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The Role of Nutrition for the Aging Population: Implications for Cognition and Alzheimer's Disease

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Abstract

Improved life expectancy worldwide has resulted in a significant increase in age-related diseases. Dementia is one of the fastest growing age-related diseases, with 75 million adults globally projected to develop the condition by 2030. Alzheimer's disease (AD) is the most common form of dementia and represents the most significant stage of cognitive decline. With no cure identified to date for AD, focus is being placed on preventative strategies to slow progression, minimize the burden of neurological disease, and promote healthy aging. Accumulating evidence suggests that nutrition (e.g., via fruit, vegetables, fish) is important for optimizing cognition and reducing risk of AD. This review examines the role of nutrition on cognition and AD, with specific emphasis on the Mediterranean diet (MeDi) and key nutritional components of the MeDi, namely xanthophyll carotenoids and omega-3 fatty acids. Given their selective presence in the brain and their ability to attenuate proposed mechanisms involved in AD pathogenesis (namely oxidative damage and inflammation), these nutritional compounds offer potential for optimizing cognition and reducing the risk of AD.

INTRODUCTION

The Aging Population

By 2020, the world will reach a demographic milestone, with the number of people aged ≥65 years exceeding the number of children aged <5 years for the first time since record-keeping began. By 2030, it is estimated that the world's older population (≥65 years) will reach 1 billion, equating to 12% of the total global population; by 2050, it is estimated that they will represent 16.7% (or 1.6 billion) of the total global population (He et al. 2016). This aging trend is predicted to continue and is driven largely by increases in life expectancy resulting from, in part, improvements in socioeconomic status, greater access to healthcare, and advances in technology. Although increases in life expectancy are one of humanities greatest achievements, the growing and aging population presents significant social and economic challenges. Of particular concern is the increasing prevalence of age-related diseases (e.g., cardiovascular disease, macular degeneration, and dementia) (US Natl. Inst. Aging World Health Organ. 2011) in parallel with the growing population and increases in life expectancy (see **Figure 1**). For this reason, emphasis is now being placed on strategies to promote healthy aging, with the aim of minimizing the burden of disability and disease in later life and maximizing the quality of life for individuals in their later years. Discussion in this review focuses on the role of nutrition with respect to the aging process, cognition, and Alzheimer's disease (AD).

The Aging Process

In order to devise strategies for successful aging, it is important to understand the biology of aging, the mechanisms that contribute to the aging process, and the link between aging and disease. Aging is a highly complex and multifactorial pathophysiological process that occurs gradually over time and causes structural and functional alterations within an organism (Kowald & Kirkwood 1996). Aging is caused by a gradual and lifelong accumulation of cellular and molecular damage. Throughout our lives, many of the cells in our body can degenerate and replicate themselves between 50 and 70 times (depending on the cell type and the amount of damage it encounters). Once a cell reaches its limit (known as the Hayflick limit) (Hayflick 1998), it is unable to continue replication and enters apoptosis (programmed cellular death). As more and more cells reach

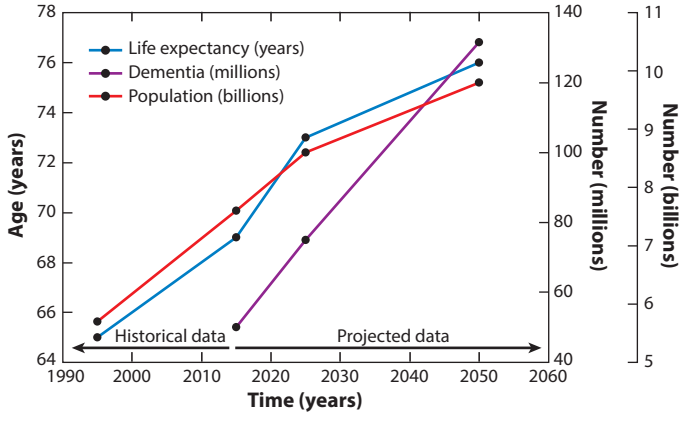

Figure 1

Historical trends and future projections for worldwide life expectancy, population growth, and dementia.

their limit, declines in physical and mental capacity appear (Farley et al. 2011). Unlike the cells in our body, most of the cells (i.e., neurons and glial cells) in our brain cannot divide and therefore cannot replace themselves. Thus, neurons and glial cells are more susceptible to structural and/or functional loss. Of note, neuronal loss is not uniform across the brain and neurons in the entorhinal cortex, hippocampus, and amygdala are particularly susceptible to cellular damage. Although aging is not synonymous with disease, the deterioration in cellular function increases the risk of disease and disability as the cellular response in both the body and the brain becomes less efficient.

There are many biological mechanisms that underlie the aging process. Understanding these mechanisms is challenging, as they are influenced by many internal and external factors such as genetics, life events in childhood (e.g., interactions with peers) and adulthood (e.g., new career, parenthood), occurrence of health conditions (e.g., cardiovascular disease), and lifestyle habits (e.g., smoking). In addition, the processes that contribute to aging are subject to the laws of change and therefore vary greatly from molecule to molecule, cell to cell, and individual to individual. The biological mechanisms that contribute to the aging process include (but are not limited to) decreased proteostasis (i.e., biological pathways within cells that control the biogenesis, folding, trafficking, and degradation of proteins), decreased neuroplasticity (the brain's ability to compensate for injury and disease and respond to changes in the environment), chronic inflammation, neuroinflammation, oxidative damage [i.e., cumulative exposure to unstable molecules known as reactive oxygen species (ROS), which results in tissue injury and damage to nucleic acids, lipids, carbohydrates, and proteins], accumulation of mitochondrial DNA mutations (which impairs mitochondrial function and leads to a shortage of energy supply), deregulation of neurosignals and neurotransmitters (e.g., serotonin), and cardiometabolic risk factors such as metabolic syndrome and its associated components (Miquel et al. 2018, Vauzour et al. 2017).

The Brain and the Aging Process

As cellular replication continues and individuals gradually age, the brain is subject to a number of both structural and cognitive changes. One of the main structural changes includes a reduction in brain size (i.e., cerebral atrophy). In general, brain volume decreases by approximately 5% per decade after the age of 40 (Scahill et al. 2003). Importantly, changes in brain size are not uniform across brain regions, as some regions (e.g., the prefrontal lobe, which is responsible for decision making, and the hippocampus, which is involved in short- and long-term memory and spatial memory) are affected more than others (e.g., the occipital lobe, which is important for visual function) (Peters 2006). Of interest, age-related decreases in the volume and integrity of white matter (which primarily comprises myelinated axons and facilitates communication between brain regions) are much greater than the decreases observed in gray matter (which consists of neuronal cell bodies, glial cells, synapses, and capillaries and is necessary for muscle control and sensory perception) (Salat et al. 1999). Aging also causes structural changes to neurons, including a decrease in the number and length of dendrites, fewer axons, loss of dendritic spines, and a significant loss of synapses (Pannese 2011).

Cognition and the Aging Process

Changes in cognition also occur as an individual ages. Cognition refers to the mental process of acquiring information and understanding through thoughts, experiences, and the senses. Cognitive abilities can be broadly classified into two groups: crystallized and fluid abilities. Crystallized abilities refer to skills and memories that have been acquired over an individual's lifetime, e.g., general knowledge and vocabulary. These abilities are known to improve throughout life until

approximately 60 years when they plateau (Harada et al. 2013). Fluid abilities refer to the capacity to process, manipulate, and transform information to complete a task at a point in time, e.g., problem-solving and reasoning. A general finding, albeit under test conditions, is that deteriorations in these cognitive abilities can begin surprisingly early in life (during the twenties or thirties) (Salthouse 2009). Indeed, the findings of a recent study involving >3,000 participants suggest that decline begins as early as 24 years of age (Thompson et al. 2014). Cognition can also be divided into specific domains such as memory, perception, language, decision-making, planning, and reasoning. Again, some cognitive domains such as speech, language, and procedural memory (e.g., remembering how to play the piano) remain stable as we age, whereas other domains such as prospective memory (e.g., remembering to perform a specific action in the future) and executive function (e.g., multitasking or planning) decline with increasing age (Murman 2015). When initial age-related changes occur, the brain is able to compensate (e.g., using additional brain regions and neural circuitry for computational support), and this enables individuals to continue to function normally. For example, it has been shown that older adults require more prefrontal circuitry than younger adults when completing the same working memory task (i.e., short-term maintenance and manipulation of information involving executive processes such as reasoning and decision-making) (Reuter-Lorenz & Park 2014). However, as neuronal damage increases (due to internal and external factors), the brain can no longer compensate for these changes and individuals begin to show subtle cognitive decline (Raz 2009). This reduces the efficiency and effectiveness of neurons to communicate with one another and leads to signs and symptoms of cognitive decline. Therefore, it is unsurprising that structural and functional changes in the brain correlate with cognitive performance. For example, Morrison & Baxter (2012) reported that a circa 50% loss of a dendritic spine subtype in the dorsal lateral prefrontal cortex caused a loss of dynamic plasticity important for working memory.

