
Mushrooms	Yes (limited) [206]	Yes (limited) [207,208]	--	Mixed (limited) [208]	Yes (limited) [208]	Yes (limited) [209–215]
Curcumin (turmeric)	--	--	--	--	Yes (limited) [216]	Yes (limited) [216,217]
Gingseng	--	--	--	--	Yes (limited) [216]	--
Eggs	--	Yes (limited) [218]	--	--	--	Yes (limited) [218]
Ultra-Processed Food Consumption	Mixed (limited) [219]	Yes [220–223]	Mixed (limited) [221]	--	Mixed (limited) [219]	Yes (limited) [224,225]

3.1. Docosahexaenoic Acid (DHA) and Other Omega-3 Fatty Acids

A plethora of findings have indicated protective effects for dementia with the consumption of omega-3 fatty acids, including docosahexaenoic acid (DHA; [106]). For example, in population-based studies, greater DHA was associated with a reduced risk of all-cause dementia and AD dementia (from the Framingham offspring study [107]), and increased omega-3 consumption was associated with better cognitive functioning in older adults aged 60+ years (from National Health and Nutrition Examination Survey [112]). Among patients with AD, randomized controlled trials showed that daily consumption of omega-3 fatty acids improved neurodegenerative markers of neurofilament light (NfL, important for indicating neuroaxonal impairment) and chitinase-2-like protein 1 (YKL-40, a marker of neuroinflammation and gliosis activation; [114]), along with reducing functional decline [109]. A recent review also suggested that chronic deficiency in DHA (omega-3 fatty acid) and estradiol may contribute to AD pathology for Aβ deposits in early stages of sporadic AD [115].

Additional work in populations with the apolipoprotein E (APOE) ε4 allele—which is associated with an increased genetic risk factor for AD—has shown that higher DHA intake is associated with greater cortical thickness in AD-vulnerable brain regions in cognitively normal middle-aged adults [116], and protective effects for memory functioning [117] and greater fluid intelligence abilities in older adults [113]. In adult APOE ε4 allele carriers, weekly consumption of omega-3 fatty acids with seafood was associated with a reduced risk of cognitive decline in multiple cognitive domains in older adults [103], while higher intake of omega-3 fatty acids (DHA and eicosapentaenoic acid omega-3 fatty acid chains) was associated with slower cognitive decline in middle-aged carriers (from the Doetinchem Cohort Study [104]). Regarding AD, findings showed that daily omega-3 fatty acid consumption may reduce the effects of lifetime stress (lifetime stress has been linked with the development of AD [226,227]) on AD development [108]. A recent review further describes the potential neuro-preventative and therapeutic effects of DHA as a nutraceutical in neurological diseases and in particular for cognitive impairment, as DHA—particularly via the enzyme calcium-independent phospholipase A2—may help reduce the burden of Aβ and tau pathology [118].

Other clinical trial findings did not observe an impact of omega-3 fatty acids with cognitive functioning over 3 years in older adults with memory complaints [105], nor was slowing of cognitive and functional decline observed in patients with mild-to-moderate AD [110]. However, in a systematic review, findings showed that omega-3 polyunsaturated fatty acids supplements were associated with improved cognitive functioning in cognitively healthy older adults or those with mild cognitive complaints, but no consistent changes in cognition were found in patients with AD in 5 randomized clinical trials out of 24 [111]. Although some findings did not observe support for protective benefits of omega-3 fatty acids in those with extant cognitive decline, findings suggest that omega-3 fatty acid supplementation may provide cognitive benefits in populations who are cognitively healthy or with mild cognitive complaints. Other findings suggests that omega-3 fatty acids may also provide the greatest supplement benefits in APOE ε4 carriers for prevention [228]. The mixed findings regarding omega-3 fatty acids with cognitive functioning and cognitive/functional decline may be attributed to the variance in cognitive impairment status (cognitive healthy vs. memory complaints vs. AD), dosage of omega-3 fatty acids, and baseline nutritional status with omega-3 fatty acid consumption. The cognitive benefits of omega-3 fatty acids for those with AD are modest, when any is detected [111]. Therefore, omega-3 fatty acid consumption may be the most beneficial as a dietary intervention, in the context of a broader dietary intervention, as opposed to an isolated supplement interven-

tion [111], and may provide an effective approach for preventative treatment or early-stage intervention in contrast to those with established neurocognitive impairment.

While omega-3 fatty acids have been linked to benefits for cognition [109,110,228], the underlying mechanism is unclear. It has been suggested that omega-3 fatty acids may attenuate the inflammatory response and oxidative stress, thereby improving cognitive functioning [229,230]. These mechanisms are distinct from the ketogenic diet, which induces ketosis and relies on the ketone bodies as alternative energy substrates. Omega-3 fatty acids do not induce ketosis and are not metabolized the same way. The cognitive benefits from omega-3 fatty acids are not due to energy substitution, but rather their bioactive role in neural integrity and function [230].

3.2. Other Fatty Acids

Other fatty acids that are considered "healthy" that may have promising benefits in mitigating dementia. For example, omega-3 fatty acids (e.g., DHA, α-linolenic acid, eicosapentaonoic acid) and omega-6 fatty acids (e.g., linoleic acid, γ-linolenic acid and arachidonic acid) are found in food sources—including vegetable oils [231]—and have been linked with attenuating AD pathology and cellular mechanisms (e.g., apoptosis; [232]). Importantly, an increased ratio of dietary omega-6 to omega-3 fatty acids has been associated with risk of AD and increased cognitive decline [233,234]. A lower ratio of omega-6 to omega-3 fatty acids has also been associated with better hippocampal dependent spatial memory abilities in cognitively healthy older adults [235]. Other work has suggested that balancing α-linolenic (omega-3 fatty acid) and γ-linolenic (omega-6 fatty acid) acids may have promising therapeutic effects for cognitive impairment [232]. In the most recent work, greater highly unsaturated plasma lipid levels are associated with lower incidence of AD in women but no such association was seen for men [236], raising the possibility that this may have some relationship to the greater incidence of AD in women [237].

3.2.1. Olive Oil

One dietary source rich in "healthy" fatty acid with promising results in enhancing cognitive functioning and combating cognitive decline is olive oil [238]. In longitudinal studies, greater olive oil consumption was associated with a reduced risk of neurodegenerative-related mortality (from the Nurses Healthy Study [120]), and the risk of dementia-related death was reduced by 29% in those with the APOE ε4 allele who consumed olive oil at ≥7 g/day (from the Nurses' Health Study I and Healthy Professionals Follow-Up Study [121]). Other work from randomized trials investigating extra virgin olive oil showed better cognitive functioning across fluency and memory tasks in cognitively healthy older adults [239], and long-term intake of both high and moderate phenolic extra virgin olive oil resulted in improved cognitive functioning for global cognition, attention, and fluency tasks after 12 months compared to the Mediterranean diet in older adults with MCI [119]. Overall, these findings suggest that olive oil—particularly extra virgin olive oil—may support cognitive resilience in aging adults with varying cognitive statuses.

3.2.2. Avocados

Avocados and avocado oil are another "healthy" dietary source rich in omega-3, omega-6 and monounsaturated fatty acids [240] that has received increasing attention in human nutrition [241]. Although avocados and avocado oils have a higher ratio of omega-6 fatty acids (i.e., linoleic acid) relative to omega-3 fatty acids (i.e., α-linolenic acid [240]), avocados have been suggested to provide neurocognitive benefits [233–235], and it may be important to evaluate other nutrient-dense fatty acid sources that have a similar biochemical profile to olive oil. Notably, avocado oil contains higher levels of omega-3 and omega-6 levels, polyunsaturated fatty acids, and saturated fatty acids, and

a lower proportion of vitamin E relative to olive oil [240]. Given the antioxidant effects of avocado oil—including phytosterols (e.g., β-sitosterol) and tocopherols (e.g., vitamin E, which is still enriched in avocado oil but to a lesser extent than olive oil; [125])—it is proposed that avocado oil may also provide benefits for combating cognitive decline and neurodegeneration [125,242], despite having a higher omega-6 fatty acid ratio.

However, limited investigations and trials have examined the potential cognitive benefits of avocados or avocado oil. In the work that exists, avocado consumption was associated with better cognitive functioning for global cognition, immediate and delayed recall, verbal semantic fluency, processing speed, and executive functioning in healthy older adults (from the National Health and Nutrition Examination Survey from 2011–2014 [122]) and avocado extracts may provide neuroprotection against neurological damage induced by rotenone (associated with accumulation of alpha-synuclein and Aβ [126,127]). Randomized clinical trials in cognitively healthy mid-to-late life adults have also shown that daily avocado consumption improved spatial working memory, sustained attention abilities [123], and inhibitory control [124], and additionally increased lutein levels [123,124]. Despite that avocados are good sources for calcium, iron, magnesium, zinc ω-6 linoleic acid, and flavonoids, and have compounds with acetylcholinesterase inhibition effects [127] that may contribute to cognitive and neuroprotective benefits, further investigations and clinical trials are needed for the potential clinical utility of avocados/avocado oil in mitigating cognitive decline.

3.2.3. Coconut Oil

Coconut oil is another functional oil that is widely used in both food and pharmaceutical products with nutritional values comparable to olive oil [243], but contains more saturated fats (e.g., lauric acid) and minimal omega-3 and omega-6 fatty acids [244]. Emerging evidence with the use of coconut oil has suggested benefits for cognitive functioning and a potential therapeutic treatment for AD [129,245]. For example, a 21-day longitudinal pilot study with AD patients found that consuming a Mediterranean diet rich in coconut oil (20 mL twice a day) improved episodic memory, semantic memory, and temporal orientation abilities, with sex-specific effects observed in women with mild-to-moderate AD and in males with more severe AD [68]. Conversely, in a randomized, placebo-controlled trial with mild-to-moderate AD patients, a 24-week virgin coconut oil (orally 30 mL/day) intervention did not show an improvement in global cognition, except for those with an APOE ε4 allele [128]. Despite general support for coconut oil providing cognitive benefits in AD populations [129], inconsistent findings may be attributed to differences in study design (pilot study vs. randomized clinical trial), dosage (40 mL/day vs. 30 mL/day), duration, and examining specific risk factors (i.e., sex and APO ε4 allele). It is plausible that coconut oil may exert a synergic effect with adherence to a Mediterranean diet and may be most beneficial for those with an elevated risk for AD (e.g., women and APOE ε4 allele carriers) and potentially in established dementia due to AD. Given these limited findings, further work is needed to elucidate the potential role of coconut oil as a non-pharmaceutical therapeutic agent for those who are cognitively impaired and the potential use as a preventative intervention for mitigating cognitive decline.

3.3. Creatine

Recent investigations examining the use of creatine—a compound synthesized from amino acids (arginine, glycine, and methionine) that is rapidly delivered to skeletal muscles and the brain [132,246]—supplements have shown promising evidence in support of benefits for brain health [246], heathy cognitive aging [133], and age-related diseases such as AD [132]. Creatine levels tend to decrease while age progresses, which may

contribute to age-related changes in brain activity [247]. In older adults, people with higher resting creatine levels performed better on cognitively demanding tasks compared to those with lower levels [134,137], and intake of creatine was associated with cognitive benefits for intelligence [138], better overall cognitive functioning (from the National Health and Nutrition Examination Survey from 2001–2002 [130]), and improvements in memory abilities for global memory [138], long-term memory [135], and short-term memory [134]. Additionally, in a rat model, a creatine supplement was linked with neuroprotective benefits against Aβ-induced cytotoxicity on hippocampal neurons [139].

