Chapter 3
Nutritional, Dietary, and Lifestyle Approaches for Prevention and Management of Alzheimer's Disease

Supta Sarkar and Madhubalaji Chegu Krishnamurthi

Abstract Neurodegenerative disorders have grabbed global attention as it resulted in morbidity and disability worldwide. Neurodegenerative diseases pertaining to the central nervous system are heterogeneous disorders characterized by the progressive degeneration of its structure and function. Alzheimer's disease is one of the most frequently occurring neurodegenerative disorders and is the major cause of dementia. Worldwide 50 million people are suffering from dementia (among 60–70% belongs to Alzheimer's disease), and it is increasing at the rate of ten million new cases per year. There is a vast evidence for possible dietary risk factors in the development of Alzheimer's disease and cognitive decline with age. Therefore, diet and nutrition are essential in modulating the risk of Alzheimer's disease. Epidemiological evidence demonstrates a protective role of dietary supplementation of antioxidants, polyunsaturated fatty acids, B complex vitamins, essential elements, and polyphenols, which could protect the brain from oxidative and inflammatory damage. Furthermore, consumption of fish, fruits, vegetables, coffee, and light-to-moderate alcohol reduces the risk of Alzheimer's disease. Adherence to a healthy diet and the dietary patterns like the Mediterranean diet or DASH diet are associated with a lower risk of Alzheimer's disease. This chapter focused on the epidemiological evidence linking many nutrients, foods, and dietary habits to Alzheimer's disease.

Keywords Alzheimer's disease · Nutrition · Diet · Dietary pattern · Dietary recommendation

S. Sarkar (✉)
Department of Foods and Nutrition, College of Community Science, Professor Jayashankar Telangana State Agricultural University, Hyderabad, Telangana, India

M. Chegu Krishnamurthi
Plant Cell Biotechnology Department, CSIR – Central Food Technological Research Institute, Mysuru, Karnataka, India

Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, India

S. Rajagopal et al. (eds.), *Role of Nutrients in Neurological Disorders*, Nutritional Neurosciences, https://doi.org/10.1007/978-981-16-8158-5_3

3.1 Introduction

Alzheimer's disease is a neurodegenerative and progressive disorder characterized by deterioration in intellect, affecting memory, thought, language, reasoning, learning, orientation, comprehension, judgment, as well as behavior and impairment of everyday activities (Abate et al. 2017). Alzheimer's disease, primarily causing dementia worldwide, accounts for 50–60% of all cases (Morris 2009). The global prevalence of dementia is expected to double every 20 years, and it will be more than 80 million people by 2040 (Morris 2009) and the estimate of Alzheimer's disease cases is projected to reach 106.8 million worldwide by 2050; hence, it is a growing public health issue with a global socioeconomic burden (Hu et al. 2013).

Alzheimer's disease has a complex, multifactorial neuropathophysiology involving the deposition of extracellular 4 kDa peptide amyloid beta (Aβ) plaques and somatodendritic makeup of hyperphosphorylated tau protein-producing intraneuronal neurofibrillary tangles, which are both associated with synaptic and neuronal loss and neuroanatomic dysfunctions, including those involving cholinergic transmission (Swaminathan and Jicha 2014; Kamphuis and Wurtman 2009; Bazan et al. 2011). Besides these critical pathological characteristics of Alzheimer's disease, there is ample evidence that increased oxidative stress, abnormalities in mitochondrial dysfunction and the development of cellular energy, and chronic inflammatory responses lead to the degenerative cascade of this complex disease (Swaminathan and Jicha 2014). Alzheimer's disease is broadly divided into two primary forms: early onset and late-onset. The uncommon early onset form of Alzheimer's disease (about 1% of all cases of Alzheimer's disease) is characterized by autosomal-dominant genetic mutations, symptoms starting before age 60, and genetically induced Aβ overproduction (Mosconi and McHugh 2015). Less than 1% of Alzheimer's cases are caused by particular mutations in three genes for amyloid precursor protein (APP), presenilin-1, and presenilin-2, all associated with Aβ metabolism (Abate et al. 2017). At a cellular level, dysfunction in the processing of βAPP results in an overabundance of the 42 amino acid Aβ42 peptide oligomer, which initially impairs synaptic function. Aβ42 triggers damaging signals (accompanied by early apoptosis) and changes in gene expression, which emulate neurodegeneration and Alzheimer's disease characteristics. Neuroinflammatory degeneration related to Aβ42 is an essential contributory factor to the neuropathology of Alzheimer's disease (Bazan et al. 2011). On the other hand, the most common form of late-onset Alzheimer's disease (onset after 60 years of age), which accounts for >99% of the total population of Alzheimer's disease, is a multifactorial disease of unknown origin most likely to develop from the complex interaction between genetic and environmental factors (Mosconi and McHugh 2015). Late-onset Alzheimer's disease has been correlated with several risk factors, including demographics (i.e., old age, female gender, low education), ancestry or inheritance (i.e., family history of first-degree, epsilon 4 allele of the apolipoprotein E gene [APOE? 4]), medical status (i.e., hypertension, cardiovascular disease), cognitive status (i.e., objective and subjective cognitive decline), environmental factors (i.e., pollutants,

environmental toxins), and lifestyle factors (poor diet, low physical or social activities, chronic stress) (Mosconi and McHugh 2015).

At present, there is no cure for Alzheimer's disease, and the existing therapies only momentarily alleviate the symptoms (Sindi et al. 2015; Kamphuis and Wurtman 2009). The prevailing medical therapies improve the transmission of acetylcholine and other neurotransmitters, along with various multidisciplinary strategies which focus on improving the quality of life and reducing symptom burden (Swaminathan and Jicha 2014). There are two major challenges concerning Alzheimer's disease: the delay in diagnosis and the lack of neuroprotective or curative pharmacological treatment. In fact, Alzheimer's disease is only recognized in the later stage when cognitive performance begins to decline (Abate et al. 2017). The G8 Dementia Summit and World Health Organization (WHO) have identified dementia and Alzheimer's disease prevention as a major public health concern (WHO 2012; G8 Dementia Summit Declaration 2013). Thus, there is a strong unmet need for effective prevention and therapeutic strategies. Furthermore, evidence showed the potential role of nutrition in such strategies is rapidly gaining interest (Kamphuis and Wurtman 2009).

Diet and nutrition have been increasingly recognized as the potential factors influencing the susceptibility of Alzheimer's disease by preventing or delaying cognitive decline (Mosconi and McHugh 2015; Kamphuis and Wurtman 2009). Thus, a potential role for nutrition in the prevention and management of Alzheimer's disease seems likely. A growing body of literature, from preclinical to epidemiological, provides evidence of dietary and nutrient trends associated with Alzheimer's disease risk biomarkers, suggesting that dietary nutrients may modulate the risk of Alzheimer's and cognitive function. Nutrients effect on the deposition of Aβ and associated neuronal damage even several years before the potential onset of symptoms (Mosconi and McHugh 2015). Several nutrients such as monounsaturated and ω-3 fatty acids, antioxidants, vitamins, and polyphenols have been documented to minimize the risk of Alzheimer's disease, whereas saturated fat intake, high-calorie intake, and excessive alcohol intake have been identified as risk factors (Hu et al. 2013). The combined effect of dietary fats with the level of plasma cholesterol is of great importance due to the role of cholesterol involved in both Aβ production and deposition. Besides, the protein APOE?4, which is a known genetic risk factor for Alzheimer's disease is the key cholesterol transporter in the brain (Abate et al. 2017).

This chapter will discuss the impact of nutrition, diet, and dietary pattern on Alzheimer's disease, the most common cause of dementia. Dietary and lifestyle approaches for prevention and management of Alzheimer's disease will also be focused in the later section.