Neurodegeneration

Dementia is the umbrella term used to describe a collection of neurological disorders that cause deterioration in cognition (e.g., memory, thinking, behavior, and the ability to perform everyday tasks) beyond what is associated with normal aging. Dementia represents the most significant stage of cognitive decline and is one of the fastest growing age-related diseases, with incidence rates doubling every 6.3 years (on average) from 65 to 95 years of age. Globally, the number of people with dementia is believed to be almost 50 million. Every 20 years this figure is expected to almost double, reaching 75 million by 2030 and 131.5 million by 2050 (ADI 2018). AD is the most common form of dementia (accounting for approximately 60%–70% of cases) followed by vascular dementia, dementia with Lewy bodies, and frontotemporal dementia (Alzheimer's Assoc. 2016). Mild cognitive impairment (MCI) is an intermediate stage between the normal changes in cognition associated with aging and early dementia. Although MCI is a risk factor for AD, some individuals with this condition do not progress (Petersen et al. 2009). Individuals with the condition exhibit a decline in their cognitive abilities; however, these changes are not significant enough to impact their ability to function as normal and carry out everyday activities. AD is characterized by extracellular amyloid plaques, which comprise amyloid-β (Aβ) as a result of sequential cleavage of the amyloid precursor protein (APP). β-secretase 1 (BACE1) cleaves amyloid precursor protein with further intramembrane cleavage performed by γ-secretase (presenilins 1 or 2, respectively), thus resulting in Aβ peptides and neurofibrillary tangles (Vassar et al. 1999). Hyperphosphorylated tau proteins compose intracellular neurofibrillary tangles, which is another key part of AD pathology. Clearance of APP is aided by α-secretase activity, which precludes the formation of Aβ peptides (Lammich et al. 1999). Aβ-degrading enzymes such as neprylisin and insulin-degrading

enzyme can help in the clearance of Aβ peptides, thus reducing the formation of amyloid plaques. The associated costs of dementia worldwide include a mixture of indirect care (i.e., care given by family members and friends), direct social care (i.e., formal care given outside of the medical care system such as home care, transport, or nursing home services), and direct costs (i.e., medical costs such as medication and hospital care) and are estimated to amount to $1 trillion in 2018. This equates to approximately $43,680 per person annually and, worryingly, is expected to increase to a staggering $2 trillion by the year 2030 (Wimo et al. 2017). To date, pharmacological strategies for the treatment of dementia (in particular, AD) remain elusive and researchers continue to work toward a cure. Focus is also now being directed toward preventative strategies for AD. Such strategies are essential to alleviate the individual, societal, and economic burdens of AD.

Nutrition and Neurodegeneration

Emerging evidence suggests that healthy lifestyles throughout life may reduce the risk, or delay the onset, of cognitive decline in later life. It has been reported that a modest one-year delay in AD onset through some form of lifestyle intervention would result in 9.2 million fewer people worldwide with AD by 2050 (Brookmeyer et al. 2007). Indeed, it has been suggested that a third of AD cases could be averted by modification of lifestyle (Barnes & Yaffe 2011). Recently, it has been suggested that approximately 35% of dementia cases are attributable to a combination of nine risk factors (Livingston et al. 2017). These include early childhood education (up to 12 years), mid-life hypertension, mid-life obesity, hearing loss, late-life depression, diabetes, physical inactivity, smoking, and social isolation. Of interest, educational attainment is strongly correlated with socioeconomic status, which in turn is associated with better health outcomes [e.g., via more physical activity (Talaei et al. 2013) and healthier diets (Nolan et al. 2012)]. Specifically, there is a growing body of evidence to suggest that good nutrition is important for optimal cognition (Valls-Pedret et al. 2015) and maintenance of cognition (Pelletier et al. 2015) and is also associated with reduced risk of AD in later life (Otaegui-Arrazola et al. 2014). Here we present and discuss the role of nutrition for cognition and AD, with an emphasis on dietary patterns (MeDi) and key nutritional components of the MeDi, namely xanthophyll carotenoids and omega-3 fatty acids (ω-3 FAs).

DIETARY PATTERNS

Examining the role of nutrition as a whole (i.e., in the form of dietary patterns) is valuable, as it reflects our daily eating behaviors and patterns. Several studies have examined the role of adherence to dietary patterns in slowing down age-related cognitive decline and reducing the risk of AD. Here, we focus on the MeDi, as it is one of the most widely studied dietary patterns.

Mediterranean Diet

The MeDi is characterized by a high intake of plant food (vegetables, legumes, fruits, cereals), a high intake of olive oil [as the major source of monounsaturated fatty acids (MUFAs)], a moderate intake of fish [as a source of polyunsaturated fatty acids (PUFAs)], a low to moderate intake of dairy products (mostly in the form of cheese and yogurts), a low to moderate consumption of alcohol (mostly wine and generally with meals), and a low consumption of saturated fats, meat, and poultry. Adherence to the MeDi is typically determined using a composite score of foods and nutrients. Generally, a high score is given for healthy items (e.g., olive oil) and a low score is given

for unhealthy items (e.g., meat). Overall, a higher score is indicative of better adherence to the MeDi.

Mediterranean diet: observational and interventional evidence. There is a general consensus that greater adherence to the MeDi is associated with better cognitive performance, slower rates of cognitive decline (Lourida et al. 2013), a reduced risk of developing MCI (Roberts et al. 2010) and AD (Aridi et al. 2017), and a reduced risk of progressing from MCI to AD (Singh et al. 2014). A recent systematic review examined 47 observational (cross-sectional and longitudinal population-based) studies and concluded that adherence to dietary patterns such as the MeDi is associated with slower rates of cognitive decline and significant reductions in AD rates (Solfrizzi et al. 2017). A recent meta-analysis of longitudinal studies (Loughrey et al. 2017) also reported significant associations between MeDi adherence and both episodic memory and global cognition in healthy older adults. However, some studies have found no association between MeDi adherence and cognitive function or a reduction in the rate of cognitive decline (Cherbuin & Anstey 2012, Kesse-Guyot et al. 2013). Of interest, a study by Knight et al. (2016) concluded that positive relationships between MeDi adherence and cognitive outcomes were more consistent among studies that examined pathological brain aging (e.g., conversion from MCI to AD), suggesting that the MeDi may be more beneficial in the prodromal stage (i.e., a timeframe before the clinical manifestation of neurodegenerative disease). Of note, there appears to be a trend toward poorer dietary patterns among cognitively impaired versus healthy individuals (Gardener et al. 2012).

MeDi interventional studies in comparison to low-fat diets have shown to improve cognition among healthy middle-to-older-aged adults (Valls-Pedret et al. 2015). Specifically, Loughrey et al. (2017) found improved performance in delayed recall (i.e., the ability to remember something after a period of rest or distraction), working memory, and global cognition among healthy individuals receiving a MeDi intervention in comparison to controls. To date, the impact of a MeDi intervention on cognitive performance among cognitively impaired individuals has not been performed.

Limitations of the Mediterranean diet. Although the MeDi is one of the most widely studied dietary patterns, it is important to highlight that there is a lack of consistency in the scoring systems used to estimate dietary intake of the various nutritional components of the MeDi. A recent systematic review by Zaragoza-Martí et al. (2018) identified 28 variations of the MeDi scoring system used to estimate adherence. Some scoring systems were based on the food pyramid, whereas others adopted the original scoring system created by Trichopoulou et al. (1995). This may, in part, account for this discordance between some studies examining adherence to the MeDi and disease outcomes. This lack of consistency between studies was also apparent in a review by Sofi et al. (2014). The authors applied 10 sets of MeDi adherence scoring criteria to the same nutritional data and reported a poor correlation between most indices and adherence scores ranging from 23% to 88%. It has also been reported that the definitions of the quantities for each food group vary considerably between studies (Davis et al. 2015). Therefore, caution should be taken when interpreting the results of studies that have used the MeDi. Despite this, there is good evidence that the MeDi can play a positive role in cognitive health.

Neuroprotective properties of the Mediterranean diet. The underlying mechanisms by which the MeDi may provide neuroprotection are not fully understood. This diet provides a rich source of unsaturated fatty acids, antioxidants, and vitamins. Therefore, it has been posited that the multiple nutritional components of the MeDi may work synergistically and in a dose-dependent manner to mitigate and/or reduce risk factors associated with AD (Aridi et al. 2017). These include reducing vascular risk factors such as hypertension, dyslipidemia, and abnormal

glucose metabolism (Huhn et al. 2015); counteracting the effects of oxidative stress (Billingsley & Carbone 2018); attenuating inflammatory pathways (Gu et al. 2010); and preserving white matter microstructures in multiple brain regions (Pelletier et al. 2015). It is likely that certain components of the MeDi contribute to the proposed neuroprotective mechanisms of action. For example, it has been suggested that vitamin D can reduce Aβ production and increase Aβ clearance (Grimm et al. 2017). However, diet is more than the sum of its individual components and given the complex interactive nature of nutrients and their metabolism, it is also likely that the components of the human diet are strongly influenced by synergy or competition between compounds. For example, antioxidant nutrients can protect lipids from oxidation (Gupta et al. 2009), and calcium can inhibit the absorption of iron (Lonnerdal 2010). Accepting that the MeDi is important in promoting healthy aging and reducing the risk of cognitive decline in later life, what remains to be fully understood is the exact contribution of specific nutritional components within the MeDi that are likely to be conferring these neuroprotective benefits.

TARGETED NUTRITION

Studying the role of global nutrition is important, as it reflects daily eating patterns and behaviors. However, advances in science and technology have increased our capacity to fully elucidate the unique neuroprotective mechanisms of specific nutrients that are likely to be driving the positive results that have been observed. We now discuss specific nutrients, namely carotenoids and ω-3 FAs, which are major constituents of the MeDi and are also present in the brain.