Findings regarding creatine and AD also suggest that this may be a potential therapeutic approach [248]. For instance, in patients with AD, creatine supplementation (20 g/day for 8 weeks) was associated with increased (~11%) creatine levels in the frontal and parietal brain regions, and improved global cognition, fluid cognitive abilities, working memory, inhibitory control, and oral reading abilities [136]. Although promising but limited evidence supports the use of creatine as therapeutic target for neurocognitive impairment, a review suggests that supplemental creatine has a greater public and commercial support compared to supporting evidence in the literature [249]. Notably, previous preliminary, limited and promising creatine investigations have variability in their study designs (e.g., cognitively normal vs. cognitively impaired populations, dosage, duration, small sample sizes), suggesting the need for further investigation to determine the effectiveness of creatine in neurocognitive populations.

3.4. Flavonoids

Emerging evidence in cognitively impaired populations has suggested the benefits of consuming flavonoids—classified as a polyphenolic metabolite, contributing to fruits', vegetables', and flowers' pigmentation—to combat cognitive decline [53,250]. Increased consumption of flavonoids has been linked with a reduced risk for objective cognitive decline [251], subjective cognitive decline [252], and AD [253–255]. Cognitive benefits have been reported across several types of flavonoids. For example, in cognitively healthy aging adults, consumption of cocoa-based flavonoid was associated with better cognitive performance for hippocampal-dependent memory performance, suggesting benefits for age-related cognitive decline and hippocampal-dependent memory function [256]. Interestingly, some findings from a recent review suggest that flavonoids may be neuroprotective because they modulate endoplasmic reticulum stress—the cellular process involving the accumulation of misfolded or unfolded proteins in the endoplasmic reticulum that plays an important role in the development in neurodegenerative diseases—through apoptosis and autophagy [257]. It is possible that the antioxidant and anti-inflammatory properties from these natural food compounds may provide a therapeutic option for treating AD, given that some findings suggest these compounds may stimulate cholinergic neurotransmission (aligning with conventional AD anti-cholinesterase medications) and suppress some AD-related pathology (e.g., beta-site amyloid precursor protein-cleaving enzyme 1 [258]).

3.4.1. Anthocyanin Flavonoids

Investigations with anthocyanins—a class of polyphenols characterized by red, blue, and purple pigments in fruits and flowers [259]—have demonstrated promising results for cognitive functioning. Particularly, the effects of blueberries have been well-documented [260,261]. For instance, consumption of blueberries was associated with an improvement in lexical access and associative memory abilities, and a decrease in daily life self-reported memory encoding difficulty in mid-to-late life adults with subjective cognitive decline [140], as well as improvements in task switching accuracy and repetition recall errors during a word list recall task in healthy aging adults [153,154]. The consumption of

blueberries may also increase neural activation in the left inferior parietal lobe, left precentral gyrus, and left middle frontal gyrus during a working memory task in patients with MCI [151]. Intake of blueberries with bilberry supplement showed enhanced hippocampal-dependent memory and neurogenesis in older adults at risk for dementia [141]. However, it is important to note that while cognitive benefits from blueberry consumption are supported within systematic reviews, the concluding evidence for blueberry consumption recommendations are limited due to the methodological heterogeneity [261].

Other anthocyanin investigations argue for similar benefits. In randomized, controlled trials, consumption of cranberries [142] and Montmorency tart cherry juice [152] improved memory performance in cognitive healthy older adults. In MCI populations, concord grape juice improved memory functioning [262], while elderberry juice improved visuospatial cognitive flexibility [149] and overall cognitive flexibility [150]. Anthocyanin consumption has also demonstrated neuroimaging effects with grape juice consumption, including improvements in regional perfusion in the right accumbens, caudate nucleus, and entorhinal cortex in healthy older adults [142], as well as reduced oxidative stress response and inflammation, stimulation of brain metabolism (as illustrated via PET imaging), and neurogenesis [145]. In a large post-mortem study (the Rush Memory and Aging Project), people with more strawberry and pelargonidin (anthocyanidin for orange-red hues in fruits, flowers, and vegetables) consumption had fewer phosphorylated tau tangles [146]. Additionally, anthocyanin has demonstrated other effects that may indirectly benefit cognitive health, such as consumption of elderberry juice resulting in reduced peripheral blood-based inflammatory markers in patients with MCI [149], and additionally, consumption of grapes has been suggested to promote a healthy gut microbiome (i.e., diverse gut bacteria [145]).

Despite evidence that frequent consumption of polyphenols (fruits and vegetables) may decrease the risk of probable Alzheimer's disease in a population based study [143] and one meta-analysis supporting cognitive benefits of polyphenols [144], conclusions are limited by the heterogeneity of available studies. For instance, a meta-analysis of anthocyanin clinical trials did not observe a significant difference in cognitive functioning among cognitively impaired and healthy adults [147], and a review of polyphenol clinical trials did not show conclusive neuroprotective effects for AD [148]. However, preclinical studies with polyphenols and AD posits that polyphenols (quercetin, resveratrol, Epigallocatechin-gallate, curcumin, and fisetin) exert neuroprotective effects [148]. The methodological heterogeneity of investigations with polyphenols [144] may further limit the clinical implications of polyphenols for preventative treatment in cognitively impaired populations; therefore, further work is warranted to elucidate their clinical utility.

3.4.2. Flavonoids with Coffee and Tea

Findings from previous investigations suggest that caffeine is neuroprotective against neurodegeneration [263], consumed in coffee [264] and tea [265]. In mid-to-late life adults (from a United Kingdom Biobank cohort study), drinking 2–3 cups of coffee or tea was associated with a reduced risk for developing dementia [155]. In older adults, daily coffee consumption was associated with 46% reduced risk of cognitive decline (OR = 0.54) in older adults [159], while greater self-reported habitual coffee consumption was associated with slower cognitive decline in executive functioning, attention, and overall cognitive function domains (from the Australian Imaging, Biomarkers, and Lifestyle study [158]). Greater self-reported habitual coffee consumption also showed a reduced risk for transitioning from MCI to AD, a slower rate of Aβ accumulation, and a lower likelihood of progressing to a higher Aβ burden status in cognitively healthy older adults [158]. A meta-analysis further supported these findings, showing that daily consumption of coffee (1 to 2 cups)

was linked with the lowest risk of developing cognitive disorders compared to those who did not consume coffee daily or had more than 3 cups of coffee a day [157].

Regarding tea drinking, greater tea consumption was associated with better focused and sustained attention, and psychomotor processing speed in older adults [160], and additionally, more frequent green tea consumption was associated with a reduced risk of incident dementia [161], and a 44% reduced risk of cognitive decline (OR = 0.56; [159]). Frequent green tea drinking was also associated with decreased level for cerebrospinal fluid total-tau protein AD biomarkers but not for Aβ or phosphorylated tau in cognitively healthy older adults (from the Chinese Alzheimer's Biomarker and LifestylE study [162]). However, findings from an AD mouse model (aged 3xTg-AD mice) showed that treatment with a green tea polyphenol epigallocatechin gallate and nicotinamide—a vitamin B3 precursor—was associated with restoring green tea-associated polyphenol levels and promoting the clearance of intraneuronal Aβ aggregates in hippocampal neurons [163]. Although these preclinical findings offer potential mechanistic insight into how green tea compounds may impact AD pathology and cognitive functioning, further human clinical trials are warranted to determine whether such effects are replicable in humans, given species-biological differences.

Interestingly, when considering overall caffeine consumption, women who self-reported caffeine consumption above the median levels of caffeine ($M_{\text{caffiene intake}}$ = 261 mg) had decreased risk of incident dementia or cognitive impairment as compared to those consuming below median amounts ($M_{\text{caffiene intake}}$ = 64 mg) in women aged 65+ years [156]. This finding is particularly important given that women are more likely to develop AD and dementia compared to men [266,267].

3.4.3. Other Flavonoids

Findings from other types of flavonoids have shown promising results in cognitively impaired populations. For instance, one review suggests that consumption of genistein—a flavonoid primarily found in soy-based products—is linked with rapid improvement in cognitive functioning and a reduction in Aβ accumulation [268]. Additionally, in an older adult Japanese cohort study, citrus-rich diets have been linked with a decrease in all-cause dementia [82]. In a rat model, findings showed that naringenin reversed cognitive impairment that was induced by investigating the neurotoxicant trimethyltin—an organotin compound linked with neuroinflammation, p-tau and Aβ accumulation, and oxidative stress in the hippocampus [269,270]—and hippocampal neuronal loss [271]. Other work with a dietary supplement, Ginkgo biloba extract EGb 761—derived from the dioecious *Ginko biloba* L. tree, which is native to Asia and rich in flavonoids, such as quercetin, kaempferol, and isorhamnetin—suggests that ECb 761 may have neuroprotective effects against AD pathophysiology (e.g., reduced p-tau and Aβ plaques, improved cerebral blood flow and mitochondrial function protection), but the therapeutic effect and underlying mechanism of this dietary supplement is unclear due to heterogeneity of methods and outcomes [272].

3.5. Vitamin Supplements

Evidence supporting the use of supplements for treating and preventing cognitive impairment are limited, but the work that exists shows the potential for promising cognitive benefits [178,273].

3.5.1. Vitamin B

There is interest in whether supplements of vitamin B help cognitively impaired populations, but there are discrepancies across previous investigations, potentially due to methodological differences [274]. In older adults, higher dietary intake of vitamins B2,

B9 and B12 was associated with better cognitive performance for global cognition [164,165], while B9 and B12 vitamins were associated with better categorical verbal fluency, immediate and delayed memory recall, processing speed, working memory and sustained attention [164]. Similarly, in older adults, greater dietary niacin (vitamin B3) was inversely associated with poor cognitive functioning for word learning, delayed recall, verbal semantic fluency and working memory (from the National Health and Nutrition Examination Survey from 2011–2014 [275]). Intake above the recommended dietary allowance for vitamin B2 [165] and greater dietary niacin (vitamin B3 [174,275]) was linked with a lower risk of cognitive decline in healthy older adults, while intake of vitamin B1 showed a borderline trend towards slowing cognitive decline in patients with amnesic MCI or mild AD [276]. Additionally, a J-shape relationship between the 5-year global cognitive decline rate and vitamin B1 intake has been proposed in cognitively healthy older adults—such that both low and excessively high intake may be associated with greater cognitive decline, while moderate intake may be protective [99]. Vitamin B1 may exert dose-sensitive effects on cognitive trajectories, whereas deficient intake of vitamin B1 may impair the thiamine-dependent neural processes in neurotransmission and energy metabolism [165]. Conversely, excessive intake of vitamin B1 may result in adverse long-term metabolic effects leading to neural compensatory response for the thiamine-dependent neural process in older adults [99].