3.1.1 Risk Factors

Several factors are contributing to the risk of Alzheimer's disease (Fig. 3.1), including older age, genetic factors (particularly the presence of the allele APOEε4), family

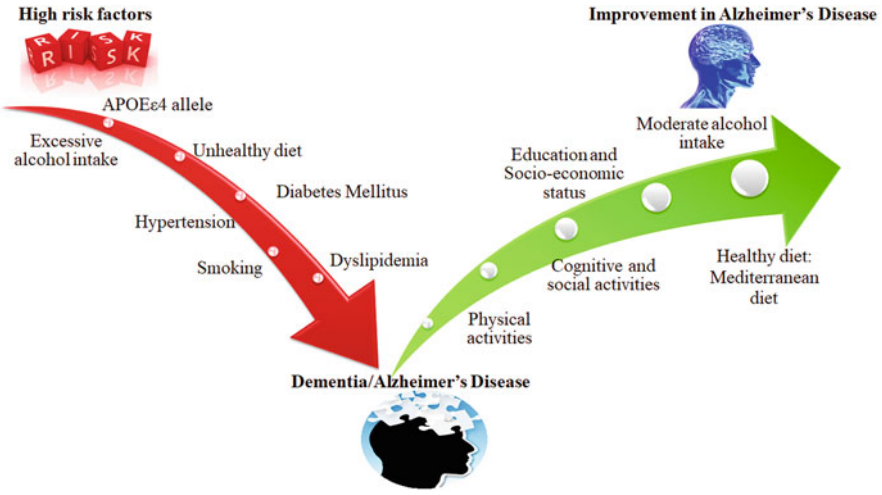

Fig. 3.1 Risk factors associated with Alzheimer's disease

history, obesity, diabetes mellitus, hypertension, and hypercholesterolemia, cardiovascular problems, lifestyle factors like dietary pattern, excessive alcohol consumption, smoking; a history of head injury, anxiety, stress, depression, and also low physical activity (Sindi et al. 2015; Barnard et al. 2014; Morris 2009). A vast amount of studies have also suggested that dietary and lifestyle factors may influence risk, raising the possibility that preventive strategies with diet may be effective (Barnard et al. 2014).

3.2 Role of Nutrients in Prevention and Management of Alzheimer's Disease

The "precautionary principle" is applied in toxicology under circumstances where there is significant ground for concern about the health effects on exposure and where available evidence precludes a thorough risk evaluation (European Commission 2000). A similar approach may be extended to nutrition and other lifestyle-related exposures, particularly in conditions such as Alzheimer's disease, where there may be a long period of latency between exposure and the disease manifestation (Barnard et al. 2014). A nutritional and dietary approach to prevent or slow the progression of Alzheimer's disease can be a promising strategy and thus has been widely explored (Abate et al. 2017). It is well known today that certain dietary nutrients, including polyunsaturated fatty acids (PUFA), vitamins, essential elements, and polyphenolic compounds, may significantly affect the aging of the brain, contributing to enhanced memory and motor skills. All of these compounds have powerful antioxidant and anti-inflammatory activity (Abate et al. 2017; Hu et al. 2013) and have the ability to enhance cognition. However, it is not limited to

their antioxidant properties, since they often involve particular complex molecular and cellular processes that promote brain plasticity (Abate et al. 2017). In this section, we will discuss different nutrients which play a role in the prevention or management of Alzheimer's disease.

3.2.1 Antioxidants

Multiple studies have shown that Alzheimer's disease involves oxidative and inflammatory activities, but it is not clear if such processes are a cause or consequence of the disease or both (Morris 2009). Oxidative stress and the inflammatory mechanism eventually contribute to a disruption of the functioning and signaling of neuronal cells, leading to neuronal cell death (Morris 2009; Gustafson et al. 2015). Oxidative stress occurs when the intracellular capacity to expel free radicals is surpassed, resulting in changes in DNA, lipids, polysaccharides, and proteins, as well as changes in the homeostatic redox balance. A common and early characteristic of Alzheimer's pathology is oxidative stress. Some of the pathogenic factors, such as oxidative damage, accelerated amyloidogenic APP processing, mitochondrial dysfunction, and Aβ accumulation, are observed at synaptic terminals of the brains of Alzheimer's disease patients and animal models, which are associated with synaptic dysfunction. This is crucial because synaptic disruption is a key factor in cognitive impairment during aging and Alzheimer's disease progression (Gustafson et al. 2015). The antioxidant, which offers the most protection, is still debatable. Some antioxidants ideally target cytosolic oxidative stress pathways, while others typically function as mitochondrial cofactors that can reduce the intrinsic mechanisms of oxidative stress (Swaminathan and Jicha 2014). There are several potential sites of activity and complex antioxidant-influenced cellular pathways. The hypothesis that antioxidant therapy can prevent or delay the Alzheimer's disease progression has led to many studies suggesting potential risks and advantages of antioxidant therapy for the treatment of Alzheimer's disease (Swaminathan and Jicha 2014). Antioxidants such as vitamins E and C constitute the body's innate defense mechanisms to combat oxidative stress (Morris 2009).

In animal models, dietary supplement studies with antioxidants exhibited better learning attainment and memory retention. At death, the brains of the antioxidant-fed animal models unveiled less neuronal cell loss and less evidence of oxidative damage and inflammation (Morris 2009). Thus, dietary nutrients with antioxidant properties may have positive effects in Alzheimer's disease and those at risk for the disease by reducing oxidative stress, particularly when used in combination (Gustafson et al. 2015). It has been shown that the dietary intake of antioxidants in foods is superior to supplements in human studies on cognition and risk of developing Alzheimer's disease (Zandi et al. 2004; Morris et al. 2002). Several nutrients, particularly vitamin C, vitamin E, and carotenoids, and non-nutrient food ingredients such as polyphenols and anthocyanins, have direct antioxidant activity. Furthermore, some essential elements such as selenium, zinc, and copper serve as cofactors for

proteins or enzymes with antioxidative potential (Scarmeas et al. 2018). Thus, the intake of dietary antioxidants could have an effect on the development of cognitive impairment.

3.2.2 Dietary Fat

Changes in fatty acid composition and levels have important implications on neuronal integrity during aging and for the development of Alzheimer's disease (Morris and Tangney 2014; Gustafson et al. 2015).

3.2.3 Saturated Fat and Trans Fat

Several studies, although not all, have suggested an association between intake of saturated or trans fats with Alzheimer's disease (Barnard et al. 2014; Morris and Tangney 2014; Hu et al. 2013). The Chicago Health and Aging Project has shown that the population with higher saturated fat intake had twice the risk of developing the disease (Morris et al. 2003). A moderate intake of saturated fatty acids has been associated with an increased risk of Alzheimer's disease and dementia, especially among APOEε4 carriers (Laitinen et al. 2006). Trans-fatty acid can also potentially increase the risk of Alzheimer's or trigger an earlier occurrence of the disease by increasing Aβ production through increasing amyloidogenic processing and by decreasing APP through non-amyloidogenic processing (Hu et al. 2013). Additional evidence of probabilistic associations between saturated or trans fat intake and Alzheimer's risk stems from the fact that the APOEε4 allele, which is strongly correlated to Alzheimer's disease, produces a protein that plays a crucial role in the transportation of cholesterol. Also, the observational studies indicate that consumption of high-fat foods and increased blood cholesterol concentrations may contribute to Aβ production or its aggregation in the brain tissues (Barnard et al. 2014).

3.2.4 Monounsaturated fatty acid (MUFA)

Monounsaturated fatty acids (MUFAs) and their derivatives have anti-inflammatory effects (Borniquel et al. 2010). Intake of higher monounsaturated fatty acid was associated with better cognitive function, while higher saturated fatty acid was linked with worse cognitive function (Hu et al. 2013).