Carotenoids

Carotenoids are naturally occurring plant pigments that are ubiquitous throughout nature and synthesized de novo by photosynthetic organisms (plants, algae, cyanobacteria) and some nonphotosynthetic organisms (Alcaino et al. 2016). Carotenoids are lipid-soluble C_{40} (tetraterpenoids) compounds and are classified as carotenes (which are pure hydrocarbons and contain no oxygen) or xanthophylls (which are oxygen derivatives and more polar than carotenes). Importantly, carotenoids cannot be synthesized de novo by humans and so they must be obtained from the diet, primarily through the leaves of edible plants and dark green, yellow, orange, and red vegetables and fruits. Of the 750+ carotenoids found in nature, 40 to 50 are found in the human diet (Khachik 2006) and approximately 18 are found in human blood, of which α-carotene, β-carotene, lycopene, lutein (L), zeaxanthin (Z), and β-cryptoxanthin are the most common (Khachik et al. 1992).

Owing to their powerful antioxidant and anti-inflammatory properties, carotenoids are now known to play an important role in human health. Indeed, a higher consumption of carotenoids has been shown to be related to a lower risk of cardiovascular disease, some cancers (e.g., prostate) and eye diseases (e.g., age-related macular degeneration) (Bernstein et al. 2016, Fiedor & Burda 2014). A growing body of evidence also supports a role for carotenoids in cognition and brain health. A number of carotenoids (mainly L, Z, anhydrolutein, α- and β-cryptoxanthin, α-carotene, *cis*- and *trans*-β-carotene, and *cis*- and *trans*-lycopene) have been identified in brain tissue, including in the hippocampus, cerebellum, and frontal, occipital, and temporal cortices (Craft et al. 2004, Johnson et al. 2013, Vishwanathan et al. 2016). In blood and most tissues, the xanthophyll carotenoids account for just 40% of total carotenoid concentrations, whereas carotenes account for approximately 60% of carotenoids present (Kaplan et al. 1990); in the brain, the xanthophyll carotenoids account for more than 65% of total carotenoids, suggesting preferential uptake of xanthophylls across the blood–brain barrier (BBB) (i.e., a semipermeable membrane separating

the blood from the cerebrospinal fluid) and selective accumulation into brain tissue (Craft et al. 2004). The xanthophyll carotenoid L is one of the most concentrated carotenoids in the brain (Craft et al. 2004). It is for this reason that the majority of the research to date has studied the role of L in cognition. Of interest, studies have shown that carotenoid concentrations are lower in individuals with MCI (Rinaldi et al. 2003) and AD (Mullan et al. 2017, Nolan et al. 2014) when compared to individuals free of cognitive impairment. Additionally, plasma carotenoid concentrations (L and β-carotene in particular) correlate inversely and significantly with AD severity (Wang et al. 2008).

Carotenoids: observational evidence. Population-based and cross-sectional studies have shown that higher concentrations of carotenoids [measured in blood and via self-report (i.e., questionnaires)] are associated with better cognitive performance in healthy individuals (Feeney et al. 2017, Johnson et al. 2013). However, a systematic review (Crichton et al. 2013) of cross-sectional and epidemiological studies reported conflicting findings regarding the potential effectiveness of carotenoids in reducing dementia risk. The authors in that review suggested that the inconsistencies in their findings may have been due to the heterogeneity in the study designs adopted, as the methods used to assess both antioxidant status and cognition varied widely between studies. In addition, some studies made minimal adjustments for potential confounders (e.g., education, diet), whereas other studies used extensive statistical modeling.

The carotenoids L, Z, and meso-zeaxanthin (MZ) are preferentially concentrated in the central retina [macula lutea, which is part of the central nervous system (CNS)] where they are collectively referred to as macular pigment (MP). Interestingly, MP levels correlate positively and significantly with brain concentrations of L and Z (Vishwanathan et al. 2016). Therefore, the measurement of MP can be used as a noninvasive clinical biomarker of brain nutrition and, potentially, cognitive health, given that higher MP levels have been associated with better cognitive performance in both healthy (Ajana et al. 2018, Feeney et al. 2013) and cognitively impaired individuals (Renzi et al. 2014).

Higher consumption of green leafy vegetables (rich in the xanthophyll carotenoid L) in particular has shown to be significantly related to slower rates of cognitive decline in cognitively healthy individuals (Morris et al. 2018). A systematic review by Loef & Walach (2012) suggested that higher consumption (>200 g or at least 3 servings/day) of vegetables (measured using food frequency questionnaires) was associated with a reduced risk of AD and a slower rate of cognitive decline. Additionally, higher carotenoid concentrations (measured in blood and via self-report) have been associated with a lower risk of AD mortality (Feart et al. 2016, Min & Min 2014). Overall, observational evidence suggests that greater carotenoid consumption is associated with better cognitive performance and a reduced risk of cognitive decline.

Carotenoids: interventional evidence. A number of interventional studies in healthy individuals have observed improvements in various domains of cognition following carotenoid supplementation. These include verbal learning (Lindbergh et al. 2016), verbal reasoning (Zamroziewicz et al. 2016), episodic memory (e.g., remember where you parked your car in a multistory car park) (Power et al. 2018), attention (Hammond et al. 2017), processing speed (Bovier & Hammond 2015), and reaction time (Renzi et al. 2013). To date, no improvements in cognition have been observed among AD patients following carotenoid supplementation (Nolan et al. 2015), suggesting that early intervention is likely to be important.

Neuroprotective properties of carotenoids. The exact mechanisms underlying the relationship between carotenoids and cognitive health and function have not yet been fully elucidated.

Carotenoids are premised to be neuroprotective because of their chemical composition and localization within biological membranes, thus bestowing antioxidant and anti-inflammatory properties at their storage locations. These properties can help mitigate the processes involved in neurodegeneration; namely, oxidative stress and inflammation (Mohammadzadeh et al. 2017). As noted previously, oxidative damage refers to tissue injury due to cumulative exposure to unstable molecules known as ROS. Examples of ROS include free radicals, singlet oxygen, and hydrogen peroxide. ROS are the inevitable by-product of aerobic metabolism, and although important for homeostasis and cell signaling (Droge 2002), cellular dysfunction arises when the cellular system is overwhelmed by the concentration of ROS relevant to the antioxidant capacity of the cell. If the cellular components (e.g., DNA, proteins) are unrepaired, tissue damage and, eventually, cell death occur. Owing to its high oxygen demand and high amounts of PUFAs, the brain is particularly vulnerable to oxidative damage. In addition, the integrity of the BBB is also reduced as individuals age. This results in the brain having a higher susceptibility to oxidative damage. Because of their conjugated double-bond structure, carotenoids are efficient scavengers of ROS (namely singlet oxygen and peroxyl radicals), primarily through direct energy transfer (i.e., a process known as physical quenching). They can also neutralize ROS via electron acceptance, electron donation, or hydrogen abstraction or acceptance (Bouayed & Bohn 2012, Kaulmann & Bohn 2014). Carotenoids with a higher number of conjugated double bonds have a greater capacity to scavenge ROS and thus are more powerful antioxidants. Carotenes are located within the inner part of the lipid bilayer, whereas xanthophylls are positioned perpendicular to the membrane surface (Bone & Landrum 1984). Because of their lipid solubility, carotenoids are incorporated into lipid membranes where they can interact with plasma, mitochondria, and nucleus membranes within cells. As a result, carotenoids can reduce the susceptibility of cellular membranes and lipoproteins to oxidative damage through free-radical scavenging (Bouayed & Bohn 2012).

Carotenoids can also affect the structural and dynamic properties of membranes (e.g., thickness, permeability) (Gruszecki & Strzalka 2005). For example, it has been suggested that L can facilitate the transfer of compounds (e.g., molecules or nutrients) from one cell to another via gap junctions (i.e., intercellular membrane proteic structures). Gap junction channels contribute to sharpened neuronal activity, which has been proposed to underlie cognitive processes such as memory, perception, and learning (Sohl et al. 2005). It has also been shown that the xanthophylls L and Z can positively impact neural efficiency, whereby individuals with higher levels of these xanthophyll carotenoids required less brain power to complete the same tasks as individuals with lower levels of these carotenoids (Bovier & Hammond 2015, Lindbergh et al. 2016).

Under normal conditions, inflammation is a protective physiological response to endogenous and/or exogenous agents. However, persistent inflammation over a prolonged period results in chronic inflammation and is harmful to the body, as it can cause cellular damage, which in turn can result in the development of chronic disease. Inflammation of nervous tissue is known as neuroinflammation and can lead to synaptic dysfunction and death of neurons within the brain. Chronic neuroinflammation is a hallmark typically associated with neurodegenerative diseases such as Parkinson's disease and AD (Skaper et al. 2018). The deployment of neuroinflammation is carried out exclusively by microglia, a series of cells that reside permanently next to the neurons and that constitute the immune system of the CNS. Thanks to the insulating effect of the BBB, the peripheral immune system is excluded from acting on the CNS. However, when a neuroinflammatory episode develops, the microglia can become activated at levels that compromise the insulating role of the BBB, thus allowing the entry of circulating immune cells into the CNS and thereby aggravating inflammation (Zhang et al. 2016a). Evidence suggests that the anti-inflammatory properties of carotenoids can play a positive role in neurological disorders. These include modulation of inflammatory cells and proinflammatory enzymes, downregulation of proinflammatory molecule

production, and attenuation of inflammatory gene expression (Guest & Grant 2016). For example, it is posited that carotenoids can influence the immune properties of microglia, which in turn can inhibit the production of proinflammatory molecules such as cytokines.