Other work has shown that increased incidence of all-cause dementia was associated with elevated homocysteine levels [277]—a sulfur-based amino acid formed from methionine [278] that can be modulated by vitamin B and is linked with AD pathology [175]. Other studies revealed worse memory functioning with higher homocysteine in older adults with subjective cognitive decline or amnesic MCI (from the Czech Brain Aging Study [172]), as well as greater risk for cognitive dysfunction with low vitamin B12 or elevated homocysteine levels in older adults with the APOE ε4 allele [279]. Cognitively impaired older adults had higher proportions of folate deficiency, suggesting that folate (vitamin B9) may protect against cognitive impairment [168]. In adults with MCI, folic acid supplementation resulted in improved cognitive functioning [166], while in patients with symptomatic AD, folic acid and vitamin B12 supplementation resulted in better global cognitive functioning [167]. However, other work has shown that folic acid (vitamin B9) supplementation was associated with a ~35% higher risk for AD (HR = 1.34) and a ~61% higher risk for vascular dementia, but this was counteracted when it was combined with other B vitamins (from the 2006–2010 United Kingdom Biobank cohort study [169]), suggesting that the proper combination of vitamins is critical.

Intake of B vitamins have shown potential brain imaging effects in cognitively impaired populations. For instance, in MCI patients, intake of B vitamins was associated with a slower rate of brain atrophy [measured via volumetric brain magnetic resonance imaging (MRI) scans] in MCI patients [170], and intake of folic acid (vitamin B9) was associated with an improvement in plasma Aβ-related biomarkers [166]. In AD patients, folate (vitamin B9) and cobalamin (vitamin B12) were associated with increased cerebral blood flow [176], whereas folate (vitamin B9) was associated with a reduction in hippocampal and amygdalar volume, when given alone, but this reduction was counteracted when it was combined with other B vitamins [169], and homocysteine levels were correlated with greater white matter hyperintensity [176]. These discrepant AD findings with vitamin B suggest a synergistic benefit of combined vitamin B9 and B12 intake [176]. Additionally, greater dietary niacin (vitamin B3) intake modified AD biomarkers, including Aβ-42, phosphorylated JNK, and phosphorylated ERK1/2 in healthy older adults [174]. Further, meta-analyses support the preventative roles of vitamin B [173] and folate [177] in mitigating cognitive decline in older adults.

3.5.2. Vitamin D

In addition to vitamin B, vitamin D has shown cognitive benefits, such that serum vitamin D levels were associated with overall cognitive functioning [180]. In non-demented older adults (from the Washington Heights-Inwood Columbia Aging Project), greater intake of vitamin D from food sources was associated with a reduced risk for developing dementia [181], and the risk of dementia was found to be inversely related with serum 25-hydroxy vitamin D concentrations in individuals with type 2 diabetes (from the UK Biobank [182]). Longitudinal findings showed that vitamin D supplementation was linked with a longer dementia-free time and a lower dementia incidence rate (from the National Alzheimer's Coordinating Center database from 2005–2021 [183]), suggesting that low vitamin D levels may be associated with cognitive impairment [180]. Interestingly, lower vitamin D levels were associated with an elevated AD risk in those who have genetic risk for lower vitamin D levels [184], and findings showed that giving daily vitamin D supplementation (800 IU/day) resulted in improved cognitive functioning and decreased plasma Aβ-related biomarkers for Aβ42, amyloid precursor protein, β-site amyloid precursor protein cleaving enzyme 1, amyloid precursor protein messenger ribonucleic acid, and β-site amyloid precursor protein cleaving enzyme 1 messenger ribonucleic acid in AD patients [185]. Conversely, other studies did not reveal an association between vitamin D levels and incidence of dementia or cognitive impairment in Swedish older adult men [179]. The Cochrane Database of Systematic Reviews argued that available evidence, thus far, with vitamin or mineral supplementation does not support a meaningful effect for preventing cognitive decline [186] or a role for intervention once MCI is present [178]. Given the limited investigations examining vitamin D with cognitive impairment, variability in sample characteristics (e.g., non-demented older adults, AD patients, studies including all men), study design (longitudinal vs. trial), dosage of vitamin D, and baseline differences in vitamin D levels may contribute to these inconsistent findings. Further investigation of the potential benefits of vitamin D in populations without extant cognitive impairment may show the greatest benefits, given previous findings decreasing the risk of dementia [181–183] and improved cognitive functioning [180,185].

Overall, intake of vitamin D may play a role in cognitive functioning in aging populations, but the evidence for neurocognitively impaired populations remains mixed. Future clinical trials examining the impact of vitamin of D on cognitive functioning in such populations while considering vitamin D baseline differences, cognitive status, and genetic risk is imperative.

3.5.3. Other Vitamins

Studies have shown better cognition in people with higher vitamin C levels (i.e., better attention, processing speed, recall and recognition abilities [187]) and in those with higher levels of vitamin B6 [280], while those with higher vitamin E levels had lower risk for development of dementia [188] and a slower rate of cognitive decline in AD patients receiving combination therapy with vitamin E and cholinesterase inhibitors as compared to cholinesterase inhibitors alone [190]. However, findings supporting the use of vitamin E for neurocognitive impairment prevention are inconsistent. A longitudinal randomized clinical trial did not observe vitamin E (400 IU/day) benefits for the prevention of AD [189], while another trial showed that vitamin E (2000 IU/day) resulted in slower functional decline in older adult men with mild-to-moderate AD [191]. It is possible that vitamin E may provide cognitive benefits in those with extant cognitive impairment, but the heterogeneity in study design, variation in genetic predisposition, cognitive status, and dosage may contribute to inconsistent findings for vitamin E as potential therapeutic agent in cognitively impaired populations, warranting further investigation.

3.5.4. Multivitamins

Intake of multivitamin/mineral supplements may support adequate micronutrient intake [194]. The intake of multivitamins has been proposed to have cognitive and psychological functioning benefits but the work is limited [195]. Findings from clinical trials showed better immediate recall memory (from the COcoa Supplement and Multivitamin Outcomes Study Web [197]) and improved episodic memory, along with modest benefits for global cognitive functioning in older adults [198]. Meta-analyses further support these findings, showing that multivitamin–mineral supplements were associated with cognitive benefits for global cognitive functioning and episodic memory [198].

Regarding cognitively impaired populations, multivitamin–mineral supplementation resulted in less cognitive decline compared to the previous year, along with higher global cognitive and executive functioning performance in patients with MCI (from the COcoa Supplement and Multivitamin Outcomes Study Web for the Mind [196]). Vitamins have also demonstrated benefits for targeting various AD pathological markers, but it is possible that the combination of vitamins with other compounds may have a synergistic effect for preventing AD-related cognitive impairments [199].

3.5.5. Vitamin Deficiency

Complementing the suggested benefits of vitamin supplements with neurocognitive impairment, vitamin deficiency may contribute to AD pathophysiology [281]. In Korean cognitively normal older adults, lower zinc levels in diets have been found to be associated with greater Aβ deposition (measured via PET scans; [282]). Systematic reviews and meta-analyses also indicate that low vitamin D levels may contribute to the development of dementia [283–285]. However, few randomized clinical trials with vitamin D supplementation have attempted to address whether vitamin D supplementation, particularly in those with low levels, may prevent cognitive impairment [285]. Work investigating vitamin supplementation and AD suggests that adequate vitamin B consumption may be beneficial by reducing homocysteine levels, indirectly protecting against AD pathology development [286]. Specifically, vitamin B6 and B12 [170,175], and folic acid (vitamin B9 [177]) may mitigate the association between homocysteine levels with neurocognitive impairment, with studies reporting high serum folate levels and normal homocysteine levels associated with reduced cognitive impairment in older adults [168]. In neurocognitively impaired populations, lower serum folate (vitamin B9) and vitamin B12 levels, and elevated homocysteine levels were observed in MCI and AD patients [166], while higher homocysteine levels and lower folate acid levels were correlated with an increased risk for AD [287]. Interestingly, supplementation of methionine (essential amino acid typically found in fish, meat, and dairy products) at a higher ratio relative to homocysteine may reduce the rate of brain atrophy and the risk of dementia in older adults [288]. While vitamin deficiencies, particularly for folate and vitamin B12, appear to contribute to cognitive impairments and supplementation of these vitamins may mitigate the impact of homocysteine, more investigations and clinical trials are needed to determine impact of vitamin deficiencies on the development of neurocognitive impairments.

3.6. Other Foods That Should Be Noted

Other foods and flavonoids may benefit cognitive functioning and combat cognitive decline and dementia. Cocoa-flavonoids appear to enhance cognitive functioning and may provide a potential dietary intervention for mitigating cognitive decline [202], potentially including in cognitively impaired populations [203]. Longitudinal findings have found that dietary supplementation of cocoa extract helped hippocampal-dependent memory function (from the COcoa Supplement and Multivitamin Outcome Study [204]), and chocolate

consumption appeared to be linked with a slower rate of cognitive decline (from the Three-City study [200]) in healthy older adults. Despite these promising findings, further work examining this relationship between cocoa flavonoids with cognitive functioning, specifically in AD and dementia populations, is warranted.

Mushrooms have also demonstrated beneficial effects for neurocognitive health across the lifespan [289] and promising results for combating AD related pathology [209]. Edible and medicinal mushrooms may enhance neurite growth within the brain through stimulation of nerve growth factor [210], protect against neuronal cell death (apoptosis; via lysophosphatidylethanolamine from the *G. frondosa* mushroom variant in animal models [211,212]), development of AD pathology (i.e., from *G. lucidum* mushrooms; [213]), and may reduce neurodegeneration with regular mushroom consumption (assessed by effects on neuroinflammatory response, oxidative stress and apoptosis [214,215]). In older adults, greater consumption of mushrooms was associated decreased risk for developing all-cause MCI [206] and all-cause dementia [207], and was associated with better cognitive functioning for attention and processing speed, and verbal episodic memory (from the 2011–2014 from the National Health and Nutrition Examination Survey [208]). However, further work is warranted to further elucidate the neurocognitive benefits in aging adults, particularly for those with extant cognitive impairment.

In addition to mushrooms, in non-demented older adults, curcumin (active ingredient in turmeric) also has been linked with improved memory and attention abilities, along with decreased accumulation of Aβ and tau (assessed by positron emission tomography (PET) scans [216]). In preclinical animal models, findings generally support the role of curcumin with improving cognitive functioning for spatial learning and memory, and reducing oxidative stress [217]. Additionally, in Korean older adults who consume ginseng, findings showed an association between lifetime consumption of ginseng and better cognitive functioning [216].

Eggs are an excellent source of macronutrients and micronutrients—including high-quality protein, essential vitamins (i.e., vitamins A, D, E, K, B1, B2, B5, B6, B9 and B12), essential minerals (i.e., phosphorus, calcium, potassium, copper, iron, magnesium, manganese, selenium and zinc), and fatty acids (i.e., omega-3 and omega-6, with higher amounts of omega-3; [290]). In older adults (from the Rush Memory and Aging Project cohort), weekly consumption of more than one egg was associated with a ~47% reduced risk of AD-dementia (HR = 0.53), and a ~38–49% reduced risk for AD pathology (HR ranged 0.51 to 0.62 [218]).