3.2.5 *Polyunsaturated Fatty Acid (PUFA)*

Numerous studies have investigated the effects of PUFAs in preventing or slowing Alzheimer's disease, while elevated intake of PUFA might be beneficial to Alzheimer's disease (Hu et al. 2013). The ability of PUFA to avoid neuronal loss and cognitive impairment derives from the evidence that PUFAs are vital components of neuronal cell membranes, retaining membrane fluidity necessary for neural network connectivity of the synaptic vesicle fusion and neurotransmitter (Joseph et al. 2009). Long-term ω-3 supplementation to the animal models showed that a decreased ω-6/ω-3 ratio reduced Aβ, prevented neuronal failure and increased cognitive function in Alzheimer's (Abate et al. 2017).

The ω-3 long-chain PUFAs (ω-3 LC-PUFA's), which are primarily docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), control the excitability of the neuronal membrane and enhance the capacity for neuronal transmission, thus improving memory and learning (Abate et al. 2017). In addition, ω-3 LC-PUFA's modulate the inflammatory processes by functioning in several different ways at the level of the immune system with respect to (1) controlling the expression of cytokines and chemokines, (2) decreasing prostaglandins and eicosanoids, and (3) inducing proresolutive factors, resolvins, and protectins which are involved in inflammation resolution (Abate et al. 2017). Interestingly, Freund Levi et al. (2014) reported that ω-3 LC-PUFAs rich diet significantly improved the levels of DHA in the brain, and indicating that supplementation of ω-3 LC-PUFA's like DHA and EPA might directly impact neuroinflammatory pathways. Thus LC-PUFA's may hold promise for the prevention and treatment of Alzheimer's disease (Morris 2009). Furthermore, studies demonstrated that DHA has effects in reducing Aβ production (Abate et al. 2017). The major mechanism involved in the DHA-induced reduction of Aβ may be due to multiple implications: changes in the structure of lipid raft, alterations in the processing of APP, and induction of anti-amyloidogenic chaperones for APP (Abate et al. 2017). In comparison to the pro-inflammatory effect of other members of the ω-6 PUFA family (Bazan et al. 2011), ω-3 DHA exhibits anti-inflammatory and inflammatory mitigating properties. Supplementation of dietary ω-3 polyunsaturated fatty acids has been reported to influence gene expression that could affect inflammatory processes (Hu et al. 2013). Metabolic trials have shown that diets with a high ratio of saturated to polyunsaturated or monounsaturated fats contribute to poor plasma cholesterol profile, which may play a central role in Alzheimer's disease due to its involvement in both the generation and deposition of Aβ (Morris 2009). The most important genetic risk factor for Alzheimer's disease is the APOEε4, which is predominantly responsible for regulating cholesterol transport in the brain. Diet-induced hypercholesterolemia accelerates Aβ deposition in the brain, whereas a diet rich with unsaturated fat exhibits superior memory and learning (Morris 2009). The primary role of lipids in maintaining neuronal integrity has clear insinuations for dietary impact in Alzheimer's disease prevention and management.

3.2.6 Carbohydrate

It has been indicated that type 2 diabetes mellitus patients are at elevated risk of developing Alzheimer's disease (Williams et al. 2010). The common mechanism has been proposed to be the deficient brain insulin signaling pathway. With increased exposure to glucose, several proteins in neurons are prone to glycation, which is an important contributor to Alzheimer's disease (Hu et al. 2013). Therefore, a high dietary intake of carbohydrates may be detrimental to Alzheimer's. However, sufficient information is not available to establish the association between a high carbohydrate diet and Alzheimer's disease. A prospective study by Luchsinger et al. (2007) indicated that carbohydrate content in food was not associated with a higher risk of the disease.

3.2.7 Vitamins

Vitamins are strong antioxidants. Their potential to maintain healthy cognition and inhibit cognitive decline is heightened by the fact that the brain is highly susceptible to damage from oxidative stress. The brain is a major oxygen metabolizer, accounting for 20% of the body's consumption, and has relatively weak antioxidant protective mechanisms. It also contains a large amount of prooxidants such as polyunsaturated peroxidizable fatty acids, along with high iron levels. Accumulation of free radicals in the brain environment leads to a steady decline in cognitive abilities, intensifying dementia (Abate et al. 2017). Studies have revealed that antioxidants protect the brain from oxidative and inflammatory damages (Morris 2009).

3.2.8 Vitamin B Complex

Because of their involvement with neuronal metabolic pathways, most of the B complex vitamins are directly or indirectly linked with neuronal health. Such vitamin deficiency has been directly associated with the development of specific neurological disorders (Swaminathan and Jicha 2014). Reportedly, vitamin B_6 reduces oxidative stress in Alzheimer's disease (Hashim et al. 2011). Several studies have indicated that elevated levels of serum homocysteine and lower folate and B_{12} levels are linked with increased risk of Alzheimer's disease, as it is observed that level of homocysteine to be significantly higher in Alzheimer's disease patients (Morris et al. 2003; Morris 2012; Nilforooshan et al. 2011). Older individuals with higher homocysteine levels appear to have lower vitamin B status and lower cognition (Abate et al. 2017). B vitamins can contribute to Alzheimer's by hindering oxidative stress and diminishing homocysteine concentrations (Hu et al. 2013). Increased dietary folate

intake has been reported to reduce Alzheimer's disease risk (Corrada et al. 2005). Nonetheless, few studies confirmed that vitamin B did not play a significant role in cognitive or neuropsychological functions (Kwok et al. 2011). The reasons for this inconsistency might be due to differences in study design, dissimilar pathological conditions of the patients, and the varied measurements of the results.

3.2.9 Vitamin C

Vitamin C has been shown to reduce the development of Aβ oligomers and oxidative stress (Murakami et al. 2011). Prospective observational studies have indicated that the combined use of vitamin C and vitamin E for at least 3 years has been associated with a decrease in Alzheimer's disease prevalence and incidence (Zandi et al. 2004). However, there are contradictory studies on the impact of vitamin C supplementation on Alzheimer's disease (Devore et al. 2010). Overall, however, there is ample evidence ensuring healthy levels of vitamin C may have a protective effect against Alzheimer's disease, thus avoiding vitamin C deficiency from a normal healthy diet is likely to be more advantageous than taking supplements (Harrison 2012).

3.2.10 Vitamin E

Vitamin E is a lipid-soluble potent chain-breaking antioxidant that has been found to confer neuroprotection by inhibiting oxidative and scavenging Aβ-associated free radicals (Hu et al. 2013). Vitamin E is perhaps the most extensively investigated vitamin for its role in protecting membrane phospholipids against peroxidation (Gustafson et al. 2015). Supplementation of vitamin E for patients with moderate Alzheimer's disease showed that it delayed the progression of the disease and therefore reduced the likelihood of institutionalization (Zandi et al. 2004). The Chicago Health and Aging Project found higher vitamin E intake from food sources to be correlated with decreased incidences of Alzheimer's disease (Morris et al. 2005) and dementia (Devore et al. 2010). The level of evidence for dietary tocopherols is high, with a low intake showing deleterious impact (Gustafson et al. 2015). The best evidence for antioxidant defense against Alzheimer's disease is a high intake of vitamin E in the diet. Thus, for the dietary management of Alzheimer's disease, vitamin E should be obtained from foods rather than taken as supplements (Barnard et al. 2014).