It has also been suggested that carotenoids may be neuroprotective because of their ability to suppress the accumulation of Aβ (Obulesu et al. 2011). Molecular modeling of cryptocapsin and Z suggests that these carotenoids have the capacity to inhibit Aβ aggregation, possibly because of the presence of keto-κ and β-ionone hydroxylated rings, respectively (Lakey-Beitia et al. 2017). A study in mice showed that carotenoid supplementation improved the resistance of red blood cells (RBCs) to oxidative damage induced by Aβ (Nakagawa et al. 2011). This is significant, as it has been suggested that alterations in RBCs decrease oxygen delivery to the brain. This in turn can lead to brain hypoxia (Mohanty et al. 2008), which contributes to the pathogenesis of AD.

Omega-3 Fatty Acids

In addition to carotenoids, fats and oils are an important part of our diet (and a major component of the MeDi), as they provide fatty acids (FAs) necessary for storing energy and form the biological membranes of cells and their organelles. FAs are nonbranched molecules composed of carbon and hydrogen and an acid group on one end. They can be completely saturated or contain one or more unsaturations (i.e., double bonds) in their structure. The number of carbons and unsaturations of a FA determines its name and its classification. Short-chain FAs are usually saturated (i.e., without double bonds) and long-chain FAs can have either a single unsaturation (i.e., MUFAs) or several unsaturations in their structure (i.e., PUFAs). The PUFA family can be dichotomized into the ω-3 family and the omega-6 (ω-6) family. Each family has a specific FA as a precursor of the rest of the family members. In the case of the ω-3 family, the precursor FA is α-linolenic acid (ALA); and in the case of the ω-6 family, the precursor FA is linoleic acid (LA). Each of these two precursor FAs (ALA and LA) are essential (i.e., we cannot synthesize them and must obtain them from our diet) (Collins et al. 1971). The metabolism of ALA in the ω-3 family produces docosahexaenoic acid (DHA) as its final product with appreciable amounts of the previous FA in the synthesis route known as eicosapentaenoic acid (EPA). In the case of the ω-6 family, the final product of LA metabolism is arachidonic acid (ARA).

ω-3 FAs are obtained from the diet mainly via the consumption of fish, seafood, or shellfish. These foods contain high amounts of EPA and DHA. Different types of fish contain different amounts and ratios of EPA and DHA, which are influenced by the metabolic characteristics of the fish and their diet among other variables. EPA and DHA can also be obtained by consuming food supplements produced from fish, krill, or *Calanus* oil extract. Approximately 30% of the FAs present in fish oil comprise EPA and DHA (Calder & Yaqoob 2009). At present, however, the ratio of ω-6 FAs to ω-3 FAs in the human diet is 10–20:1 in favor of ω-6 FAs (Sheppard & Cheatham 2018) in contrast to the 1:1 ratio that humans consumed in the Paleolithic (Kuipers et al. 2010). This is due to the currently high consumption of ω-6 rich oils (sunflower oil and soybean oil, which are rich in ALA), meat and eggs (both rich in ARA), the lower consumption of oily fish (rich in EPA and DHA), and the consumption of farmed fish, which are low in DHA and EPA (Sheppard & Cheatham 2018). The consequence of this imbalance between ω-6 and ω-3 intake is the prevalence of obesity, increased inflammatory status, loss of insulin sensitivity, and imbalanced cognitive behavior (Zamberletti et al. 2017). Importantly, humans do not bear any enzyme to convert ω-6 FAs into ω-3 FAs.

The brain is a lipid-dense organ, with gray matter consisting of approximately 40% lipids and white matter consisting of 50%–70% lipids. ARA and DHA are found in large amounts in the brain and are located in the phospholipids that make up the membranes of microglia and

neurons, including myelinated axons (Hamazaki et al. 2015). Given that ω-3 FAs (in particular, DHA) are key components of lipids in the brain, they have an important role in maintaining brain structure and function. DHA is important for neuronal differentiation, synaptogenesis, and synaptic function (Hashimoto et al. 2017). DHA is the predominant ω-3 FA involved in cerebral metabolism and as a consequence has been extensively studied. In contrast, EPA is found at very low concentrations in the human brain, approximately 275 times lower than those of DHA in the mouse brain (Chen et al. 2009) and below detection levels in the human brain (Hamazaki et al. 2015). It has been hypothesized that the low presence of EPA in the brain may be due to high catabolism of this ω-3 FA in brain tissue (Chen et al. 2009).

Omega-3 fatty acids: observational evidence. Given the abundance of ω-3 FAs (primarily DHA) in the brain, it is reasonable to suggest that these nutrients are important for cognition and brain health. For more than two decades, there has been a continuous interest in the role of ω-3 FAs for healthy cognition and the prevention of AD. Many longitudinal and cross-sectional studies among healthy individuals have shown that greater consumption of ω-3 FAs (primarily from fish) is associated with better cognitive performance (Dangour et al. 2009, Ubeda et al. 2012) and a reduced risk of dementia (Barberger-Gateau et al. 2007, Roberts et al. 2010). Meta-analyses have reported a 5%–11% decreased risk for AD for every 100 g/week increased intake in fish (Wu et al. 2015, Zhang et al. 2016b). Higher intake of ω-3 FAs (from dietary sources and via supplementation) has also been positively associated with gray matter volumes in areas such as the hippocampus and orbital frontal cortex (Raji et al. 2014). Lower plasma concentrations of ω-3 FAs have been associated with greater cognitive decline in both cognitively intact (Lukaschek et al. 2016) and cognitively impaired individuals (Schaefer et al. 2006). Of interest, ω-3-FA levels (in brain and tissue) are depleted in individuals with MCI and AD in comparison to cognitively healthy individuals (Cunnane et al. 2012, Huang 2010). Indeed, it has been suggested that lipids could be used as a blood-based biomarker in detecting preclinical AD in healthy individuals. Mapstone and colleagues identified a set of ten lipids from peripheral blood that predicted phenoconversion to amnestic MCI or AD within three years (Mapstone et al. 2014). Another study has shown that ω-3 FAs are positive predictors of a composite memory performance score independent of confounders, including age, years of education, sex, and socioeconomic status (Phillips et al. 2012). Using the method developed by Mapstone et al. (2014), analysis from our research center also found significant differences in lipids [PCaa (40:6), PCaa (38:6), PCae (38:4)] between mild-to-moderate AD patients and healthy controls (J.M. Nolan, R. Moran, R. Mulcahy, A. Howard, L. Matthews, D.I. Thurnham, J.L. Griffin & A. Koulman, unpublished results). However, we suggest that differences in the lipid profile are of dietary origin given that it has previously been shown that this population group has poorer dietary patterns (Gardener et al. 2012). Indeed, our results suggest that lipids will provide poor biomarkers per se for AD but instead reflect the effects of a potentially beneficial diet in the elderly. Although it is important to note that some studies have observed no relationship (Ammann et al. 2013, Devore et al. 2009), overall observational evidence suggests that greater intake of ω-3 FAs is associated with better cognitive performance and a reduced risk of AD.

Omega-3 fatty acids: interventional evidence. The evidence for a beneficial effect of ω-3-FA supplementation on cognition is less clear from clinical trials. Some interventional studies performed in healthy individuals have observed improvements in cognition, whereas others have found no positive effects (Flodgren & Berg 2016). Supplementation trials with dosages ranging from 900 mg–2.2 g/day have observed improvements in a number of cognitive domains, including episodic memory, visual recognition memory, reaction time, and executive function among healthy

individuals between 50 and 75 years (Kulzow et al. 2016, Yurko-Mauro et al. 2010). Increases in gray matter volume of the frontal, temporal, parietal, and limbic areas within the left hemisphere of the brain have also been observed (Witte et al. 2014). In contrast, a systematic review involving three intervention trials ($n = 4{,}080$) found no benefit of ω-3-FA supplementation to cognition (i.e., memory, executive function or processing speed) among cognitively healthy individuals aged 60–80 years (Sydenham et al. 2012). Although the intervention periods (6, 24, and 40 months) and formulation dosages (176–847 mg DHA and 226–1,093 mg EPA) varied widely between the three studies, the cognitive measurements and outcome measures of interest were comparable between studies. Overall, results are conflicting and the evidence to support a role for ω-3-FA supplementation in healthy individuals remains unclear.

Clinical trials performed on individuals with dementia (mainly patients with AD) have also provided mixed results. Some interventional trials have reported positive benefits (Eriksdotter et al. 2015), but overall there is a growing consensus that supplementation with ω-3 FAs does not exhibit cognitive improvements in these patients. Indeed, a recent Cochrane review of three randomized clinical trials reported no cognitive benefits following six months of supplementation with ω-3 FAs for individuals ($n = 632$ in total) with mild-to-moderate AD (Burckhardt et al. 2016).

Of note, evidence is moderately stronger for interventional studies examining individuals with early-stage cognitive impairment (i.e., not clinically confirmed dementia). However, only a small number of studies examining the impact of ω-3-FA supplementation on cognition have been performed in this population group. Baleztena et al. (2018) reported no benefits in global cognitive function following 12-month supplementation with 750 mg of DHA and 120 mg of EPA. However, the sample was not stratified by degree of impairment (i.e., no, very mild, and mild cognitive decline) and, instead, was viewed collectively. This may have influenced the outcome of the study. Also, other ingredients such as vitamin B_{12} (5 mg) and *Ginkgo biloba* (60 mg) were present in the formulation tested in that study. A meta-analysis of 15 interventional trials suggested a benefit of DHA supplementation in terms of improving episodic memory among mildly impaired individuals (Yurko-Mauro et al. 2015). Other studies have also reported benefits in memory (episodic, short-term, working, and immediate verbal), processing speed, and attention (Lee et al. 2013, Mazereeuw et al. 2012).