Anti-inflammatory diets (as previously discussed) have been linked with better cognitive aging and potential neuroprotective effects in reducing the risk or progression of AD [65,291], while higher inflammatory diets are associated with increased AD mortality risk (1.5-fold) in middle-aged adults [292]. Nevertheless, investigations are needed to determine the potential underlying mechanisms contributing to these observed benefits [293].

3.7. Avoidance of Ultra-Processed Food

Avoidance for ultra-processed foods—characterized as foods manufactured through industrial processing typically involving 5+ ingredients, such as emulsifiers, anticaking agents, interesterified oils (industrially modified fats designed to alter the melting point of the fat), etc. [294]—has been suggested to be protective against risk for all-cause dementia [295], while greater consumption of ultra-processed foods was found to be linked with greater cognitive decline [220]. In older adults (from the National Health and Nutrition Examination Study from 2011–2014), findings showed a U-shape relationship between ultra-processed food and verbal semantic fluency, and attention and processing abilities: both high and low levels of ultra-processed food consumption were associated with worse

cognitive functioning, whereas moderate consumption of ultra-processed food was associated with better cognitive functioning in older adults [219]. However, the worse functioning among those with low levels of ultra-processed foods may have been driven by dietary changes in individuals who changed their diet after developing chronic conditions [219]. Ultra-processed food consumption is associated with an inflammatory response and oxidative stress [296]. The high consumption of ultra-processed food may contribute to elevated neuroinflammation, which has been linked with poor cognitive functioning in aging adults [297]. Conversely, low consumption of ultra-processed foods may reflect restricted (see Section 2.2) or unbalanced diets (i.e., low overall food intake with residual ultra-processed foods), potentially leading to nutrient deficiencies that impact cognitive functioning [219].

Regarding AD and dementia findings, intake of ultra-processed food was linked with higher risk for AD [221,222] and dementia [223]. Specifically, a 2.5-fold increased risk for AD was associated with excessive consumption of ultra-processed food (10+ servings a day) in mid-to-late life adults [221]. Ultra-processed diets have been linked with increased inflammation, which can lead to several chronic diseases [224], along with smaller total brain volume, smaller total gray matter volume, and larger lateral ventricle volumes in older adults (from the Framingham Heart Study [225]). Further investigations examining this relationship are warranted to determine potential underlying mechanisms contributing to increased risk for dementia and AD, as well as how ultra-processed foods may contribute to overall cognitive health across the lifespan. Such findings may inform potential tailored preventative treatment avenues to reduce the risk of onset of cognitive impairment.

4. Individual Agents with Potential Impact

Dietary interventions contain an array of nutrients with individual food components contributing to distinct nutritional profiles. Dietary intervention advice as potential target for preventing neurocognitive impairment may involve interactive benefits among the individual nutrients. Nevertheless, there is evidence for several specific individual nutrients that is important to note.

First, resveratrol (mostly found in red grapes) has been found to improve memory performance in healthy older adults [298] but not for patients with MCI [299]. Resveratrol also preserved hippocampal volume and connectivity in patients with MCI [299], along with improved hippocampal glucose metabolism, and hippocampal activity in healthy older adults [298]. In aged mice, resveratrol was associated with reversing cognitive disturbances that were induced by a high fat diet [300], along with promotion of neuronal rejuvenation [300], and reversal of the effects of cholesterol [301]. In AD mouse models, resveratrol was found to modulate cholesterol metabolism and processing of amyloid precursor protein in the isoprenoid mediation of the processing of Aβ in the SAMP8 mouse model of AD [302].

Second, there is support (albeit limited) for the genus Salvia (i.e., sage) with potential cognitive and neurological effects in mitigating dementia and AD, yet further investigations are needed to further understand the effects contributing to cognitive functioning and neurodegeneration [303].

Third, the use of oroxylum indicum—a Ayurvedic medicinal product that is traditionally used in various Asian countries—extract was found to increase cognitive functioning for episodic memory in older adults with cognitive complaints [304].

Fourth, animal models examining specific nutrients have suggested potential neuroprotective effects for dementia for the following nutrients: astaxanthins (derived from marine micro-organisms, such as microalgae [305]), centella asiatica (a traditional medicine in Ayurvedic and Chinese cultures [305]), epigallocatechin-gallate (polyphenol in green

tea [306,307]), quercetin (bioflavonoid, prevalent in fruits and vegetables [308]), yokukansan (herbal medicine that is traditional in Japanese cultures [309]), N-acetylcysteine (commonly used antioxidant [310]), berberine (protoberberine alkaloid used in traditional Chinese medicine [311]), walnut dietary supplementation (high in antioxidants and protective against neuroinflammation [312]), β-lactolin (whey-derived lacto-tetrapeptide [313]), royal jelly (secreted from worker honeybee hypopharyngeal and mandibular glands [314]), boldine (alkaloid that is derived from Chilean tree pumus boldus bark and leaves [315]), and Cistanche flavonoids (polyphenols that activate the Keap1-Nrf2-ARE signaling pathway and enhance oxidative defense [316]).

Fifth, traditional medicine practices have shown benefits for combating cognitive decline and neurodegenerative diseases potentially through mechanisms that may target aging-related cellular and molecular pathways through oxidative stress modulation and mitochondrial protection [317]. For example, in amnesic MCI patients, the use traditional Chinese medicine found specific altered brain activity, such as in the dorsolateral prefrontal cortex [318]. Emerging evidence has also supported the benefits of curcumin (i.e., turmeric) that is traditionally used in Indian and Chinese cuisine in AD and healthy aging populations [319], along with a traditional medical multi-herb, Sheng-Hui-Yi-Zhi, in AD populations [177].

Sixth, in an AD mouse model, electroacupuncture (middle point of the parietal bone of mice) has impacted cognitive functioning for spatial working memory and learning through regulating tau phosphorylation [320].

Seventh, intermittent fasting, has been shown to mitigate the increase of brain lipoprotein lipase levels [321], improve working memory abilities, and reduce neuroinflammation, Aβ plaques and tau pathology [322] in AD mouse models. Another transgenic (3xTg) AD mouse model showed that a calorie-restricted diet without prolonged fasting was associated with reduced Aβ plaque density and neuroinflammation, but not with improvements in tau pathology [322]. It is possible that intermittent fasting may result in the utilization of ketones as an alternative energy source instead of glucose in a calorie-restricted diet, potentially contributing to the neurocognitive benefits [323,324], as with the ketogenic diet described above.

Eighth, antioxidant and serum carotenoids—specifically lutein and zeaxanthin, and β-cryptoxanthin serum levels—were inversely related with incidence of AD and all-cause dementia [325].

Ninth, in a quercetin-fed mouse model, findings suggests that quercetin may exert neuroprotective effects for promoting regeneration of normal functioning neurons that were impaired by D-gal [326].

Tenth, high levels low-density lipoprotein cholesterol levels have been reported to be associated with increased risk for AD in several reviews [327–330]. Other work showed inconsistent associations between statin medicine (lowering cholesterol) use and the risk of Alzheimer's disease and related dementias (ADRD), with findings revealing ADRD diagnoses increased by ~46% (HR = 1.46) with the first initiation of statins, whereas after one year there was no difference in ADRD incidence (HR = 1.00; data from Kaiser Permanente Northern California [331]).

Despite these promising effects, prospective investigations are needed to elucidate the effects of specific individual agents in food, such as polyphenols, antioxidant, and vitamin supplementation levels to inform potential tailored interventions in mitigating neurocognitive impairment. Combination therapies may also merit significant further investigation, as is supported by the synergistic effects of the combination of the polyphenol quercetin and DHA on inflammatory and oxidative responses [332].

5. Gut Microbiome

Emerging evidence emphasizes the dynamic interplay between the gut and brain—referred as the "gut-brain axis"—and suggests that altered gut microbiota may be associated with cognitive impairment [46]. In patients with cognitive impairment (MCI or AD), findings showed lower levels of *Dorea*—a diverse genus of bacteria in gut microbiome contributing to a healthy gut—and elevated biomarkers of gut dysfunction, including diamine oxidase (can indicate mucosal damage and impaired ability to breakdown histamine), D-lactic acid (linked with increased intestinal permeability and impaired barrier functioning), and endotoxins (proinflammatory markers; [47]). Patients with AD dementia, MCI, and subjective cognitive decline (from the Amsterdam Dementia Cohort study) were found to have a lower abundance of specific groups of microbiota (*Lachnospiraceae* family for *Roseburia hominis*, *torques*, *Marvinbryantia* spp., and *Lacnoclostridium*) that were predictive for positive Aβ and phosphorylated tau [333]. However, other work did not reveal differences in alpha (i.e., within sample variety) and beta (i.e., between sample variety) diversity between cognitively normal controls and patients with MCI [334]. Gut microbiome dysbiosis may be associated with cognitive impairment [47], with findings showing decreased abundance of gut microbiome genera was associated with attention and executive functioning abilities in MCI patients [334]. Findings suggest that gut microbiome interventions may be a plausible strategy for combatting neurocognitive impairment, with previous findings showing a prebiotic intervention increased the abundance of *Bifidobacterium*—a genus associated with a healthy gut microbiome—and improved global cognitive functioning in older adults [335], along with a nicotinamide mononucleotide treatment—a compound linked with mitigating AD-related pathology—which increased intestinal short-chain fatty acid-producing bacteria (e.g., *Lactobacillus* and *Bacteroides*) and improved AD related pathology in a transgenic mouse model [336]. This is important given that a recent review suggests that the use of nicotinamide adenine dinucleotide precursors, including nicotinamide mononucleotide, showed promising benefits for AD treatment [337].

Several systematic reviews also indicate further support for the potential role that the gut microbiome may play in AD pathogenesis, and potential targeted therapeutic interventions [338–345]. However, further investigations and clinical trials are needed to elucidate the potential benefits, treatment options, and pathogenetic mechanisms underlying AD for the impact of specific gut microbiota in cognitively impaired populations. Findings from such investigation may inform potential avenues for early preventative treatment for onset of cognitive impairment.

5.1. Modifiable Factors for Microbiome–Gut–Brain Axis

Diet plays a critical role in the gut microbiome [346,347]. Several factors have been suggested to affect the gut microbiome in daily diets, such as fiber, carbohydrates, proteins, micronutrients, short-chain fatty acids, processed food consumption [348], probiotics [349], polyphenols [350], and fermented foods [351]. Therefore, it is possible that diet and food interventions may support a healthy and diverse gut microbiota, which may contribute to healthy cognitive aging and mitigate further cognitive decline. Table 3 summarizes the gut microbiome and potential modifiable factors for the microbiome-gut-brain axis with age-related cognitive functioning and in neurocognitively impaired populations.

5.1.1. Fiber

One modifiable dietary factor to support a healthy gut microbiota is fiber [352]. A decrease in fiber has been linked with adverse impact on gut microbiota (quantified by reduced microbiota diversity) leading to several detrimental health conditions, including cancer, diabetes [352], gastrointestinal diseases, and aging-related inflammation [348].