3.2.11 Vitamin D

Vitamin D may have little role in Aβ mechanisms, and its potential link with Alzheimer's disease may include pathways such as antioxidative, anti-inflammatory, vascular, or metabolic pathways (Hu et al. 2013). Observational studies provide vast evidence that a low concentration of vitamin D is a risk factor for developing Alzheimer's disease (Abate et al. 2017). Furthermore, as Alzheimer's disease patients have a lower levels of serum vitamin D which was associated with cognitive decline (Annweiler et al. 2013). Five months of vitamin D_3 supplementation improved learning and memory (Landel et al. 2016), which has been demonstrated in animal models of Alzheimer's disease. Vitamin D supplementation has also reported inducing expression of immune and inflammatory response proteins, neurotransmitter activity, and endothelial and vascular processes with a substantial decrease in amyloid plaques and astrogliosis. Thus, the guidelines of the Endocrine Society for keeping vitamin D_3 concentrations above 75 nmol/L should be considered to minimize the risk of Alzheimer's disease (Grant 2016).

3.2.12 Vitamin A

Vitamin A and β-carotene could be key molecules for the prevention of Alzheimer's disease and its therapy due to their ability to inhibit both Aβ oligomerization and fibrils formation (Hu et al. 2013). In an in vitro study, Takasaki et al. (2011) demonstrated a possible correlation between vitamin A, β-carotene, and Alzheimer's disease with apropos to anti-Aβ oligomerization. Furthermore, low serum and plasma concentrations of vitamin A and β-carotene have been indicated in Alzheimer's disease patients, whereas a higher β-carotene plasma level was associated with better memory performance (Hu et al. 2013). However, more clinical studies are required to establish the potential benefit of vitamin A supplementation in Alzheimer's disease patients.

3.3 Minerals

Minerals too play an important role in the pathophysiology of Alzheimer's disease when consumed in excess or scanty.

3.3.1 Selenium

Selenium is one of the essential micronutrients in humans and is reported to have antioxidant properties. However, it is toxic at higher doses (Rayman 2000). Selenium plays an important role in antioxidative defense and inflammatory disease (Hu et al. 2013). A significantly lower level of plasma selenium has been reported in Alzheimer's disease patients (Cardoso et al. 2010). Several supplementation trials have demonstrated intervention of selenium improved cognition (Chandra 2001; Cornelli 2010; Scheltens et al. 2010); however, the effect of selenium supplementation in Alzheimer's disease requires validation.

3.3.2 Copper

Copper is essential for life, but it is also toxic when consumed in excess. High circulating serum copper has been reported in Alzheimer's disease patients, which are associated with high risk (Squitti 2012; Ventriglia et al. 2012). Thus, copper dysfunction is thought to play a role in Alzheimer's pathology (Hu et al. 2013). Even though a prospective, randomized supplementary trial showed that oral copper supplementation did not affect the progression of Alzheimer's disease(Kessler et al. 2008), some studies have indicated that excessive intake of iron and copper may contribute to cognitive problems (Brewer 2009, 2012; Stankiewicz and Brass 2009). Individuals with a high dietary intake of saturated fat in conjunction with high copper were reported to have cognitive decline (Loef and Walach 2012).

3.3.3 Iron

Iron facilitates oxidative stress in Alzheimer's disease, and disparity in iron homeostasis may be a potential risk for the disease (Hu et al. 2013). Irrespective of baseline iron status, its supplementation has been reported to improve attention and concentration in older children and adults (Falkingham et al. 2010). However, excessive dietary intake of iron, along with high saturated fat, should be avoided in the elderly (Loef and Walach 2012).

3.3.4 Zinc

In Alzheimer's disease patients, cognition loss has been associated with zinc deficiency (Hu et al. 2013). Animal supplementation trial revealed intervention of zinc

had reduced both Aβ and tau pathologies in Alzheimer's disease models (Corona et al. 2010). However, limited data is available for clinical studies.

3.3.5 Aluminum

Like many other minerals Aluminum's role in Alzheimer's disease also remains controversial. Some researchers have reported aluminum's as neurotoxic when present in large amounts in the body (Barnard et al. 2014) but aluminum has been found in the brains of individuals with Alzheimer's disease (Crapper et al. 1976). Prevalence of Alzheimer's was also found to be higher in areas of the United Kingdom and France where water from tap contained higher aluminum concentrations (Barnard et al. 2014). However, due to limited data, its role in Alzheimer's disease risk cannot be ascertained.

3.3.6 Polyphenols

Polyphenols are phytonutrients present in many fruits and vegetables. The advantageous role of dietary polyphenols has been proposed as a potential functional food to prevent memory weakening. Their effects may be not only due to their properties of antioxidant and anti-inflammation but also due to their ability in modulating enzyme activity and regulating intracellular signaling pathways and gene expression (Choi et al. 2012; Obrenovich et al. 2010). Polyphenols, particularly flavonoids, has the potential to modulate those neuronal signaling cascades, improving memory and learning (Abate et al. 2017). Polyphenol supplementation can play a role in the prevention by inhibiting Aβ oligomer formation as well as destabilizing preformed Aβoligomers (Ono et al. 2003) and thereby attenuating cognitive deterioration (Hartman et al. 2006; Ho et al. 2009). The phenolic curcumin also has a potential role in the prevention and treatment of Alzheimer's disease. Curcumin, a bioactive yellow-pigmented component of *Curcuma longa*, (commonly called turmeric in India) has potent anti-inflammatory, antioxidant, and anticancer properties (Abate et al. 2017). An animal study showed that curcumin reduced pro-inflammatory cytokines, oxidative damage, Aβ production, and ameliorating cognitive deficits (Frautschy et al. 2001). In addition, it has been reported that curcumin decreased the oxidation of lipoprotein and the formation of free radicals in Alzheimer's disease and in other neurodegenerative disorders (Kim et al. 2005). However, further studies are necessary to demonstrate the effects of polyphenols in delaying or prevention of Alzheimer's disease.

While there are many new medical treatment approaches for Alzheimer's disease, the most important advantages of these nutritional interventions are their safety, especially when in the form of diets, utility, low cost in comparison to supplements, and suitability for prevention.

3.4 Role of Diet in Prevention and Management of Alzheimer's Disease

Nutrients are not consumed individually in isolation. In the case of diet, different nutrients are consumed in combination. Thus, recognizing the role of diet in the prevention and management of Alzheimer's disease is more important. Understanding dietary patterns rather than individual nutrients or food groups, might help in better to understanding of the role of diet in amelioration of diseases. This section will discuss the role of different food components and diet patterns for prevention or slowing Alzheimer's disease.

3.4.1 Role of Food Components in the Prevention and Management of Alzheimer's Disease

3.4.1.1 Fish

Epidemiological studies indicate that fish consumption has a protective effect against cognitive decline, which can reduce the risk of dementia and Alzheimer's disease (Scarmeas et al. 2018; Huang et al. 2005; Morris et al. 2005). The positive factor is thought to be associated with ω-3 LCPUFA's like EPA and DHA (Hu et al. 2013). Several studies indicated that higher blood ω-3 level is associated with reduced cognitive decline.

3.4.1.2 Fruits and Vegetables

Frequent consumption of fruits and vegetables in medium or great proportion might reduce the risk of Alzheimer's disease and dementia (Scarmeas et al. 2018; Barberger-Gateau et al. 2007; Hughes et al. 2010). Fruits and vegetables are enriched with micronutrients like antioxidants, bioactive compounds such as vitamins, minerals, and polyphenols which are important to the brain and also have low or no saturated or trans fats (Morris et al. 2006), which might be linked with their higher intake and lower Alzheimer's disease incidence. Slower rates of cognitive decline and decreased risk of dementia have been detected in individuals who consume more vegetables and fruits (Scarmeas et al. 2018). Benefits were reported to be greater on higher consumption of vegetables over fruits (Morris et al. 2006). Many foods of plant sources are rich in several B vitamins. Vitamin B_{12}, folate and vitamin B_6 act as cofactors for the methylation of homocysteine, which is reported to be associated with a higher risk of cognitive impairment at elevated serum homocysteine levels (Morris 2012; Smith et al. 2010; Barnard et al. 2014).