It has also been suggested that individuals with very-early-stage AD may benefit from ω-3-FA supplementation (Freund-Levi et al. 2006, Mazereeuw et al. 2012). Exploratory analysis by Hooper et al. (2017) and Andrieu et al. (2017) reported less cognitive decline among an ω-3-FA supplementation group compared to placebo in individuals with a cognitive impairment (but not dementia) and a low ω-3-FA index at baseline. In totality, the evidence from interventional studies suggests that ω-3-FA supplementation should be targeted toward specific population groups (i.e., individuals with MCI, very-early-stage AD, or a low ω-3-FA index). Healthy individuals may also attain benefits, but the overall impact of supplementation in this group remains unclear.

It is clear from the above summary that intervention trials examining the impact of ω-3 FA on cognition are inconsistent. This ambiguity may be due to the variations in cognitive status, FA dosage, or duration of supplementation. The apolipoprotein E4 (APOE4) status of an individual may also be important to consider, as studies have observed varying results between APOE4 carriers and noncarriers following ω-3-FA supplementation (Salem et al. 2015). Therefore, results from studies that do not take APOE4 status into consideration may be limited in their interpretation and study design. It has also been suggested that any positive effects of ω-3-FA supplementation may be masked by the negative effects of high levels of *trans* and saturated FAs in the body. It has been previously noted that the overall dietary fat composition, in addition to the amount of unsaturated fat present in the body, is vital for brain function (Morris et al. 2005). Indeed, it has

been suggested that high levels of saturated and *trans*-fatty acids are associated with an increased risk of neurological disorders (Barnard et al. 2014).

Neuroprotective properties of omega-3 fatty acids. The exact biological mechanisms by which ω-3 FAs confer cognitive benefits are not yet fully understood. However, it has been suggested that their properties may help to mitigate processes involved in the pathogenesis of AD, namely inflammation. As noted above, neuroinflammation is inflammation that occurs in the CNS that can lead to synaptic dysfunction and the death of neurons. It has been suggested that DHA plays an important role in the control and resolution of neuroinflammation. This role is performed by a number of pathways, including being converted into bioactive lipid metabolites such as endocannabinoid epoxides (molecules that are responsible for antiangiogenic effects, vasodilatory actions, and regulation of platelet aggregation) (McDougle et al. 2017). Furthermore, DHA downregulates the expression of genes involved in the synthesis of proinflammatory eicosanoids produced from ARA (Smedt-Peyrusse et al. 2008). Studies in murine models have shown that DHA promotes neurogenesis and neuritogenesis, sustains neuronal survival (Akbar et al. 2005), and thus improves spatial learning performance (He et al. 2009) and memory (Sugasini et al. 2017). Neuronal membranes primarily comprise lipids and thus are highly susceptible to lipid peroxidation, which can lead to cellular damage and an increased risk of cognitive impairment (Shichiri 2014). It has also been suggested that ω-3 FAs are implicated in upregulating the expression of antioxidant enzymes and downregulating genes associated with production of ROS (Sakai et al. 2017). Additionally, ω-3 FAs are also important for membrane homeostasis, which is associated with reduced cognitive decline (Agrawal & Gomez-Pinilla 2012).

Given that DHA is a key component of lipids in the brain, it is posited that it is directly involved in enhancing neuronal health by stimulating neurogenesis and neuronal function such as increasing the expression of myelin-related proteins that can facilitate axonal transmission and thus better neuronal signaling (Salvati et al. 2008). Despite EPA being stored in the brain in low amounts, it has been demonstrated that this ω-3 FA is important for neural efficiency. This suggests that EPA may positively influence pathways that regulate high-order cognitive functions (Bauer et al. 2014). It has also been suggested that EPA can facilitate enzymatic processes required to inhibit neuronal damage from inflammation and oxidative stress (Okabe et al. 2011). The neuroprotective benefits of ω-3 FAs may also be mediated indirectly through their established role as protectors against cardiovascular disease, which is also a risk factor for neurodegenerative disease. Higher intake of ω-3 FAs has been associated with reductions in vascular risk factors such as plasma triglycerides, resting heart rate, and blood pressure and improvements in vascular function, including myocardial filling and cerebral blood flow (Mozaffarian & Wu 2011).

CAROTENOID AND OMEGA-3 FATTY ACID SYNERGY

The combination of carotenoids and ω-3 FAs may potentially offer advantages in biochemical response to carotenoids and additional cognitive benefits to these nutritional compounds in isolation. A study ($n = 49$) involving healthy women aged 60–80 years observed a superior biochemical response among individuals receiving a combination of L or DHA in comparison to L and DHA alone, suggesting that the presence of DHA facilitated uptake of L (Johnson et al. 2008). Indeed, our recent work has identified that the blood response to carotenoid intervention in the presence of ω-3 FAs (430 mg of DHA and 90 mg of EPA) exhibits significantly greater increases in circulating xanthophyll carotenoids (L, Z, and MZ) (Nolan et al. 2018). Furthermore, this pilot work has suggested that some of the patients that were supplemented with carotenoids and ω-3 FAs demonstrated improvements in their ability to carry out everyday activities with

specific improvements noted in memory, sight, and mood. We are now in the process of examining this finding in a larger clinical trial of patients with AD [Memory Investigation with Nutrition for Dementia (re-MIND), trial registration number ISRCTN11892249].

CONCLUSION

Over the past two decades, we have learned that nutrition is important for brain health and can positively impact on cognition and AD risk. It is our view that nutrition is important for optimization of cognition and as a preventative measure for neurological disease, such as AD. One major challenge, however, is compliance with good nutrition and access to good diets such as the MeDi. Another challenge relates to the quality of healthy foods, as recent evidence suggests that the nutritional value of certain fruits and vegetables is declining (White & Broadley 2005).

Regarding the MeDi, there is strong evidence to show that adopting or adhering to this dietary pattern can play a positive role in cognitive health among healthy individuals and reduce their risk of developing AD. Continued research, specifically MeDi interventional studies involving cognitively impaired individuals, will add to the current knowledge base. Carotenoids and ω-3 FAs are key components of the MeDi and, given that these nutrients are present in brain tissue, it is likely that they play a significant role in maintaining cognition and reducing the risk of cognitive decline. Much of our work to date has focused primarily on the role of carotenoids for cognitive health and disease. We have shown that lower carotenoid concentrations (in both tissue and blood) are associated with poorer cognitive status in healthy individuals (Feeney et al. 2013, 2017) and that patients with AD are deficient in these nutrients (Nolan et al. 2014). Furthermore, our research has observed improvements in cognition following carotenoid supplementation in healthy individuals (Power et al. 2018). Moreover, the presence of ω-3 FAs in the brain and their potential role in neuroprotection and synergy with carotenoids have led us to investigate these nutritional compounds in conjunction with the xanthophyll carotenoids. Our previous interventional work with AD patients observed no benefit of carotenoid supplementation to cognition (Nolan et al. 2015). However, recent pilot work in which individuals with AD were supplemented with a formulation containing a combination of carotenoids and ω-3 FAs yielded positive results in terms of improved biochemical response and carer-reported improvements in the ability of AD patients to perform daily activities, with specific improvements noted in memory, sight, and mood (Nolan et al. 2018). Future work will examine this finding in a larger study (the re-MIND trial), which is currently underway.

It is clear from this review that cognitively impaired individuals have poorer dietary patterns and are deficient in both carotenoids and ω-3 FAs in comparison to cognitively healthy individuals. Therefore, it is likely that specific population groups (i.e., individuals with MCI, very-early-stage AD, or a low ω-3 FA and/or carotenoid index) will benefit from nutritional intervention; however, well-designed and appropriately powerful intervention trials are needed to confirm this hypothesis. Indeed, this has prompted our current research, which is examining the impact of 24-month nutritional supplementation (carotenoids and ω-3 FAs) on cognition in mildly impaired individuals in comparison to age-matched controls [Cognitive impAiRmEnt Study (CARES), trial registration number: ISRCTN10431469].

In conclusion, this is an exciting time for research on nutrition in cognitive health. Advancements in technologies have allowed us to design and conduct clinical trials with meaningful outcome measures in the populations of interest. It is our view that, on the basis of the totality of evidence already available, major investment in the role of nutrition for cognitive health and neurological diseases such as AD is truly merited. The need for preventative strategies to promote healthy aging and minimize the burden of neurological disease is timely and essential given the

challenges of the aging population. It is our view that given their selective presence in brain tissue and their ability to attenuate the mechanisms involved in the pathogenesis of AD (namely oxidative stress and neuroinflammation), the MeDi and, in particular, carotenoids and ω-3 FAs offer potential for optimizing cognition and reducing the risk of AD.

DISCLOSURE STATEMENT

R. Power and A. Prado-Cabrero are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. J.M. Nolan does consultancy work as a director of NOW-Science Consultancy Ltd. and Nutrasight Consultancy Ltd. for companies with an interest in food supplements. R. Mulcahy does consultancy work for the Howard Foundation Holdings Ltd.