This is important given that the Western diet is typically comprised of ultra-processed foods and small amounts of dietary fiber [348]. Western countries also tend to have a higher incidence of dementia [353]. Recent systematic reviews and meta-analyses have suggested the benefits of dietary fiber interventions in support of a healthy gut microbiota [346,347], modulating the immune system [354], and reducing inflammation [355], potentially impacting cognitive functioning. However, prior work examining the potential benefits of fiber and the gut microbiota for cognitive impairment is limited. In the work that exists, findings showed elevated fiber intake was inversely correlated with AD imaging biomarkers (18-F fluorodeoxyglucose uptake; [101]) and higher intake of soluble fiber was linked with a lower risk of developing disabling dementia [356] in mid-to-late life adults. Fiber was also found to decrease the burden of white matter hyperintensities in dementia-free older adults [357]. However, a large study with cognitively normal older adults did not observe a correlation between Aβ burden and fiber intake [358]. Given the limited studies investigating associations between fiber, the gut microbiota, and cognitive impairment, further investigations examining fiber subtypes (e.g., soluble vs. insoluble), cognitive status, dietary patterns, and specific AD biomarkers are warranted to delineate this potential relationship.

Limited findings from rodent models have also provided support for dietary fiber intake with benefits for cognition and AD. In a familial AD (5xFAD) mouse model, lack of fiber impaired hippocampal neurogenesis and accelerated cognitive decline for memory functioning [359], while in a wild-type mouse model, low fiber intake was associated with gut microbiota dysbiosis and was associated with hippocampal synaptic loss, suggesting that fiber intake may reduce the risk of cognitive decline [360]. Overall, the limited evidence between fiber intake and cognitive functioning suggests that fiber may be a critical factor in the associations between the gut microbiome, and cognitive functioning and AD pathology. Further investigations and clinical trials examining this relationship are warranted to determine the potential therapeutic benefits of fiber in preventing neurocognitive decline.

5.1.2. Fatty Acids

Dietary fat impacts the gut and intestinal microbiome, and a high fat diet can be harmful [348]. However, short-chain fatty acids (e.g., omega-3 fatty acids) have been suggested to mitigate dementia (see Section 3. Specific Dietary Components earlier in this paper; [106]), as described previously in this review, and have also been found to support the gut microbiome [361], especially through fermentation of dietary fiber [362]. Reviews examining short-chain fatty acids and the gut microbiome with AD (in human and rodent models) suggest that short-chain fatty acids may play a critical role in the pathophysiological process of AD [362,363]. In patients with AD, significantly lower levels of short-chain fatty acids were observed and linked with gut dysbiosis [364]. In contrast, in patients with MCI, a modified Mediterranean ketogenic diet (rich in healthy fatty acids) was associated with greater gut microbiota diversity, increased levels of short-chain fatty acids, decreased cerebrospinal fluid Aβ and tau proteins [365], and reduced levels of GABA and GABA-producing microbes (*Alistipes* sp. CAG:514 [366]). Greater amounts curcumin in this diet was linked with lower levels of bile salt hydrolase-producing microbes in prediabetics with MCI, suggesting potential alterations in bile acid metabolism and nutrient absorption [366]. Additionally, a review of the limited clinical trials examining omega-3 fatty acids and the gut–brain axis with cognitively impaired older adults observed a modest effect on cognitive functioning improvement in MCI patients but did not observe effects in AD patients [339]. It is also important to note that these clinical trials were short-term (4 to 18 months) randomized trials with small sample sizes, which may contribute to the limited findings.

Table 3. *Summary of Findings for the Gut Microbiome and Modifiable Factors for the Microbiome-Gut-Brain Axis Across Cognitive Stages and Neuropathological Outcomes*. Summary of the gut microbiome and potential gut microbiome modifying factors across cognitive stages and associated changes with neuropathology. "Yes" indicates studies with findings in support of each category presented. "Mixed" indicates that studies that have findings in support or null findings for each category. The dashes indicate insufficient research in that category. Given the emerging research in this field, we have highlighted findings that are suggest promising findings but are not replicated in other studies as "(limited)". (MCI = mild cognitive impairment; AD = Alzheimer's disease.).

Gut Microbiome and Modifiable Factors	Delays MCI Onset [References]	Reduces Risk for AD Dementia/Neurocognitive Decline [References]	Reduces MCI-to-Dementia Conversion [References]	Improves Cognitive Functioning in Dementia Populations [References]	Improves Age-Related Normal Cognitive Functioning [References]	Reduces AD-Related Pathology/ Neurophysiology [References]
Gut Microbiome	Mixed [46,47,334]	Mixed [46,334]	Mixed [333]	Mixed [335]	Yes [335]	Yes [333,336,337]
Fiber	Mixed [356,357]	Mixed [101,367,368]	Yes (limited) [358]	--	Yes [355,359,360]	Mixed [101,359,360]
Short-Chain Fatty Acids	Mixed [363,365]	Mixed [361,362,364]	Yes (limited) [339]	Yes (limited) [339]	Mixed [355,357,359,360]	Mixed [101,359,360]
Polyphenols	Mixed (limited) [369]	Mixed (limited) [350,370–372]	--	Yes (limited) [369]	--	Yes (limited) [369]
Fermented Foods/Probiotics	Mixed (limited) [373,374]	Mixed (limited) [375,376]	Yes (limited) [377]	Yes [374,377,378]	Yes [373]	Yes (limited) [378]
Acupuncture/ Moxibustion	Mixed (limited) [379]	Mixed (limited) [379]	--	--	--	Mixed (limited) [379]

Regarding mouse models of AD, supplementation of short-chain fatty acid was linked with an increase in Aβ plaque deposition [380,381] and tau tangles, along with elevated levels of polyunsaturated fatty acid metabolites and their associated oxidative enzymes in the brain [381] in germ-free AD mice (i.e., mice free of any bacteria, beneficial or otherwise). Similarly, in wild type mice, findings showed that the ketogenic diet was associated with increased inflammation and hypoxia, as well as worse memory and cognitive flexibility ability performance, which collectively contributed to an increased risk for cognitive impairment [382]. Conversely, in other work with an AD mouse (with the APOE ε4 allele) model, the ketogenic diet was associated with improved alpha and beta gut microbiota diversity, cognitive functioning for learning, memory and executive functioning, and brain metabolites for neurotransmitter balance, mitochondrial functioning, lipid metabolism, and redox homeostasis—with female AD mice demonstrating the greatest benefits for restoring gut microbiota diversity and brain metabolites [383]. Findings from these rodent models suggest that gut microbes may influence the metabolization of polyunsaturated fatty acids, and these metabolites may drive neuroinflammation contributing to accelerated AD pathogenesis. However, findings from these models also suggest that individuals who are genetically vulnerable to AD (i.e., APOE ε4 allele carriers) may benefit from a ketogenic diet by attenuating neuroinflammation and oxidative stress states, while enhancing cognitive functioning. Other work suggests that increasing short-chain fatty acid producing gut bacteria may provide anti-inflammatory and antioxidant benefits in the brain [375]; therefore, prospective studies are need to further understand their role AD pathology.

5.1.3. Other Gut Microbiome Modifiable Factors

Several other factors have been suggested to impact the gut microbiota and serve a potential role in neurocognitive impairment disorders, but findings regarding these associations are limited. First, a bidirectional relationship between polyphenols and the gut microbiome has been observed [350], and several reviews document the potential roles of polyphenols and the gut microbiota in neurodegenerative diseases [370–372]. In the work that exists regarding these associations in those with AD or MCI, findings showed an improvement in memory functioning, decreased gut and brain inflammation levels, and increased levels of 21 gut metabolites with a blueberry-mulberry extract in a mouse model of AD [369]. Second, fermented foods have shown to promote healthy gut microbiota [375]. This may be due to the probiotic and/or prebiotic properties that are typically found in fermented food [376]. Clinical trials have shown that probiotic supplementation improved gut microbiota diversity [373] and resulted in cognitive benefits in patients with MCI [373,374] and AD [377]. In a triple transgenic mouse model of AD (3xTg-AD), long-term administration of a multi-strain probiotic formula was associated with an improvement in memory functioning, along with reduced Aβ deposition and neuroinflammation [378]. Lastly, a recent review suggests that acupuncture and moxibustion therapy may regulate gut microbial homeostasis through the neuroendocrine system by improving intestinal inflammation and suppressing excessive immune responses in cognitively impaired populations [379]. Overall, several factors have been suggested to modulate the gut microbiota and may provide neurocognitive protection, but investigations are limited. Prospective investigations and trials with replication studies are needed to elucidate this relationship and potentially inform tailored therapeutic interventions to mitigate cognitive decline.

6. Other Important Non-Dietary and Non-Nutritional Modifiable Factors

In addition to dietary- and nutrition-related factors with cognitive decline in aging populations and patients with dementia, it is important to briefly note other potential

modifiable factors that have also been investigated and demonstrated benefits in mitigating neurocognitive impairment. A summary of findings for age-related cognitive functioning and neurocognitive impairment populations for each factor discussed in further detail below is presented in Table 4.

6.1. Cardiovascular Factors

Cardiovascular diseases have been frequently linked with AD and dementia [384] with elevated risk observed across the lifespan [385–387]—including those with early onset cardiovascular disease before the age of 60 [388], mid-life cardiometabolic disease [389], and mid-life adults and late-life adults with ideal cardiovascular health metrics were found to have decreased risk of dementia (from the Finnish Cardiovascular Risk Factors, Aging, and Dementia study [385]). In older adults who are carriers of the APOE ε4 allele, cardiovascular disease was associated with elevated the risk of AD by ~129% (HR = 2.29 [386]), whereas other work did not observe an association between cardiovascular health and the APOE ε4 allele-associated risk of dementia [390]. Although the APOE ε4 allele is associated with an elevated risk factor for AD and dementia [116], diagnosed cardiovascular disease may exacerbate this risk in those who are genetically vulnerable, whereas poor overall cardiovascular health may attenuate or obscure the impact of APOE ε4 allele on AD and dementia risk. On the other hand, mid-to-late life adults with cardiovascular disease who met the recommended guideline levels for lifestyle factors (i.e., smoking, diet, physical inactivity, and body mass index; [388,391]), or who met the intermediate or ideal levels of cardiovascular health metrics [385] had a lowered risk of dementia and a slower trajectory of cognitive decline [392]. In young to middle-aged adults, cardiovascular risk factors across the lifespan were associated with a greater cognitive decline and associations were more pronounced in early adulthood (Coronary Artery Risk Development in Young Adults study [387]). A recent meta-analysis provides further support that cardiovascular diseases and associated risk factors are generally associated with dementia, and findings suggest that strategies targeting cardiovascular disease prevention may reduce the prevalence of dementia [393].

6.2. Environmental Factors

Environmental factors have been proposed to contribute to dementia, such as air quality, trace elements, toxic heavy metals, occupational-related exposures, etc. [394,395], with findings showing more support for an association with air pollution and incidence of dementia [394,396]. For example, fine air pollutant particle ($PM_{2.5}$) exposure was associated with an increased risk of AD development (95% increased risk [397,398]), with a greater risk in heavier polluted regions (~120% increased risk [397]) and in males and Native Americans with increasing $PM_{2.5}$ exposure [398]. Air pollutants may trigger the oxidative stress response [399], leading to development of AD pathology [398–400], particularly with higher fine particulate matter ($PM_{2.5}$) concentrations in the environment, which have been associated with Aβ plaques in MCI patients [401] and increased dementia severity [400]. Environments with greater exposure to air pollution were associated with higher levels of AD pathology biomarkers in cognitively normal mid-to-late life adults with an increased risk for AD (APOE ε4 allele carriers [402]) and with all-cause dementia [403]. A review investigating environmental pollutants with AD and Parkinson's disease in epidemiological studies further supports that exposure to environmental pollutants (e.g., metals, pesticides, nanoparticles) increases the risk for these neurodegenerative diseases [404]. Lowering exposure to air pollutants may provide protection against neurocognitive impairment but further work is needed to understand this relationship, given inconsistent and limited findings.