3.4.1.3 Dairy and Dairy Products

A lower milk or dairy product consumption has been identified to be associated with reduced cognitive function. Dairy consisting of vitamin D, phosphorus, and magnesium may reduce the risk of cognitive impairment by decreasing vascular alterations and structural changes in the brain that occur with cognitive decline (Hu et al. 2013). In respect to fat intake from milk products, it has been found that moderate intake of unsaturated fats decreased the risk of Alzheimer's, while saturated fat was associated with an increased risk of the disease at midlife (Laitinen et al. 2006). Lower incidence of vascular dementia was reported in individuals aged 30 years or older who consume milk every day in comparison to those who consume milk less than four times a week (Yamada et al. 2003). Another study by Ozawa et al. (2014) found that the incidence of Alzheimer's disease and dementia was reduced in participants aged 60 years or older who reported high consumption of milk and dairy products.

3.4.1.4 Tea and Coffee

Tea and coffee are the most common sources of not only caffeine but also other biologically active compounds, including catechins, L-theanine, polyphenols, and other compounds (Wang and Ho 2009; Song et al. 2012). Several neuropharmacological activities have been suggested for tea and coffee ingredients, including antioxidant, anti-inflammatory, and neuroprotective effects (Islam et al. 2018; Song et al. 2012). Therefore, tea and coffee were relevant contributors to Alzheimer's disease, which were associated with decreased risk. Studies reported that coffee consumption is negatively associated with the risk of Alzheimer's disease (Scarmeas et al. 2018), whereas drinking tea was associated with lower risks of cognitive impairment and decline (Feng et al. 2010; Ng et al. 2008). But it has been found to be beneficial with mild to moderate consumption only (about three cups per day) (Scarmeas et al. 2018). In general, consumption of tea or coffee may have a protective impact on cognitive decline, although few studies report no association. Therefore, further prospective studies for evaluating the association of tea and coffee with Alzheimer's disease are strongly required.

3.4.1.5 Alcohol

Epidemiological evidence indicates that light-to-moderate consumption of alcoholic beverages was associated with a reduced risk of Alzheimer's disease, particularly among APOEε4 non-carriers (Panza et al. 2009). Resveratrol and other polyphenols in red wine have been found to reduce plaque formation and to protect against neurotoxicity caused by Aβ (Ho et al. 2009, 2013). Moderate consumption of beer was thought to be a protective factor for Alzheimer's disease due to the toits content of bioavailable silicon (González-Muñoz et al. 2008). Therefore, alcohol intake was

proposed to have a beneficial effect on Alzheimer's disease. However, heavy drinking (>2 drinks), in conjunction with heavy smoking and APOEε4, was associated with poor cognitive outcomes and an earlier onset of Alzheimer's disease (Harwood et al. 2010).

3.4.2 Role of Dietary Pattern and Diet in Prevention and Management of Alzheimer's Disease

A dietary pattern is the consumption of a combination of several food components that exert an overall effect of diet on human health. The majority of epidemiological studies of diet and Alzheimer's disease have focused on detecting associations between adherence to a specific diet, dietary patterns and the risk of reducing Alzheimer's disease. This section has discussed the effect of healthy or unhealthy dietary patterns and diets such as the Mediterranean and DASH diet on Alzheimer's disease.

3.4.2.1 Healthy Dietary Pattern

A healthy dietary pattern is characterized with the consumption of whole grains, breakfast cereal, fruits, vegetables, fresh dairy products, fish, vegetable fat, nuts, and tea (Kesse-Guyot et al. 2012). Reports have shown that the highest adherence to a healthy diet had a better cognitive performance (Kesse-Guyot et al. 2012; Samieri et al. 2008) and was associated with a decreased risk of Alzheimer's disease (Eskelinen et al. 2009).

3.4.2.2 Western Dietary Pattern

A Western dietary pattern is characterized by higher consumption of red and processed meats, refined grains, sweets, high-fat dairy products, butter, potatoes, high-fat gravy, and low intakes of fruits and vegetables (Li et al. 2017). A high-fat Western dietary pattern may contribute to the development of Alzheimer's disease by impacting Aβ deposition and inducing oxidative stress (Hu et al. 2013).

3.4.2.3 Mediterranean Diet

Mediterranean diet is the most extensively studied dietary pattern. The Mediterranean diet is a typical diet consumed in the Mediterranean region, which is plant focused and is characterized by a high intake of vegetables, fruits, cereals, legumes, bread, potatoes; high intake of MUFA, PUFA with nuts and olive oil, whereas low

intake of saturated fatty acids; a moderately high intake of fish; a low intake of red meat and poultry; a low-to-moderate intake of milk products; and a regular moderate intake of alcohol. Several recent systematic studies, reviews, and meta-analysis showed that higher adherence to a Mediterranean diet was favorably associated with slower cognitive decline and reduced risk of progression from mild cognitive impairment to Alzheimer's disease, and also reduced mortality in Alzheimer's disease patients (Tangney et al. 2014; Scarmeas et al. 2006; Mosconi and McHugh 2015). Superior adherence to the Mediterranean diet has been reported to not only reduce the risk of Alzheimer's disease but also for stroke, depression, and other neurodegenerative diseases (Sofi et al. 2010; Psaltopoulou et al. 2013). The body of evidence confirmed that a Mediterranean diet which includes a higher intake of MUFA, ω-3 polyunsaturated fatty acids, high levels of antioxidants from fruit and vegetables, fish, and low-to-moderate alcohol consumption might be protective against Alzheimer's disease (Panza et al. 2009, 2014; Barberger-Gateau et al. 2007; Huang et al. 2005; Morris et al. 2003). The role of nutrients in these foods in Alzheimer's disease is explained in the previous section.

3.4.2.4 DASH Diet

The Dietary Approaches to Stop Hypertension, commonly known as the DASH diet, is characterized by high consumption of whole grains, fruits and vegetables, fish, poultry, low-fat milk products, and nuts; while limiting the intake of sodium, red meat, sweets, desserts, and sweetened beverages (Hankey 2012; Panza et al. 2014). DASH diet is generally recommended for the therapeutic requirement of people suffering from hypertension. But since hypertension is associated with increased risk for Alzheimer's disease, it is plausible that the DASH diet could reduce the risk of Alzheimer's disease. Studies reported a higher correlation between the DASH diet with greater cognitive improvements (Smith et al. 2010) and lower dementia incidence risk (Norton et al. 2012).

Epidemiological studies indicated a beneficial effect of adherence to certain healthy dietary patterns such as the Mediterranean diet or DASH diet on slower cognitive decline and lower risk of developing dementia, including Alzheimer's disease (Scarmeas et al. 2006; Tangney et al. 2014; Smith et al. 2010). This evidence showed that diets and dietary patterns have a significant association with the risk for Alzheimer's disease. Therefore, a healthy diet should be one of the most important interventions for the prevention or management of Alzheimer's disease.

3.5 General Dietary and Lifestyle Approaches for Prevention and Management of Alzheimer's Disease

The role and importance of different nutrients, food components, diet, and dietary patterns have been explained in the previous sections. Based on all this information, in this section, a few general dietary and lifestyle approaches are discussed which can be taken into consideration for the prevention and management of Alzheimer's disease. Although it must be noted that the conditions or degree of the disease might vary from individual to individual; and therefore, one must be careful while making any changes in the diet or before taking any supplements. Any change must be done under the direction of a physician and dietitian after taking suggested biochemical or clinical tests to understand the changes in different biochemical parameters and their correlation with comorbidities.