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LITERATURE CITED

Agrawal R, Gomez-Pinilla F. 2012. 'Metabolic syndrome' in the brain: deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition. *J. Physiol.* 590:2485–99

Ajana S, Weber D, Helmer C, Merle BM, Stuetz W, et al. 2018. Plasma concentrations of lutein and zeaxanthin, macular pigment optical density, and their associations with cognitive performances among older adults. *Investig. Ophthalmol. Vis. Sci.* 59:1828–35

Akbar M, Calderon F, Wen Z, Kim H-Y. 2005. Docosahexaenoic acid: a positive modulator of Akt signaling in neuronal survival. *PNAS* 102:10858–63

Alcaino J, Baeza M, Cifuentes V. 2016. Carotenoid distribution in nature. *Subcell. Biochem.* 79:3–33

Alzheimer's Assoc. 2016. 2016 Alzheimer's disease facts and figures. *Alzheimers Dement*. 12:459–509

Alzheimer's Dis. Int. (ADI) 2018. *Dementia statistics*. Rep., Alzheimer's Dis. Int., London. **https://www.alz.co.uk/research/statistics**

Ammann EM, Pottala JV, Harris WS, Espeland MA, Wallace R, et al. 2013. Omega-3 fatty acids and domain-specific cognitive aging: secondary analyses of data from WHISCA. *Neurology* 81:1484–91

Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, et al. 2017. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol*. 16:377–89

Aridi YS, Walker JL, Wright ORL. 2017. The association between the Mediterranean dietary pattern and cognitive health: a systematic review. *Nutrients* 9:E674

Baleztena J, Ruiz-Canela M, Sayon-Orea C, Pardo M, Anorbe T, et al. 2018. Association between cognitive function and supplementation with omega-3 PUFAs and other nutrients in ≥75 years old patients: a randomized multicenter study. *PLOS ONE* 13:e0193568

Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, et al. 2007. Dietary patterns and risk of dementia: the Three-City cohort study. *Neurology* 69:1921–30

Barnard ND, Bunner AE, Agarwal U. 2014. Saturated and *trans* fats and dementia: a systematic review. *Neurobiol. Aging* 35(Suppl. 2):S65–73

Barnes DE, Yaffe K. 2011. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 10:819–28

Bauer I, Crewther S, Pipingas A, Sellick L, Crewther D. 2014. Does omega-3 fatty acid supplementation enhance neural efficiency? A review of the literature. *Hum. Psychopharmacol.* 29:8–18

Bernstein PS, Li B, Vachali PP, Gorusupudi A, Shyam R, et al. 2016. Lutein, zeaxanthin, and meso-zeaxanthin: the basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease. *Prog. Retinal Eye Res.* 50:34–66

Billingsley HE, Carbone S. 2018. The antioxidant potential of the Mediterranean diet in patients at high cardiovascular risk: an in-depth review of the PREDIMED. *Nutr. Diabetes* 8:13

Bone RA, Landrum JT. 1984. Macular pigment in Henle fiber membranes: a model for Haidinger's brushes. *Vis. Res.* 24:103–8

Bouayed J, Bohn T. 2012. *Dietary Derived Antioxidants: Implications on Health*. Rijeka, Croat.: InTech. **https://www.intechopen.com/books/nutrition-well-being-and-health/dietary-derived-antioxidants-implication-on-health**

Bovier ER, Hammond BR. 2015. A randomized placebo-controlled study on the effects of lutein and zeaxanthin on visual processing speed in young healthy subjects. *Arch. Biochem. Biophys.* 572:54–57

Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. 2007. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement.* 3:186–91

Burckhardt M, Herke M, Wustmann T, Watzke S, Langer G, Fink A. 2016. Omega-3 fatty acids for the treatment of dementia. *Cochrane Database Syst. Rev.* 4:CD009002

Calder PC, Yaqoob P. 2009. Understanding omega-3 polyunsaturated fatty acids. *Postgrad. Med.* 121:148–57

Chen CT, Liu Z, Ouellet M, Calon F, Bazinet RP. 2009. Rapid β-oxidation of eicosapentaenoic acid in mouse brain: an in situ study. *Prostaglandins Leukot. Essent. Fatty Acids* 80:157–63

Cherbuin N, Anstey KJ. 2012. The Mediterranean diet is not related to cognitive change in a large prospective investigation: the PATH Through Life study. *Am. J. Geriatr. Psychiatry* 20:635–39

Collins FD, Sinclair AJ, Royle JP, Coats DA, Maynard AT, Leonard RF. 1971. Plasma lipids in human linoleic acid deficiency. *Nutr. Metab.* 13:150–67

Craft NE, Haitema TB, Garnett KM, Fitch KA, Dorey CK. 2004. Carotenoid, tocopherol, and retinol concentrations in elderly human brain. *J. Nutr. Health Aging* 8:156–62

Crichton GE, Bryan J, Murphy KJ. 2013. Dietary antioxidants, cognitive function and dementia—a systematic review. *Plant Foods Hum. Nutr.* 68:279–92

Cunnane SC, Schneider JA, Tangney C, Tremblay-Mercier J, Fortier M, et al. 2012. Plasma and brain fatty acid profiles in mild cognitive impairment and Alzheimer's disease. *J. Alzheimers Dis.* 29:691–97

Dangour AD, Allen E, Elbourne D, Fletcher A, Richards M, Uauy R. 2009. Fish consumption and cognitive function among older people in the UK: baseline data from the OPAL study. *J. Nutr. Health Aging* 13:198–202

Davis C, Bryan J, Hodgson J, Murphy K. 2015. Definition of the Mediterranean Diet; a literature review. *Nutrients* 7:9139–53

Devore EE, Grodstein F, van Rooij FJ, Hofman A, Rosner B, et al. 2009. Dietary intake of fish and omega-3 fatty acids in relation to long-term dementia risk. *Am. J. Clin. Nutr.* 90:170–76

Droge W. 2002. Free radicals in the physiological control of cell function. *Physiol. Rev.* 82:47–95

Eriksdotter M, Vedin I, Falahati F, Freund-Levi Y, Hjorth E, et al. 2015. Plasma fatty acid profiles in relation to cognition and gender in Alzheimer's disease patients during oral omega-3 fatty acid supplementation: the OmegAD study. *J. Alzheimers Dis.* 48:805–12

Farley A, McLafferty E, Hendry C. 2011. Theories of ageing. In *The Physiological Effects of Ageing: Implications for Nursing Practice*, pp. 7–13. Oxford, UK: Wiley-Blackwell

Feart C, Letenneur L, Helmer C, Samieri C, Schalch W, et al. 2016. Plasma carotenoids are inversely associated with dementia risk in an elderly French cohort. *J. Gerontol. A* 71:683–88

Feeney J, Finucane C, Savva GM, Cronin H, Beatty S, et al. 2013. Low macular pigment optical density is associated with lower cognitive performance in a large, population-based sample of older adults. *Neurobiol. Aging* 34:2449–56

Feeney J, O'Leary N, Moran R, O'Halloran AM, Nolan JM, et al. 2017. Plasma lutein and zeaxanthin are associated with better cognitive function across multiple domains in a large population-based sample of older adults: findings from the Irish Longitudinal Study on Aging. *J. Gerontol. A* 72:1431–36

Fiedor J, Burda K. 2014. Potential role of carotenoids as antioxidants in human health and disease. *Nutrients* 6:466–88

Flodgren GM, Berg RC. 2016. NIPH systematic reviews. In *Primary and Secondary Prevention Interventions for Cognitive Decline and Dementia*. Oslo, Nor.: Nor. Inst. Public Health

Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, Basun H, Faxen-Irving G, et al. 2006. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. *Arch. Neurol.* 63:1402–8

Gardener S, Gu Y, Rainey-Smith SR, Keogh JB, Clifton PM, et al. 2012. Adherence to a Mediterranean diet and Alzheimer's disease risk in an Australian population. *Transl. Psychiatry* 2:e164

Grimm MOW, Thiel A, Lauer AA, Winkler J, Lehmann J, et al. 2017. Vitamin D and its analogues decrease amyloid-β (Aβ) formation and increase Aβ-degradation. *Int. J. Mol. Sci.* 18:E2764

Gruszecki WI, Strzalka K. 2005. Carotenoids as modulators of lipid membrane physical properties. *Biochim. Biophys. Acta* 1740:108–15

Gu Y, Luchsinger JA, Stern Y, Scarmeas N. 2010. Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. *J. Alzheimers Dis.* 22:483–92

Guest J, Grant R. 2016. Carotenoids and neurobiological health. *Adv. Neurobiol.* 12:199–228

Gupta S, Sodhi S, Mahajan V. 2009. Correlation of antioxidants with lipid peroxidation and lipid profile in patients suffering from coronary artery disease. *Expert Opin. Ther. Targets* 13:889–94

Hamazaki K, Maekawa M, Toyota T, Dean B, Hamazaki T, Yoshikawa T. 2015. Fatty acid composition of the postmortem prefrontal cortex of patients with schizophrenia, bipolar disorder, and major depressive disorder. *Psychiatry Res.* 227:353–59

Hammond BR Jr., Miller LS, Bello MO, Lindbergh CA, Mewborn C, Renzi-Hammond LM. 2017. Effects of lutein/zeaxanthin supplementation on the cognitive function of community dwelling older adults: a randomized, double-masked, placebo-controlled trial. *Front. Aging Neurosci.* 9:254

Harada CN, Natelson Love MC, Triebel KL. 2013. Normal cognitive aging. *Clin. Geriatr. Med.* 29:737–52

Hashimoto M, Hossain S, Al Mamun A, Matsuzaki K, Arai H. 2017. Docosahexaenoic acid: one molecule diverse functions. *Crit. Rev. Biotechnol.* 37:579–97

Hayflick L. 1998. How and why we age. *Exp. Gerontol.* 33:639–53

He C, Qu X, Cui L, Wang J, Kang JX. 2009. Improved spatial learning performance of fat-1 mice is associated with enhanced neurogenesis and neuritogenesis by docosahexaenoic acid. *PNAS* 106:11370–75

He W, Goodkin D, Kowal P. 2016. *An Aging World: 2015*. Washington, DC: US Gov. Publ. Office

Hooper C, De Souto Barreto P, Coley N, Cantet C, Cesari M, et al. 2017. Cognitive changes with omega-3 polyunsaturated fatty acids in non-demented older adults with low omega-3 index. *J. Nutr. Health Aging* 21:988–93