Table 4. *Summary of Findings for Other Important Non-Dietary and Non-Nutritional Modifiable Factors, and Non-Pharmacological Based Approaches Across Cognitive Stages and Neuropathological Outcomes*. Summary of the non-dietary and non-nutritional modifiable lifestyle factors, and non-pharmacological approaches for acupuncture and music therapy findings across cognitive stages and associated changes with neuropathology. "Yes" indicates studies with findings in support of each category presented. "Mixed" indicates that studies have findings in support or null findings for each category. The dashes indicate insufficient research in that category. "Limited" indicates findings from single or small-scale studies. (MCI = mild cognitive impairment; AD = Alzheimer's disease.).

Non-Dietary and Non-Nutritional Modifiable Factors	Delays MCI Onset [References]	Reduces Risk for AD Dementia/Neurocognitive Decline [References]	Reduces MCI-to-Dementia Conversion [References]	Improves Cognitive Functioning in Dementia Populations [References]	Improves Age-Related Normal Cognitive Functioning [References]	Reduces AD-Related Pathology/ Neurophysiology [References]
Cardiovascular Disease	Mixed [386,388]	Yes [384,385,389,391,393]	Mixed (limited) [390]	--	Yes (limited) [387,392]	Mixed (limited) [386,390]
Cardiovascular Health Metrics	Yes (limited) [385]	Yes [385,391,393]	--	--	Yes [387,392]	--
Air Pollution	Mixed [397,403]	Yes [394,396,397,403,404]	--	--	Mixed (limited) [405]	Yes (limited) [398–400,402,406,407]
Neighborhood Greenness/Natural Features	Yes (limited) [408]	Yes (limited) [405]	--	--	Yes (limited) [405]	--
Neighborhood Socioeconomic Status/Deprivation	Mixed [409]	Yes (limited) [407,409]	--	--	Mixed [405]	Yes (limited) [406,407]
Age-Related Hearing Loss	Mixed [410,411]	Yes [412–416]	--	Mixed [411,417]	Yes (limited) [417]	Yes (limited) [418]
Age-Related Vision Loss	Mixed [410,419]	Yes (limited) [412,419]	--	--	--	--
Dual Sensory Impairment	Yes (limited) [419]	Yes [414,415]	--	--	--	--
Hearing Aid Use/ Sensory Restoration	Yes (limited) [420,421]	Yes [420–422]	--	Yes (limited) [422]	Yes (limited) [421]	--
Cognitively Stimulating & Leisure Activities	Yes (limited) [423]	Yes [424–427]	--	--	Yes (limited) [428]	Yes (limited) [429–431]
Cognitive Training	Yes (limited) [432]	Yes [431,433]	Yes (limited) [426]	Yes [434,435]	Yes (limited) [433]	Mixed (limited) [436,437]
Cognitively Engaging Occupation/ Employment	Yes (limited) [426,427]	Yes (limited) [431,438]	--	--	Yes (limited) [431]	Yes (limited) [430]

Table 4. *Cont.*

Non-Dietary and Non-Nutritional Modifiable Factors	Delays MCI Onset [References]	Reduces Risk for AD Dementia/Neurocognitive Decline [References]	Reduces MCI-to-Dementia Conversion [References]	Improves Cognitive Functioning in Dementia Populations [References]	Improves Age-Related Normal Cognitive Functioning [References]	Reduces AD-Related Pathology/ Neurophysiology [References]
Physical Activity	Yes [439–441]	Yes [441–443]	Mixed (limited) [444,445]	Yes [443,446,447]	Yes [448,449]	Yes (limited) [450–452]
Social Engagement	Yes (limited) [453,454]	Yes [455–458]	--	Mixed [459]	Yes (limited) [454]	Yes (limited) [459]
Leisure Activities	Yes (limited) [441,460,461]	Yes [425,441,462–464]	--	Yes (limited) [462]	Yes (limited) [461]	Yes (limited) [463,464]
Depression	Yes (limited) [465,466]	Mixed [393,467,468]	--	--	Mixed [469]	Mixed [470]
Anxiety	Yes (limited) [465,471]	Yes (limited) [472–474]	--	Mixed [474]	Mixed [470]	Yes (limited) [465]
Positive Age Beliefs	Yes (limited) [475]	Yes [475,476]	--	--	Yes (limited) [477,478]	Yes (limited) [476,479]
Mindfulness	Mixed [480,481]	Mixed [482,483]	Mixed (limited) [482,484]	Mixed [481,485]	Mixed [485,486]	--
Mediation/Movement-Based Meditation	Yes (limited) [487,488]	Yes (limited) [489,490]	--	Yes (limited) [488,491]	Yes (limited) [492,493]	Yes (limited) [492]
Self-Reappraisal/ Self-Reflection	Yes (limited) [494]	--	--	Mixed [495]	Yes (limited) [494]	--
Stress	Yes [496,497]	Yes [498,499]	--	Mixed [500,501]	Yes (limited) [502]	Yes (limited) [503–505]
Environmental Stressors	Mixed [394,407]	Mixed [406,506]	--	--	Mixed [507]	Yes (limited) [508]
Sleep Health	Mixed (limited) [509–511]	Yes [511–514]	--	Yes (limited) [467]	Mixed (limited) [511,515]	Yes (limited) [511,516]
Non-Pharmacological Approach for Acupuncture	Yes (limited) [517]	Yes (limited) [518,519]	Mixed (limited) [520,521]	Yes (limited) [518,519]	--	Mixed (limited) [521]
Non-Pharmacological Approach for Music Therapy	Yes (limited) [522]	Yes [523–526]	Yes (limited) [527]	Yes [525,526,528]	Yes (limited) [529]	Mixed [528,529]

In additional to environmental air pollutants, other environmental–psychosocial factors have also been proposed to contribute to cognitive impairment [395,530]. For instance, greater neighborhood disadvantages (e.g., house quality, employment, education, income, etc.) were associated with elevated AD cerebrospinal fluid YKL-40 and tau biomarkers in older adults (from the Vanderbilt Memory and Aging Project [406]), as well as an ~8% increase in developing AD neuropathology, and living in the most disadvantaged neighborhoods was associated with an approximately two-fold (OR = 2.18) increased risk for AD neuropathology [407]. On the other hand, in aging adults, the presence of green spaces and natural features in neighborhoods (i.e., "neighborhood greenness") was associated with a decreased risk for dementia [408] and better global cognitive functioning [405]. Additionally, higher socioeconomic classes were associated with better cognitive functioning [409], whereas air pollution and neighborhood socioeconomic deprivation were inversely associated with global cognitive functioning [405] in aging adults. Minimizing environmental–psychosocial factors, in addition to harmful environmental factors, may help mitigate the development of neurocognitive impairment.

6.3. Sensory Impairment

Age-related sensory impairments for vision and hearing (not congenital or lifelong impairments) are linked with an elevated risk for cognitive decline in older adults [410]. Previous investigations examining sensory impairments and their association with dementia have been well-documented [412,413,531]. In older adults, dual sensory impairments were associated with an increased risk for dementia [414,415], specifically Alzheimer's dementia [414]. In older adult women, dual sensory impairments were linked with an increased risk for cognitive decline (~119%) and for functional decline (~87% [419]). This sex-specific finding is particularly important given that the prevalence of AD is higher in women compared to men [237]. Single sensory impairments, particularly for hearing loss, have also been linked with cognitive decline [411] and have been estimated to account for ~8% of global dementia cases in older adults [416]. Findings suggest that untreated hearing loss may exacerbate cognitive decline in aging adults, and social isolation may mediate this relationship [411]. In older adults, increased neurofibrillary tangle burden has been associated with impaired hearing prior to cognitive impairment onset [418]. Additionally, in older adults, loneliness was found to have a stronger negative impact on cognitive functioning for episodic memory and executive functioning (from the Survey of Health, Ageing and Retirement in Europe SHARE [417]). Recent findings also suggest that the use of hearing aids may prevent or delay the onset/progression of dementia [420–422], contributing an ~19% reduction in long-term cognitive decline [422] and a lower incidence of dementia in older adults who used hearing aids [421].

6.4. Cognitively Stimulating Activities

The "use it or lost it" hypothesis, referring to regularly engaging in cognitively stimulating activities, has been proposed to contribute to healthy cognitive aging [532]. In older adults, engagement in cognitively stimulating activities was associated with greater cortical and subcortical gray matter volume [429], while greater early-life cognitive enrichment (e.g., early-life availability of cognitive resources at age of 12, socioeconomic status, frequency of engaging cognitive stimulating activities, and foreign language instruction) was linked with lower global AD pathology and less cognitive decline (from the Rush Memory and Aging Project; [430]). Additionally, findings showed that playing analog games was associated with better cognitive functioning and slower rate of cognitive decline across the lifespan [424,425,533]. Additionally, improved attentional abilities were observed with a video game that was closed-loop and motion-captured (integrated cognitive and

physical fitness) in healthy older adults [428]. It is also possible that cognitively engaging employment may be neuroprotective. For example, London taxi drivers undergo extensive training (~2 years) to navigate London's roads, and findings showed that the time spent as a London taxi driver was positively correlated with hippocampal volume [431]. Similarly, in a recent study, findings showed that among the 3.88% total deaths attributed to AD, ambulance drivers (0.91%) and taxi drivers (1.03%) in the United States of America had the lowest proportion of deaths from AD relative to other occupations provided (i.e., bus drivers, chief executives, ship captains, and aircraft pilots [438]). Postponing retirement age was associated with a decreased risk for developing dementia [426,427]. Regarding cognitive stimulation and MCI, findings showed that moderate and high levels of cognitively stimulating leisure activity were associated with better memory, working memory, attention, and processing speed abilities [423], and also prevented cognitive decline [433].

Additionally, some work also suggests that cognitive training (i.e., cognitive exercises with tasks to enhance or maintain cognitive abilities across cognitive domains) can improve cognitive performance in cognitively normal older adults [432]. In patients with MCI, cognitive training was associated with an improvement in subject cognitive complaints, auditory verbal short-term memory, visuospatial short-term memory, and learning and associative memory [434,435], as well as a reduction in cognitive decline for delayed memory and Montreal Cognitive Assessment scores [426]. Similarly, individuals with mild-to-moderate AD showed an improvement with auditory verbal short-term memory, attentional processing, overall cognitive decline, and some improvements in daily living functioning [434]. Interestingly, in older adults with sensory impairments, cognitive training was associated with benefits for cognitive functioning [433]. However, it is important to note that other work with such cognitive training programs have mixed findings. For instance, one study did not observe a difference between the processing speed training and control cognitive activities in older adults with MCI and mild AD-dementia [436], and there is less evidence for the transfer of effects to everyday cognitive performance [437]. Cognitive training findings show promising findings for a potential intervention to mitigate cognitive decline, but further work is needed, particularly for the cognitive training transfer effects to everyday cognitive functioning.