1. Overweight or obesity is associated with a decline in cognitive ability, brain atrophy, white matter changes, and disturbances of blood–brain barrier integrity. It is also associated with a higher risk of Alzheimer's disease and other dementias in late life, although conflicting results have also been reported (Gustafson et al. 2015). However, maintaining a healthy weight or BMI is always advisable for all individuals across all populations.
2. Epidemiological studies have revealed a negative relationship between caloric intake and the risk of Alzheimer's disease (Luchsinger et al. 2002; Mattson et al. 2002). Animal studies confirmed that restricting caloric intake about 30–40% from normal levels can markedly slow the pathogenesis of Alzheimer's disease (Halagappa et al. 2007). Thus, a calorific restriction may reduce the risk of Alzheimer's disease occurrence or progression.
3. The contribution of different food processing and cooking methods is often poorly considered. Food processing, cooking, and storing methods can often contribute not only to the degradation of heat-labile micronutrients, such as folates, vitamin C, and thiamine but also can lead to the formation of toxins. High temperatures, mostly for long duration while food processing and cooking, bring about different biochemical reactions and the formation of a toxic secondary substance called Advanced Glycation End-products (AGEs). AGEs are also continuously formed in the body as a part of normal metabolism under hyperglycemic and oxidative stress conditions. Receptors of AGE (RAGE) were found to act as a cell surface receptor for Aβ and promote the circulation of Aβ across the brain. Also, RAGE plays a role in the pathogenesis of many chronic diseases, such as diabetes, hypertension, cardiovascular diseases, which are identified as risk factors for Alzheimer's disease, indicating that it might be ultimately leading to Alzheimer's disease etiology (Abate et al. 2017). Therefore, it is advised to cook food at a low temperature, preferably by boiling, steaming, or poaching.
4. Intake of food rich in saturated or trans fats should be minimized. Saturated fat is primarily found in dairy products, meats, and certain fats and oils (lard, butter,

Table 3.1 List of nutrients showing protective effect in Alzheimer's disease and their dietary sources

Nutrients	Dietary sources
MUFA	Olive oil, groundnut oil, canola oil, sunflower oil, sesame oil; almonds, cashews, pistachios, and hazelnuts
ω-3 PUFA	Fish like salmon, mackerel, sardines, herring; chia seeds, flax seeds, soybean, and walnut
Vitamin E	Almonds, soybean, safflower, sunflower seeds, vegetable oils, margarine, fatty fish (e.g., sardines, salmon, herring, swordfish, and trout), whole grain cereals, egg yolk, green leafy vegetables like spinach; mangoes, papayas, avocadoes, apples, tomatoes, and red capsicum
Vitamin D	Fish (especially fatty fish) and fish liver, full-fat dairy products (or fortified low-fat), egg yolk, meat, and meat products
Vitamin A	Yellow or orange vegetables (sweet potatoes, carrots, and pumpkins), dark leafy vegetables (spinach, broccoli, and endives), and yellow or orange fruits (apricots, peaches, mangoes, and melons)
Vitamin C	Fruits like berries, citrus fruits, kiwis, litchi, and papayas; vegetables like Brussels sprouts, cauliflowers, cabbages, sweet peppers, and tomatoes
Vitamin B_6	Fish, meat, chicken liver, drumstick leaves, sunflower seeds, safflower seeds, walnut, soybean, tofu, carrot, egg, and spinach
Folate	Dark green leafy vegetables like spinach, lettuce, kale, broccoli, cauliflower, beets, asparagus, beans, peas, capsicum, cantaloupe, avocado, lentils, rajma, and citrus fruits
Vitamin B_{12}	Meat, fish, poultry, milk, *spirulina*
Polyphenols	Fruits (mainly citrus fruits, bananas, and berries), vegetables (parsley and onions), tea (black and brewed), spice like turmeric

margarine, coconut, and palm oils). Trans fats, often labeled as "partially hydrogenated oils," are found in many snacks and fried foods, which are listed on the nutrition label of the food package.

5. More of MUFA and ω-3 PUFA should be included in the diet. Dietary sources of MUFA and ω-3 PUFA are mentioned in Table 3.1.
6. The inclusion of vegetables and fruits should be given more importance as they are rich in nutrients like antioxidants, vitamins, and polyphenols which play an important role in Alzheimer's and have shown to prevent or slow the development of Alzheimer's disease.
7. Nutrients such as vitamins, antioxidants, polyphenols from different food sources should be included in the diet as they have a protective role in Alzheimer's disease. Studies have also proved that nutrients like vitamins E should come from foods sources that are more effective than supplements. It must be noted that vitamin B_{12} is found naturally only in animal foods. Thus, vegetarians are often at risk of vitamin B_{12} deficiency (Madhubalaji et al. 2019), and hence they must pay more attention to prevent such deficiencies. Different nutrients which play a role in Alzheimer's disease and their sources are mentioned in Table 3.1.

8. A lower incidence of cognitive impairment and vascular dementia has been reported in individuals who consumed milk every day. Hence, it is advised to drink a glass of milk every day to prevent the risk of Alzheimer's disease.
9. Studies have shown that brisk walking for 40 min three times per week reduces brain degeneration and enhances memory and other cognitive functions (Hotting and Roder 2013). Individuals exercising regularly are at low risk of developing Alzheimer's disease and also exercising in midlife was found to prevent developing dementia at old age (Barnard et al. 2014). Furthermore, low physical activity has long been associated with the risk of Alzheimer's disease (Mosconi and McHugh 2015; Barnard et al. 2014; Sindi et al. 2015). Thus, moderate regular exercise of about 40 min each day for at least three times a week is highly recommended.
10. Several studies have suggested that individuals who are more mentally active have reduced risk for cognitive deficits later in life (Curlik and Shors 2013; Hotting and Roder 2013; Barnard et al. 2014). Therefore, regular mental activity that promotes new learning should be followed for about 30 min per day, four to five times per week.
11. Cognitive impairment in older adults has been associated with sleep disturbances (Blackwell et al. 2011; Lim et al. 2013). Thus maintaining a sleep routine of approximately 7–8 h for most individuals is advised.
12. Consumption of alcohol has been reported to reduce the risk of Alzheimer's disease, but only when taken in a low-to-moderate level. However, one must remember that indulging in heavy drinking and smoking will lead to cognitive decline and early onset of Alzheimer's disease.

3.6 Perspective

A growing number of epidemiological studies have indicated that nutrition and diet play a major role in the prevention, development, and management of Alzheimer's disease. It also suggests that nutrition is an important modifiable risk factor for cognitive dysfunction and Alzheimer's. The existing evidence suggests that certain nutrients like unsaturated fatty acids, particularly MUFA, ω-3 PUFA; vitamins, particularly vitamin E, vitamin D, vitamin C, folate; polyphenols have a potential role in improving cognitive function or in Alzheimer's disease. Superior adherence to a healthy diet which includes higher consumption of more vegetables and fruits, fish, whole grains, unsaturated fats, and a lower intake of saturated fats, processed foods like in Mediterranean diet and DASH diet have shown beneficial effects for Alzheimer's disease prevention and management. However, sufficient information is not available to recommend daily allowance for specific nutrients required for individuals with Alzheimer's disease or its prevention. Hence, more dose-dependent studies are required to establish the same. There are also some contradictory studies available for the role of minerals such as selenium, copper, aluminum, iron.

Therefore, evaluation and validity of the interventional trials must be done, which also create an opportunity for more research in this field.