Huang TL. 2010. Omega-3 fatty acids, cognitive decline, and Alzheimer's disease: a critical review and evaluation of the literature. *J. Alzheimers Dis.* 21:673–90

Huhn S, Kharabian Masouleh S, Stumvoll M, Villringer A, Witte AV. 2015. Components of a Mediterranean diet and their impact on cognitive functions in aging. *Front. Aging Neurosci.* 7:132

Johnson EJ, Chung HY, Caldarella SM, Snodderly DM. 2008. The influence of supplemental lutein and docosahexaenoic acid on serum, lipoproteins, and macular pigmentation. *Am. J. Clin. Nutr.* 87:1521–29

Johnson EJ, Vishwanathan R, Johnson MA, Hausman DB, Davey A, et al. 2013. Relationship between serum and brain carotenoids, α-tocopherol, and retinol concentrations and cognitive performance in the oldest old from the Georgia Centenarian Study. *J. Aging Res.* 2013:951786

Kaplan LA, Lau JM, Stein EA. 1990. Carotenoid composition, concentrations, and relationships in various human organs. *Clin. Physiol. Biochem.* 8:1–10

Kaulmann A, Bohn T. 2014. Carotenoids, inflammation, and oxidative stress—implications of cellular signaling pathways and relation to chronic disease prevention. *Nutr. Res.* 34:907–29

Kesse-Guyot E, Andreeva VA, Lassale C, Ferry M, Jeandel C, et al. 2013. Mediterranean diet and cognitive function: a French study. *Am. J. Clin. Nutr.* 97:369–76

Khachik F. 2006. Distribution and metabolism of dietary carotenoids in humans as a criterion for development of nutritional supplements. *Pure Appl. Chem.* 78:1551–57

Khachik F, Beecher GR, Goli MB, Lusby WR, Smith JC Jr. 1992. Separation and identification of carotenoids and their oxidation products in the extracts of human plasma. *Anal. Chem.* 64:2111–22

Knight A, Bryan J, Murphy K. 2016. Is the Mediterranean diet a feasible approach to preserving cognitive function and reducing risk of dementia for older adults in Western countries? New insights and future directions. *Ageing Res. Rev.* 25:85–101

Kowald A, Kirkwood TB. 1996. A network theory of ageing: the interactions of defective mitochondria, aberrant proteins, free radicals and scavengers in the ageing process. *Mutat. Res.* 316:209–36

Kuipers RS, Luxwolda MF, Dijck-Brouwer DA, Eaton SB, Crawford MA, et al. 2010. Estimated macronutrient and fatty acid intakes from an East African Paleolithic diet. *Br. J. Nutr.* 104:1666–87

Kulzow N, Witte AV, Kerti L, Grittner U, Schuchardt JP, et al. 2016. Impact of omega-3 fatty acid supplementation on memory functions in healthy older adults. *J. Alzheimers Dis.* 51:713–25

Lakey-Beitia J, Doens D, Jagadeesh Kumar D, Murillo E, Fernandez PL, et al. 2017. Anti-amyloid aggregation activity of novel carotenoids: implications for Alzheimer's drug discovery. *Clin. Interv. Aging* 12:815–22

Lammich S, Kojro E, Postina R, Gilbert S, Pfeiffer R, et al. 1999. Constitutive and regulated α-secretase cleavage of Alzheimer's amyloid precursor protein by a disintegrin metalloprotease. *PNAS* 96:3922–27

Lee LK, Shahar S, Chin AV, Yusoff NA. 2013. Docosahexaenoic acid–concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. *Psychopharmacology* 225:605–12

Lindbergh CA, Mewborn CM, Hammond BR, Renzi-Hammond LM, Curran-Celentano JM, Miller LS. 2016. Relationship of lutein and zeaxanthin levels to neurocognitive functioning: an fMRI study of older adults. *J. Int. Neuropsychol. Soc.* 23:11–22

Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, et al. 2017. Dementia prevention, intervention, and care. *Lancet* 390:10113

Loef M, Walach H. 2012. Fruit, vegetables and prevention of cognitive decline or dementia: a systematic review of cohort studies. *J. Nutr. Health Aging* 16:626–30

Lonnerdal B. 2010. Calcium and iron absorption—mechanisms and public health relevance. *Int. J. Vitam. Nutr. Res.* 80:293–99

Loughrey DG, Lavecchia S, Brennan S, Lawlor BA, Kelly ME. 2017. The impact of the Mediterranean diet on the cognitive functioning of healthy older adults: a systematic review and meta-analysis. *Adv. Nutr.* 8:571–86

Lourida I, Soni M, Thompson-Coon J, Purandare N, Lang IA, et al. 2013. Mediterranean diet, cognitive function, and dementia: a systematic review. *Epidemiology* 24:479–89

Lukaschek K, von Schacky C, Kruse J, Ladwig KH. 2016. Cognitive impairment is associated with a low omega-3 index in the elderly: results from the KORA-Age study. *Dement. Geriatr. Cogn. Disord.* 42:236–45

Mapstone M, Cheema AK, Fiandaca MS, Zhong X, Mhyre TR, et al. 2014. Plasma phospholipids identify antecedent memory impairment in older adults. *Nat. Med.* 20(4):415–18

Mazereeuw G, Lanctot KL, Chau SA, Swardfager W, Herrmann N. 2012. Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. *Neurobiol. Aging* 33:1482.e17–29

McDougle DR, Watson JE, Abdeen AA, Adili R, Caputo MP, et al. 2017. Anti-inflammatory ω-3 endocannabinoid epoxides. *PNAS* 114:E6034–43

Min JY, Min KB. 2014. Serum lycopene, lutein and zeaxanthin, and the risk of Alzheimer's disease mortality in older adults. *Dement. Geriatr. Cogn. Disord.* 37:246–56

Miquel S, Champ C, Day J, Aarts E, Bahr BA, et al. 2018. Poor cognitive ageing: vulnerabilities, mechanisms and the impact of nutritional interventions. *Ageing Res. Rev.* 42:40–55

Mohammadzadeh H, Saedisomeolia A, Abdolahi M, Shayeganrad A, Taheri Sangsari G, et al. 2017. Molecular anti-inflammatory mechanisms of retinoids and carotenoids in Alzheimer's disease: a review of current evidence. *J. Mol. Neurosci.* 61:289–304

Mohanty JG, Eckley DM, Williamson JD, Launer LJ, Rifkind JM. 2008. Do red blood cell-beta-amyloid interactions alter oxygen delivery in Alzheimer's disease? *Adv. Exp. Med. Biol.* 614:29–35

Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. 2005. Fish consumption and cognitive decline with age in a large community study. *Arch. Neurol.* 62:1849–53

Morris MC, Wang Y, Barnes LL, Bennett DA, Dawson-Hughes B, Booth SL. 2018. Nutrients and bioactives in green leafy vegetables and cognitive decline: prospective study. *Neurology* 90:e214–22

Morrison JH, Baxter MG. 2012. The aging cortical synapse: hallmarks and implications for cognitive decline. *Nat. Rev. Neurosci.* 13:240–50

Mozaffarian D, Wu JH. 2011. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J. Am. Coll. Cardiol.* 58:2047–67

Mullan K, Williams MA, Cardwell CR, McGuinness B, Passmore P, et al. 2017. Serum concentrations of vitamin E and carotenoids are altered in Alzheimer's disease: a case-control study. *Alzheimers Dement.* 3:432–39

Murman DL. 2015. The impact of age on cognition. *Semin. Hearing* 36:111–21

Nakagawa K, Kiko T, Miyazawa T, Sookwong P, Tsuduki T, et al. 2011. Amyloid β-induced erythrocytic damage and its attenuation by carotenoids. *FEBS Lett.* 585:1249–54

Nolan JM, Feeney J, Kenny RA, Cronin H, O'Regan C, et al. 2012. Education is positively associated with macular pigment: the Irish Longitudinal Study on Ageing (TILDA). *Investig. Ophthalmol. Vis. Sci.* 53:7855–61

Nolan JM, Loskutova E, Howard A, Mulcahy R, Moran R, et al. 2015. The impact of supplemental macular carotenoids in Alzheimer's disease: a randomized clinical trial. *J. Alzheimers Dis.* 44:1157–69

Nolan JM, Loskutova E, Howard AN, Moran R, Mulcahy R, et al. 2014. Macular pigment, visual function, and macular disease among subjects with Alzheimer's disease: an exploratory study. *J. Alzheimers Dis.* 42:1191–202

Nolan JM, Mulcahy R, Power R, Moran R, Howard A. 2018. Nutritional intervention to prevent Alzheimer's disease: potential benefits of xanthophyll carotenoids and omega-3 fatty acids combined. *J. Alzheimer's Dis.* 64:367–78

Obulesu M, Dowlathabad MR, Bramhachari PV. 2011. Carotenoids and Alzheimer's disease: an insight into therapeutic role of retinoids in animal models. *Neurochem. Int.* 59:535–41

Okabe N, Nakamura T, Toyoshima T, Miyamoto O, Lu F, Itano T. 2011. Eicosapentaenoic acid prevents memory impairment after ischemia by inhibiting inflammatory response and oxidative damage. *J. Stroke Cerebrovasc. Dis.* 20:188–95

Otaegui-Arrazola A, Amiano P, Elbusto A, Urdaneta E, Martinez-Lage P. 2014. Diet, cognition, and Alzheimer's disease: food for thought. *Eur. J. Nutr.* 53:1–23