6.5. Physical, Social, and Leisure Activities

Extensive research has examined physical activities with neurocognitive benefits in cognitively impaired populations [448,534,535]. Higher levels of total physical activity were associated with a reduced risk for developing AD in older adults without dementia [439], along with a reduced risk for cognitive impairment [440] and incidence of all-cause dementia [442] in older adults with moderate-to-high physical activity. Additionally, higher self-reported physical activity was linked with a slower progression of axonal degeneration in middle-aged adults with autosomal dominant forms of frontotemporal lobar degeneration [450], and additionally, engaging in moderate-to-vigorous physical activity approximately 4 days per week was associated increased brain volume in frontal, parietal, and occipital lobes, as well as increased total gray and white matter volume in middle-aged adults [449]. Conversely, other studies did not reveal associations between physical activity and biomarkers for AD-related pathology in middle aged adults who are Presenilin-1 Er280A carriers without dementia [444] or with global cognitive functioning in older adults with MCI [445].

Overall, physical activity benefitting cognitive functioning across the lifespan has moderate-to-strong support [448]. In older adults, muscle resistance training was associated with an improvement in overall reaction time [446], and improved global cognitive functioning was observed with a structured multidomain lifestyle intervention—including

regular moderate-to-high intensity physical exercise, adhering to the MIND diet, cognitively stimulating activities, and monitoring cardiovascular health—in older adults at risk for cognitive decline (from the U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. Pointer) study [536]). Physical activity also has moderate support for reducing the risk of AD [443,447], with findings showing that engagement in physical (~13% reduced risk, RR = 0.87) and cognitive (~34% reduced risk, RR = 0.66) activities were associated with a reduced risk for AD [441]. It is possible that physical activity in older adults may promote brain health, such as reduction in synaptic densities, increased mitochondrial dysfunction, and alterations in metabolic rate, neuroinflammation and oxidative stress, which may impact neurodegenerative pathology [451].

Findings also provide support for the association between social activity engagement and dementia risk [453,455,456], in which more frequent social contact was associated with a ~8% lower risk developing dementia (HR = 0.92) in older adults aged 50–70 years [454]. On the other hand, in older adults, social isolation was linked with a ~28% (HR = 1.28) greater risk for incident dementia [457], while loneliness was associated with a threefold increased risk for developing all-cause dementia [458] and a 7.5-fold increase in Aβ deposition [459]. Findings from meta-analyses provide further support for social engagement having a role in preventing dementia [455,456,537].

Further, leisure activities that involve cognitive stimulation (e.g., reading, board games, etc. [460,533]) and mindfulness (e.g., meditation practices, which some consider sauna bathing as an example due to promotion self-awareness [538]) have shown promising effects in mitigating cognitive decline. In older adults, engagement in productivity activities (i.e., housework, reading, watching television or listening to the radio) was associated with the highest reduction (~10%, OR = 0.90) for risk of cognitive decline among types of leisure activities, and a ~35% (OR = 0.65) reduced risk for cognitive decline in those with the APOE ε4 allele [461]. In patients with cognitive impairment, leisure activity interventions—including virtual reality, interactive, or board-based cognitive games, such as mahjong—were associated with improved global cognition and memory functioning, and quality of life compared to non-leisure activities [462]. A meta-analysis further supports that cognitively stimulating activities reduces the risk for cognitive impairment (~31%, OR = 0.69) and dementia (ranging from ~22–42%), and is associated with better cognitive functioning later in life [425]. Moreover, the leisure activity of sauna bathing may provide protective benefits against dementia in mid-to-late life adults [463]. Findings showed that higher frequency of sauna bathing was associated with a greater reduction in the risk for dementia (~53–66% [463,464]) and AD (~65% [464]) compared to less frequent sauna use in mid-to-late life adults.

It is possible that engaging in physical, social, and leisure activities in mid-to-late life periods may provide neurocognitive benefits and potentially prevent the development of dementia. Integrating lifestyle markers of physical, social, and leisure activities in clinical assessment may help identify those who may be at greater risk for cognitive decline by revealing patterns of engagement that are linked to resilience or vulnerability. Such assessments may inform tailored prevention strategies to mitigate future cognitive decline. However, future work will be needed to help distinguish to what degree pre-clinical emergence of dementia may be impacting these lifestyle markers, rather than the other way around.

6.6. Psychosocial Factors

Psychosocial factors have shown to be potential contributing factors in cognitive aging [507] and in cognitive impairment [395,515].

6.6.1. Depression and Anxiety

Throughout the lifespan depression [509] and anxiety [539] are common. Findings have suggested that depression [467] and anxiety [472] may be linked with dementia. Anxiety is prevalent in patients with cognitive impairment [473], and those who had anxiety for at least 10 years have an elevated risk for dementia [471]. In mid-to-late life adults, cortical Aβ deposition and clinical anxiety was associated with a 7-fold elevated the risk for MCI [465], and increased anxiety may lead to a more rapid cognitive decline across several cognitive domains in preclinical AD patients [474]. Greater Aβ burden was associated with elevated anxious-depressive symptoms over time in cognitive healthy older adults [470]. Additionally, earlier-life depressive episodes [466] and late-life depression [540] have been associated with a two-fold increased risk for dementia, whereas other work did not show an association between clinical depression and an elevated risk for MCI [465]. Other findings suggest that depression may play a role in the anxiety-dementia link in older adults [468], in which late-life depression may be related to an aspect of a prodromal phase of dementia (e.g., a consequence of dementia development; [393,469]). For example, chronic or recurring depressive symptoms did not increase the risk for dementia in mid-to-late life adults, rather findings showed an increase of depressive symptoms ~11 years prior before dementia diagnosis [469]. Therefore, treating anxiety symptoms, particularly in early-to-mid-life, may provide neurocognitive benefits against cognitive decline, and increased depression symptoms may be important to monitor for future cognitive impairment.

6.6.2. Positive Age Beliefs

Throughout the lifespan positive age beliefs may be reinforced and contribute to lower stress levels and enhanced cognitive abilities in older age [477]. In older adults, findings showed that positive age beliefs or positive perceptions regarding various aspects of older age were linked with a decreased risk of dementia [479] and a lower prevalence of MCI [475]. Additionally, positive age beliefs were associated with a ~49% reduced risk of developing dementia in older adults with the APOE ε4 allele [479], and were associated with an amplification of the protective effect of the APOE ε2 allele (i.e., associated with a protective effect against AD [478]) with global cognitive functioning in older adults [476]. In contrast, older adults with negative age beliefs had a suppression of the protective effect of the APOE ε2 allele with cognitive performance [476]. Despite the limited work examining positive age beliefs with cognitively impaired populations, findings suggest that fostering positive age beliefs throughout the lifespan may provide protection against future neurocognitive impairment.

6.6.3. Mindfulness

Mindfulness-based activities have been suggested to contribute to healthy cognitive aging [486], but findings are mixed. In older adults with MCI, engagement in mindfulness-based practices or training was associated with improved cognitive functioning [480], for psychomotor processing speed and depressive symptoms [481], and everyday activity functioning [480], while those who did not engage in such training had greater cognitive decline in patients with MCI [481]. Mindful-based interventions may delay or prevent the progression from MCI to AD by targeting psychosocial factors, such as stress and depression [482]. Conversely, other investigations did not observe cognitive benefits with mind-based training in older adults with subjective cognitive functioning complaints [541], with MCI [484,542] or dementia [484]. It is possible that heterogeneity in mindfulness-based training and variation in controlling for other psychosocial factors (e.g., depression and anxiety symptoms) across investigations may contribute to differences. Further investigations and clinical trials examining this relationship are warranted.

6.6.4. Self-Reappraisal

Limited work has investigated the contribution of self-reappraisal or self-reflection, and such findings have shown potential benefits for cognitive aging. For example, higher self-reflection (i.e., evaluating one's thoughts, feelings, and behaviors) abilities were associated with better global cognitive functioning and glucose metabolism in neocortical areas that tend to sensitive in AD in cognitively unimpaired older adults (from the baseline of Age-Well and SCD-Well clinical trials; [494]). In patients with MCI, reduced self-appraisal was associated with a greater functional decline and executive functioning abilities, suggesting impaired accuracy may be a predictor of cognitive decline [495]. Taken together, impaired self-appraisal may contribute to future cognitive decline, and these perceptions may inform clinical profiles to better monitor and predict the progression of cognitive decline for those who are at risk for cognitive impairment.

6.6.5. Stress

Associations between stress and the risk for MCI, AD, and dementia are well documented [498,499,543,544]. Psychological distress [496,499] and a history of 3+ adverse childhood experiences [497] are associated with increased risk of dementia. Long-term cortisol levels may also modulate AD-related pathology [503]. Higher cortisol levels have been associated with accelerated cognitive decline in MCI patients [504] and greater morning cortisol was more prevalent in patients with AD [504], suggesting that cortisol may play a role in neurocognitive functioning. Chronic psychological stress is linked with increased cognitive decline, and this relationship may be mediated by dysregulation with the hypothalamic-pituitary-adrenal axis, leading to a pro-inflammatory response [502]. This is important given that oxidative stress is linked with AD [505] and MCI [545,546]. In addition, to the plethora of findings of association between stress and dementia, briefly discussed here, it is important to note that caregiver stress is associated with an elevated risk for dementia [500,543] and with accelerated cognitive decline [501]. It is possible that preventing or reducing psychosocial stressors may be preventative for developing future cognitive decline.

Exposures to environmental factors, such as air pollution [394] and neighborhood disadvantage areas [395,406,407], have been associated with increased risk for dementia, as previously discussed (see Section 6.2. Environmental Factors, earlier in this paper). It is possible that these factors may also exert their effects through chronic stress. For instance, air pollutant exposure can stimulate the pollution-induced stress axis activation in the brain leading to the release of cortisol and chronic dysregulation of the hypothalamic-pituitary-adrenal axis, potentially contributing to neurotoxicity, oxidative stress and the inflammatory response in the brain [508]. Additionally, neighborhood disadvantages has been associated with elevated stressed levels, particularly for poverty-related stress [506]. Food insecurity—associated with socioeconomic hardship [547,548], and the inability to shop or prepare food in older adults [549]—was linked with a greater dementia risk (~72%) in older adults [550]. Minimizing environmental [394] and psychosocial factors [507]—such as neighborhood socioeconomic deprivation [406,407] and food insecurity [550]—may reduce chronic stress exposure and, in turn, may exert a synergistic effect in mitigating neurocognitive impairment.

Meditation may be a viable option for reducing stress [551] and helping prevent AD [489], with findings showing increased gray matter volume and cortical thickness in areas related to executive control and memory in patients with AD and MCI [492]. In cognitively healthy older adults, mediation was associated with better cognitive performance for attentional regulation, but no changes in brain volume or perfusion were observed [491]. Moreover, movement-based meditation techniques, such as yoga and tai chi have also

shown benefits for cognitive functioning. Engagement with yoga was associated with cognitive benefits for memory and executive functioning in mid-to-late life adults [487], along with reductions in gray matter volume in brain regions typically associated with AD in older adult women [493]. Additionally, regular practice of tai chi was found to be associated with improved memory performance and hippocampal structure compared to walking in older adults [490], as well as better global cognitive functioning and daily living functioning in older adults with MCI [488].