References

Abate G, Marziano M, Rungratanawanich W, Memo M, Uberti D (2017) Nutrition and AGE-ing: focusing on Alzheimer's disease. Oxidative Med Cell Longev 2017

Annweiler C, Llewellyn DJ, Beauchet O (2013) Low serum vitamin D concentrations in Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis 33(3):659–674

Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, Dartigues JF, Alpérovitch A (2007) Dietary patterns and risk of dementia: the Three-City cohort study. Neurology 69(20): 1921–1930

Barnard ND, Bush AI, Ceccarelli A, Cooper J, de Jager CA, Erickson KI, Fraser G, Kesler S, Levin SM, Lucey B, Morris MC (2014) Dietary and lifestyle guidelines for the prevention of Alzheimer's disease. Neurobiol Aging 35:S74–S78

Bazan NG, Molina MF, Gordon WC (2011) Docosahexaenoic acid signalolipidomics in nutrition: significance in aging, neuroinflammation, macular degeneration, Alzheimer's, and other neurodegenerative diseases. Annu Rev Nutr 31:321–351

Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Ensrud KE, Stefanick ML, Stone KL, Osteoporotic Fractures in Men (MrOS) Study Group (2011) Association of sleep characteristics and cognition in older community-dwelling men: the MrOS sleep study. Sleep 34(10):1347–1356

Borniquel S, Jansson EÅ, Cole MP, Freeman BA, Lundberg JO (2010) Nitrated oleic acid up-regulates PPARγ and attenuates experimental inflammatory bowel disease. Free Radic Biol Med 48(4):499–505

Brewer GJ (2009) The risks of copper toxicity contributing to cognitive decline in the aging population and to Alzheimer's disease. J Am Coll Nutr 28(3):238–242

Brewer GJ (2012) Copper excess, zinc deficiency, and cognition loss in Alzheimer's disease. Biofactors 38(2):107–113

Cardoso BR, Ong TP, Jacob-Filho W, Jaluul O, Freitas MIDÁ, Cozzolino SMF (2010) Nutritional status of selenium in Alzheimer's disease patients. Br J Nutr 103(6):803–806

Chandra RK (2001) Effect of vitamin and trace-element supplementation on cognitive function in elderly subjects. Nutrition 17(9):709–712

Choi DY, Lee YJ, Hong JT, Lee HJ (2012) Antioxidant properties of natural polyphenols and their therapeutic potentials for Alzheimer's disease. Brain Res Bull 87(2–3):144–153

Cornelli U (2010) Treatment of Alzheimer's disease with a cholinesterase inhibitor combined with antioxidants. Neurodegener Dis 7(1–3):193–202

Corona C, Masciopinto F, Silvestri E, Del Viscovo A, Lattanzio R, La Sorda R et al (2010) Dietary zinc supplementation of 3xTg-AD mice increases BDNF levels and prevents cognitive deficits as well as mitochondrial dysfunction. Cell Death Dis 1(10):e91–e91

Corrada MM, Kawas CH, Hallfrisch J, Muller D, Brookmeyer R (2005) Reduced risk of Alzheimer's disease with high folate intake: the Baltimore Longitudinal Study of Aging. Alzheimers Dement 1(1):11–18

Crapper DR, Krishnan SS, Quittkat S (1976) Aluminium, neurofibrillary degeneration, and Alzheimer's disease. Brain J Neurol 99(1):67–80

Curlik DM 2nd, Shors TJ (2013) Training your brain: do mental and physical (MAP) training enhance cognition through the process of neurogenesis in the hippocampus? Neuropharmacology 64:506–514

Devore EE, Grodstein F, van Rooij FJ, Hofman A, Stampfer MJ, Witteman JC, Breteler MM (2010) Dietary antioxidants and long-term risk of dementia. Arch Neurol 67(7):819–825

Eskelinen MH, Ngandu T, Tuomilehto J, Soininen H, Kivipelto M (2009) Midlife coffee and tea drinking and the risk of late-life dementia: a population-based CAIDE study. J Alzheimers Dis 16(1):85–91

European Commission (2000) Communication from the Commission on the Precautionary principle. https://op.europa.eu/en/publication-detail/-/publication/21676661-a79f-4153-b984-aeb28f07c80a/language-en

Falkingham M, Abdelhamid A, Curtis P, Fairweather-Tait S, Dye L, Hooper L (2010) The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis. Nutr J 9(1):4

Feng L, Gwee XINYI, Kua EH, Ng TP (2010) Cognitive function and tea consumption in community dwelling older Chinese in Singapore. J Nutr Health Aging 14(6):433–438

Frautschy SA, Hu W, Kim P, Miller SA, Chu T, Harris-White ME, Cole GM (2001) Phenolic anti-inflammatory, antioxidant reversal of Aβ-induced cognitive deficits and neuropathology. Neurobiol Aging 22(6):993–1005

Freund Levi Y, Vedin I, Cederholm T, Basun H, Faxen Irving G, Eriksdotter M et al (2014) Transfer of omega-3 fatty acids across the blood-brain barrier after dietary supplementation with a docosahexaenoic acid-rich omega-3 fatty acid preparation in patients with Alzheimer's disease: the O meg AD study. J Intern Med 275(4):428–436

G8 Dementia Summit Declaration (2013) Global action against dementia. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/265869/2901668_G8_DementiaSummit%20Declaration_acc.pdf

González-Muñoz MJ, Pena A, Meseguer I (2008) Role of beer as a possible protective factor in preventing Alzheimer's disease. Food Chem Toxicol 46(1):49–56

Grant WB (2016) Using multicountry ecological and observational studies to determine dietary risk factors for Alzheimer's disease. J Am Coll Nutr 35(5):476–489

Gustafson DR, Clare Morris M, Scarmeas N, Shah RC, Sijben J, Yaffe K, Zhu X (2015) New perspectives on Alzheimer's disease and nutrition. J Alzheimers Dis 46(4):1111–1127

Halagappa VKM, Guo Z, Pearson M, Matsuoka Y, Cutler RG, LaFerla FM, Mattson MP (2007) Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. Neurobiol Dis 26(1):212–220

Hankey GJ (2012) Nutrition and the risk of stroke. Lancet Neurol 11(1):66–81

Harrison FE (2012) A critical review of vitamin C for the prevention of age-related cognitive decline and Alzheimer's disease. J Alzheimers Dis 29(4):711–726

Hartman RE, Shah A, Fagan AM, Schwetye KE, Parsadanian M, Schulman RN et al (2006) Pomegranate juice decreases amyloid load and improves behavior in a mouse model of Alzheimer's disease. Neurobiol Dis 24(3):506–515

Harwood DG, Kalechstein A, Barker WW, Strauman S, St. George-Hyslop P, Iglesias C et al (2010) The effect of alcohol and tobacco consumption, and apolipoprotein E genotype, on the age of onset in Alzheimer's disease. Int J Geriatr Psychiatry 25(5):511–518

Hashim A, Wang L, Juneja K, Ye Y, Zhao Y, Ming LJ (2011) Vitamin B6s inhibit oxidative stress caused by Alzheimer's disease-related CuII-β-amyloid complexes—cooperative action of phospho-moiety. Bioorg Med Chem Lett 21(21):6430–6432

Ho L, Chen LH, Wang J, Zhao W, Talcott ST, Ono K et al (2009) Heterogeneity in red wine polyphenolic contents differentially influences Alzheimer's disease-type neuropathology and cognitive deterioration. J Alzheimers Dis 16(1):59–72

Ho L, Ferruzzi MG, Janle EM, Wang J, Gong B, Chen TY et al (2013) Identification of brain-targeted bioactive dietary quercetin-3-O-glucuronide as a novel intervention for Alzheimer's disease. FASEB J 27(2):769–781

Hotting K, Roder B (2013) Beneficial effects of physical exercise on neuroplasticity and cognition. Neurosci Biobehav Rev 37(9):2243–2257

Hu N, Yu JT, Tan L, Wang YL, Sun L, Tan L (2013) Nutrition and the risk of Alzheimer's disease. BioMed Res Int 2013