Pannese E. 2011. Morphological changes in nerve cells during normal aging. *Brain Struct. Funct.* 216:85–89

Pelletier A, Barul C, Feart C, Helmer C, Bernard C, et al. 2015. Mediterranean diet and preserved brain structural connectivity in older subjects. *Alzheimers Dement.* 11:1023–31

Peters R. 2006. Ageing and the brain. *Postgrad. Med. J.* 82:84–88

Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, et al. 2009. Mild cognitive impairment: ten years later. *Arch. Neurol.* 66:1447–55

Phillips MA, Childs CE, Calder PC, Rogers PJ. 2012. Lower omega-3 fatty acid intake and status are associated with poorer cognitive function in older age: a comparison of individuals with and without cognitive impairment and Alzheimer's disease. *Nutr. Neurosci.* 15:271–77

Power R, Coen RF, Beatty S, Mulcahy R, Moran R, et al. 2018. Supplemental retinal carotenoids enhance memory in healthy individuals with low levels of macular pigment in a randomized, double-blind, placebo-controlled clinical trial. *J. Alzheimers Dis.* 61:947–61

Raji CA, Erickson KI, Lopez O, Kuller LH, Gach HM, et al. 2014. Regular fish consumption and age-related brain gray matter loss. *Am. J. Prev. Med.* 47:444–51

Raz N. 2009. Decline and compensation in aging brain and cognition: promises and constraints. *Neuropsychol. Rev.* 19:411–14

Renzi LM, Bovier ER, Hammond BR Jr. 2013. A role for the macular carotenoids in visual motor response. *Nutr. Neurosci.* 16:262–68

Renzi LM, Dengler MJ, Puente A, Miller LS, Hammond BR Jr. 2014. Relationships between macular pigment optical density and cognitive function in unimpaired and mildly cognitively impaired older adults. *Neurobiol. Aging* 35:1695–99

Reuter-Lorenz PA, Park DC. 2014. How does it STAC up? Revisiting the scaffolding theory of aging and cognition. *Neuropsychol. Rev.* 24:355–70

Rinaldi P, Polidori MC, Metastasio A, Mariani E, Mattioli P, et al. 2003. Plasma antioxidants are similarly depleted in mild cognitive impairment and in Alzheimer's disease. *Neurobiol. Aging* 24:915–19

Roberts RO, Geda YE, Cerhan JR, Knopman DS, Cha RH, et al. 2010. Vegetables, unsaturated fats, moderate alcohol intake, and mild cognitive impairment. *Dement. Geriatr. Cogn. Disord.* 29:413–23

Sakai C, Ishida M, Ohba H, Yamashita H, Uchida H, et al. 2017. Fish oil omega-3 polyunsaturated fatty acids attenuate oxidative stress–induced DNA damage in vascular endothelial cells. *PLOS ONE* 12:e0187934

Salat DH, Kaye JA, Janowsky JS. 1999. Prefrontal gray and white matter volumes in healthy aging and Alzheimer disease. *Arch. Neurol.* 56:338–44

Salem N Jr., Vandal M, Calon F. 2015. The benefit of docosahexaenoic acid for the adult brain in aging and dementia. *Prostaglandins Leukot. Essent. Fatty Acids* 92:15–22

Salthouse TA. 2009. When does age-related cognitive decline begin? *Neurobiol. Aging* 30:507–14

Salvati S, Natali F, Attorri L, Di Benedetto R, Leonardi F, et al. 2008. Eicosapentaenoic acid stimulates the expression of myelin proteins in rat brain. *J. Neurosci. Res.* 86:776–84

Scahill RI, Frost C, Jenkins R, Whitwell JL, Rossor MN, Fox NC. 2003. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. *Arch. Neurol.* 60:989–94

Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, et al. 2006. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. *Arch. Neurol.* 63:1545–50

Sheppard KW, Cheatham CL. 2018. Omega-6/omega-3 fatty acid intake of children and older adults in the U.S.: dietary intake in comparison to current dietary recommendations and the Healthy Eating Index. *Lipids Health Dis.* 17:43

Shichiri M. 2014. The role of lipid peroxidation in neurological disorders. *J. Clin. Biochem. Nutr.* 54:151–60

Singh B, Parsaik AK, Mielke MM, Erwin PJ, Knopman DS, et al. 2014. Association of Mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. *J. Alzheimers Dis.* 39:271–82

Skaper SD, Facci L, Zusso M, Giusti P. 2018. An inflammation-centric view of neurological disease: beyond the neuron. *Front. Cell. Neurosci.* 12:72

Smedt-Peyrusse VD, Sargueil F, Moranis A, Harizi H, Mongrand S, Layé S. 2008. Docosahexaenoic acid prevents lipopolysaccharide-induced cytokine production in microglial cells by inhibiting lipopolysaccharide receptor presentation but not its membrane subdomain localization. *J. Neurochem.* 105:296–307

Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. 2014. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. *Public Health Nutr.* 17:2769–82

Sohl G, Maxeiner S, Willecke K. 2005. Expression and functions of neuronal gap junctions. *Nat. Rev. Neurosci.* 6:191–200

Solfrizzi V, Custodero C, Lozupone M, Imbimbo BP, Valiani V, et al. 2017. Relationships of dietary patterns, foods, and micro- and macronutrients with Alzheimer's disease and late-life cognitive disorders: a systematic review. *J. Alzheimers Dis.* 59:815–49

Sugasini D, Thomas R, Yalagala PCR, Tai LM, Subbaiah PV. 2017. Dietary docosahexaenoic acid (DHA) as lysophosphatidylcholine, but not as free acid, enriches brain DHA and improves memory in adult mice. *Sci. Rep.* 7:11263

Sydenham E, Dangour AD, Lim WS. 2012. Omega 3 fatty acid for the prevention of cognitive decline and dementia. *Cochrane Database Syst. Rev.* 13:CD005379

Talaei M, Rabiei K, Talaei Z, Amiri N, Zolfaghari B, et al. 2013. Physical activity, sex, and socioeconomic status: a population based study. *ARYA Atherscler.* 9:51–60

Thompson JJ, Blair MR, Henrey AJ. 2014. Over the hill at 24: persistent age-related cognitive-motor decline in reaction times in an ecologically valid video game task begins in early adulthood. *PLOS ONE* 9:e94215

Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, Gnardellis C, Lagiou P, et al. 1995. Diet and overall survival in elderly people. *BMJ* 311:1457–60

Ubeda N, Achon M, Varela-Moreiras G. 2012. Omega 3 fatty acids in the elderly. *Br. J. Nutr.* 107(Suppl. 2):S137–51

US Natl. Inst. Aging, World Health Organ. 2011. *Global Health and Ageing*. Geneva, Switz. WHO

Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, et al. 2015. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. *JAMA Intern. Med.* 175:1094–103

Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, et al. 1999. β-Secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. *Science* 286:735–41

Vauzour D, Camprubi-Robles M, Miquel-Kergoat S, Andres-Lacueva C, Banati D, et al. 2017. Nutrition for the ageing brain: towards evidence for an optimal diet. *Ageing Res. Rev.* 35:222–40

Vishwanathan R, Schalch W, Johnson EJ. 2016. Macular pigment carotenoids in the retina and occipital cortex are related in humans. *Nutr. Neurosci.* 19:95–101

Wang W, Shinto L, Connor WE, Quinn JF. 2008. Nutritional biomarkers in Alzheimer's disease: the association between carotenoids, n-3 fatty acids, and dementia severity. *J. Alzheimers Dis.* 13:31–38

White PJ, Broadley MR. 2005. Historical variation in the mineral composition of edible horticultural products. *J. Hortic. Sci. Biotechnol.* 80:660–67

Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina AM, et al. 2017. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimer's Dement*. 13:1–7

Witte AV, Kerti L, Hermannstadter HM, Fiebach JB, Schreiber SJ, et al. 2014. Long-chain omega-3 fatty acids improve brain function and structure in older adults. *Cereb. Cortex* 24:3059–68

Wu S, Ding Y, Wu F, Li R, Hou J, Mao P. 2015. Omega-3 fatty acids intake and risks of dementia and Alzheimer's disease: a meta-analysis. *Neurosci. Biobehav. Rev.* 48:1–9

Yurko-Mauro K, Alexander DD, Van Elswyk ME. 2015. Docosahexaenoic acid and adult memory: a systematic review and meta-analysis. *PLOS ONE* 10:e0120391

Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, et al. 2010. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. *Alzheimers Dement*. 6:456–64

Zamberletti E, Piscitelli F, De Castro V, Murru E, Gabaglio M, et al. 2017. Lifelong imbalanced LA/ALA intake impairs emotional and cognitive behavior via changes in brain endocannabinoid system. *J. Lipid Res.* 58:301–16

Zamroziewicz MK, Paul EJ, Zwilling CE, Johnson EJ, Kuchan MJ, et al. 2016. Parahippocampal cortex mediates the relationship between lutein and crystallized intelligence in health, older adults. *Front. Ageing Neurosci.* 8:297

Zaragoza-Martí A, Cabañero-Martínez MJ, Hurtado-Sánchez JA, Laguna-Pérez A, Ferrer-Cascales R. 2018. Evaluation of Mediterranean diet adherence scores: a systematic review. *BMJ Open* 8:e019033

Zhang S, Dong H, Zhang X, Li N, Sun J, Qian Y. 2016a. Cerebral mast cells contribute to postoperative cognitive dysfunction by promoting blood brain barrier disruption. *Behav. Brain Res.* 298:158–66

Zhang Y, Chen J, Qiu J, Li Y, Wang J, Jiao J. 2016b. Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies. *Am. J. Clin. Nutr.* 103:330–40