As previously mentioned, engaging in mindfulness activities may contribute to healthy cognitive aging [486]. Engagement in mindfulness activities combined with mediation activities, such as the Mindfulness-Based Stress Reduction program and mindfulness-based cognitive therapy, may offer benefits for preventing neurocognitive impairment. Although work evaluating the potential synergistic effects of combined mindfulness and mediation interventions remains limited, findings suggest that such practices may increase cognitive reserve capacity and reduce cognitive decline by reducing physiological stress [483]. Other work has found improvements for memory, executive function, and processing speed abilities in older adults, but the findings were from small sample sizes with an elevated risk of bias [485]. It is possible that mindfulness–meditation engagement may serve as a mechanism for stress reduction and mitigate effects on neurocognitive impairment, but further research is warranted to evaluate this relationship.

6.7. Sleep

Associations between sleep, and risk for cognitive decline and dementia have been well documented [509–514,552]. It is important to note that sleep characteristics of decreased total sleep time, slow wave sleep, rapid eye movement sleep [515] and sleep disturbances [509] are altered in patients with AD. The glymphatic system has been proposed to contribute to the clearance of AD-related pathology during slow wave sleep, therefore disrupting deep sleep stages may contribute to AD risk [516]. Interestingly, in older adults, insomnia—characterized as chronic difficulty to initiate or maintain sleep [553], which is associated with an increased risk for MCI and AD [554,555]—was associated with faster cognitive decline, but longer sleep duration was found to a lower white matter hyperintensity burden [511]. Given the plethora of reviews that have previously examined poor sleep health and sleep disorders with cognitive decline and AD, interventions targeting poor sleep health in dementia populations have been suggested for their potential for benefits for cognitive functioning, behavioral symptoms, and attenuating AD pathology [467]. Monitoring sleep behavior in clinical evaluations may serve as a viable option for tailored sleep interventions to potentially prevent further cognitive decline.

7. Non-Pharmacological-Based Approaches: Acupuncture and Music Therapy

Non-pharmacological interventions—including acupuncture and music therapy—should also be noted in addition to the previously mentioned nutrient-based approaches and other modifiable factors with neurocognitive impairment (see Table 4). In middle-aged adults, findings showed that acupuncture treatment in those with migraines was linked with a decreased risk of developing dementia [517], while acupuncture therapy resulted in better overall cognition in patients with AD [518,519] and MCI [519]. Overall findings suggested that the use of acupuncture may provide benefits in combating AD, but there is limited supportive evidence given the low quality (e.g., not adhering to PRISMA guidelines) of studies available [520], methodological differences, and the lack of comprehensive cognitive testing [521].

Further, music therapy has shown promising results for cognitive functioning in AD and dementia patients [523,524]. For example, musical literacy was linked with a lower incidence of all-cause dementia [522], while music participation was associated with modest, overall cognitive benefits in older adults with probable MCI and dementia [525]. In patients with AD, musical therapy has shown improvements for verbal fluency and memory abilities [526,527], helped alleviate symptoms (e.g., anxiety, depression, stress; [526,529]), along with reducing caregiver distress in those with moderate-to-severe AD [526]. Similarly, music therapy has shown improvements for cognitive functioning, quality of life, and behavioral and psychiatric symptoms in MCI patients, as well as potentially reducing the progression from MCI to AD, and has also been noted for beneficial effects for quality of life in AD patinets with more severe symptoms [527].

8. General Conclusions and Future Directions

The present narrative discussed complementary and alternative approaches relating to dietary and nutrition interventions, non-pharmacological based approaches, and other important factors as potential treatment options for preventing neurocognitive impairment. Current literature investigating complementary and alternative approaches provides growing evidence for alternative approaches for AD and potentially for other dementia and cognitively impaired populations. A potential range of complementary and alternative approaches may decrease the risk of development of cognitive impairment or mitigate the progression of MCI and ADRD, while also potentially counteracting MCI and ADRD associated health-related factors—including genetic vulnerability (i.e., APOE ε4 allele [556]), poor cardiovascular [384] and metabolic [557,558] health, intake of inflammatory diets [293], and poor sleep health [387,509,510] (see Figure 1).

Generally, some evidence is beginning to suggest that complementary and alternative approaches have promising benefits for preventing further cognitive decline in those with extant cognitive impairment, but the evidence is mixed. For instance, a mindfulness-based training intervention in older adults with MCI was found to improve cognitive functioning [480,481], whereas this was not observed in older adults with subjective memory complaints [541]. Further, diet-based approaches show greater support for reducing the risk of cognitive decline and the development of dementia [559,560]. Specifically, the Mediterranean diet [561,562] and MIND diet [64,74,562] have the strongest evidence for support. Support for specific nutrients is strongest for the consumption of omega-3 fatty acids [106]. Although findings with these diet interventions generally support the notion that adhering to these diets provides preventative benefits for neurocognitive functioning, there are some inconsistent findings. For example, one study found that there was no reduced risk for the development of all-cause dementia or vascular dementia in those who adhered to the Mediterranean diet in a 20-year follow-up study in Sweden [69]. Some dietary interventions, though, also show promising evidence for impacting neurocognitive decline even when cognitive impairment is already present, such as adherence to the ketogenic diet [78]. It may be that dietary interventions are more impactful as a range of potentially beneficial nutrients can be augmented in one diet, thus resulting in additive beneficial effects. However, proposed trials with larger populations and across the lifespan, as well as replication of these investigations and trials are needed.

Future research involving these dietary interventions is warranted to examine potential interactive associations between health factors and cognitive decline that may show synergistic effects. Importantly, more research is warranted to investigate how lifestyle modifying factors, such as cardiovascular disease/factors, sleep and maintaining "healthy" levels of psychosocial factors, may impact the trajectory of cognitive decline. Recent work has revealed that multi-domain lifestyle interventions were associated with preserving

global cognitive functioning in cognitive healthy older adults [31]. While such interventions may extend to older adults with cognitive impairment, further investigations are needed to elucidate their efficacy in neurocognitively impaired populations. Lastly, future research is needed to further delineate how preventative factors or interventions may contribute to cognitive decline across the lifespan, and distinguishing this relationship particularly in age-related disease such as AD. Further examining how these factors may interact—and whether their combined effects exert a greater impact in cognitively impaired populations—is critical. Findings from such investigations may inform the development of potential avenues complementing other existing pharmacological therapies.

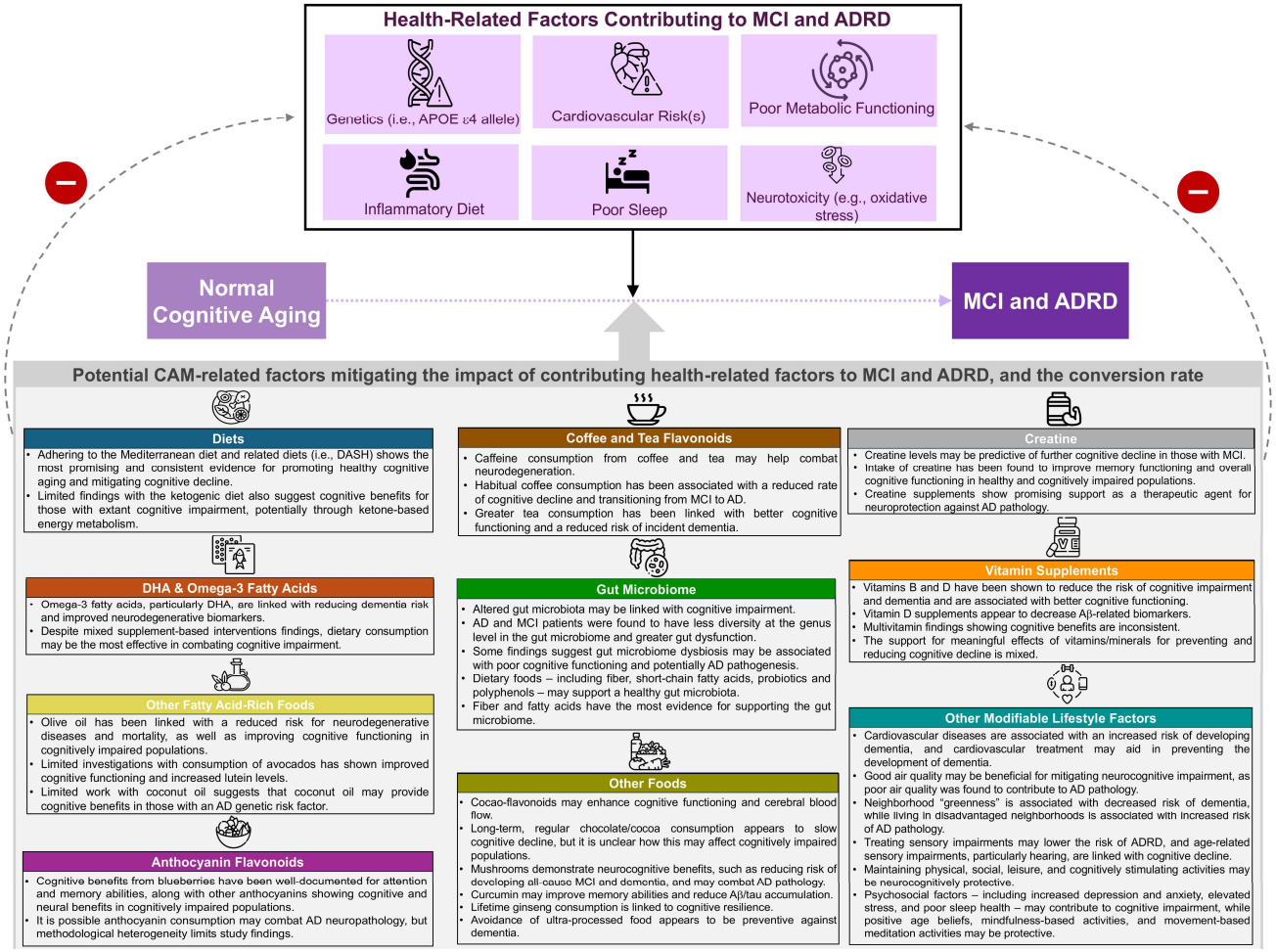


Figure 1. *Summary of nutritional complementary and alternative approach factors contributing to the prevention of cognitive impairment and dementia*. The gray arrow and box represent the potential complementary and alternative approaches (each with a brief summary) that may mitigate MCI and ADRD. The gray dashed lines with the red minus sign represents the potential complementary and alternative approaches that potentially mitigate the negative effects of the associated health-related factors—including genetic risk (i.e., APOE ε4 allele [556]), cardiovascular risk(s) [384], poor metabolic functioning [557], inflammatory diet [293], poor sleep health [387,509,510], and neurotoxicity oxidative stress response [558])—that may contribute to cognitive impairment and dementia, depicted by the solid black arrow. (MCI = mild cognitive impairment; ADRD = Alzheimer's disease and related dementias; AD = Alzheimer's disease; DASH = Dietary Approaches to Stop Hypertension; DHA = docosahexaenoic acid; Aβ = amyloid beta).

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