Huang TL, Zandi PP, Tucker KL, Fitzpatrick AL, Kuller LH, Fried LP et al (2005) Benefits of fatty fish on dementia risk are stronger for those without APOE ε4. Neurology 65(9):1409–1414

Hughes TF, Andel R, Small BJ, Borenstein AR, Mortimer JA, Wolk A et al (2010) Midlife fruit and vegetable consumption and risk of dementia in later life in Swedish twins. Am J Geriatr Psychiatry 18(5):413–420

Islam MT, Tabrez S, Jabir NR, Ali M, Kamal MA, da Silva Araujo L et al (2018) An insight into the therapeutic potential of major coffee components. Curr Drug Metab 19(6):544–556

Joseph J, Cole G, Head E, Ingram D (2009) Nutrition, brain aging, and neurodegeneration. J Neurosci 29(41):12795–12801

Kamphuis PJ, Wurtman RJ (2009) Nutrition and Alzheimer's disease: pre-clinical concepts. Eur J Neurol 16:12–18

Kesse-Guyot E, Andreeva VA, Jeandel C, Ferry M, Hercberg S, Galan P (2012) A healthy dietary pattern at midlife is associated with subsequent cognitive performance. J Nutr 142(5):909–915

Kessler H, Bayer TA, Bach D, Schneider-Axmann T, Supprian T, Herrmann W et al (2008) Intake of copper has no effect on cognition in patients with mild Alzheimer's disease: a pilot phase 2 clinical trial. J Neural Transm 115(8):1181

Kim GY, Kim KH, Lee SH, Yoon MS, Lee HJ, Moon DO et al (2005) Curcumin inhibits immunostimulatory function of dendritic cells: MAPKs and translocation of NF-κB as potential targets. J Immunol 174(12):8116–8124

Kwok T, Lee J, Law CB, Pan PC, Yung CY, Choi KC, Lam LC (2011) A randomized placebo controlled trial of homocysteine lowering to reduce cognitive decline in older demented people. Clin Nutr 30(3):297–302

Laitinen MH, Ngandu T, Rovio S, Helkala EL, Uusitalo U, Viitanen M et al (2006) Fat intake at midlife and risk of dementia and Alzheimer's disease: a population-based study. Dement Geriatr Cogn Disord 22(1):99–107

Landel V, Millet P, Baranger K, Loriod B, Féron F (2016) Vitamin D interacts with Esr1 and Igf1 to regulate molecular pathways relevant to Alzheimer's disease. Mol Neurodegener 11(1):22

Li Y, Lv MR, Wei YJ, Sun L, Zhang JX, Zhang HG, Li B (2017) Dietary patterns and depression risk: a meta-analysis. Psychiatry Res 253:373–382

Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA (2013) Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older adults. Sleep 36:1027–1032

Loef M, Walach H (2012) Copper and iron in Alzheimer's disease: a systematic review and its dietary implications. Br J Nutr 107(1):7–19

Luchsinger JA, Tang MX, Shea S, Mayeux R (2002) Caloric intake and the risk of Alzheimer's disease. Arch Neurol 59(8):1258–1263

Luchsinger JA, Tang M-X, Mayeux R (2007) Glycemic load and risk of Alzheimer's disease. J Nutr Health Aging 11(3):238–241

Madhubalaji CK, Rashmi V, Chauhan VS, Shylaja MD, Sarada R (2019) Improvement of vitamin B_{12} status with *Spirulina* supplementation in Wistar rats validated through functional and circulatory markers. J Food Biochem 43(11):e13038

Mattson MP, Chan SL, Duan W (2002) Modification of brain aging and neurodegenerative disorders by genes, diet, and behavior. Physiol Rev 82(3):637–672

Morris MC (2009) The role of nutrition in Alzheimer's disease: epidemiological evidence. Eur J Neurol 16:1–7

Morris MS (2012) The role of B vitamins in preventing and treating cognitive impairment and decline. Adv Nutr 3(6):801–812

Morris MC, Tangney CC (2014) Dietary fat composition and dementia risk. Neurobiol Aging 35: S59–S64

Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N et al (2002) Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. JAMA 287(24):3230–3237

Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS et al (2003) Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 60(7):940–946

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(12):1849–1853

Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS (2006) Associations of vegetable and fruit consumption with age-related cognitive change. Neurology 67(8):1370–1376

Mosconi L, McHugh PF (2015) Let food be thy medicine: diet, nutrition, and biomarkers' risk of Alzheimer's disease. Curr Nutr Rep 4(2):126–135

Murakami K, Murata N, Ozawa Y, Kinoshita N, Irie K, Shirasawa T, Shimizu T (2011) Vitamin C restores behavioral deficits and amyloid-β oligomerization without affecting plaque formation in a mouse model of Alzheimer's disease. J Alzheimers Dis 26(1):7–18

Ng TP, Feng L, Niti M, Kua EH, Yap KB (2008) Tea consumption and cognitive impairment and decline in older Chinese adults. Am J Clin Nutr 88(1):224–231

Nilforooshan R, Broadbent D, Weaving G, Gurton J, Moore V (2011) Homocysteine in Alzheimer's disease: role of dietary folate, vitamin B6 and B12. Int J Geriatr Psychiatry 26(8):876–877

Norton MC, Dew J, Smith H, Fauth E, Piercy KW, Breitner JC et al (2012) Lifestyle behavior pattern is associated with different levels of risk for incident dementia and Alzheimer's disease: the Cache County study. J Am Geriatr Soc 60(3):405–412

Obrenovich ME, Nair NG, Beyaz A, Aliev G, Reddy VP (2010) The role of polyphenolic antioxidants in health, disease, and aging. Rejuvenation Res 13(6):631–643

Ono K, Yoshiike Y, Takashima A, Hasegawa K, Naiki H, Yamada M (2003) Potent anti-amyloidogenic and fibril-destabilizing effects of polyphenols in vitro: implications for the prevention and therapeutics of Alzheimer's disease. J Neurochem 87(1):172–181

Ozawa M, Ohara T, Ninomiya T, Hata J, Yoshida D, Mukai N et al (2014) Milk and dairy consumption and risk of dementia in an elderly Japanese population: the Hisayama study. J Am Geriatr Soc 62(7):1224–1230

Panza F, Capurso C, D'Introno A, Colacicco AM, Frisardi V, Lorusso M et al (2009) Alcohol drinking, cognitive functions in older age, predementia, and dementia syndromes. J Alzheimers Dis 17(1):7–31

Panza F, Solfrizzi V, Giannini M, Seripa D, Pilotto A, Logroscino G (2014) Nutrition, frailty, and Alzheimer's disease. Front Aging Neurosci 6:221

Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N (2013) Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. Ann Neurol 74(4):580–591

Rayman MP (2000) The importance of selenium to human health. Lancet 356(9225):233–241

Samieri C, Jutand MA, Féart C, Capuron L, Letenneur L, Barberger-Gateau P (2008) Dietary patterns derived by hybrid clustering method in older people: association with cognition, mood, and self-rated health. J Am Diet Assoc 108(9):1461–1471

Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA (2006) Mediterranean diet and risk for Alzheimer's disease. Ann Neurol 59(6):912–921

Scarmeas N, Anastasiou CA, Yannakoulia M (2018) Nutrition and prevention of cognitive impairment. Lancet Neurol 17(11):1006–1015

Scheltens P, Kamphuis PJ, Verhey FR, Rikkert MGO, Wurtman RJ, Wilkinson D et al (2010) Efficacy of a medical food in mild Alzheimer's disease: a randomized, controlled trial. Alzheimers Dement 6(1):1–10

Sindi S, Mangialasche F, Kivipelto M (2015) Advances in the prevention of Alzheimer's disease. F1000prime Rep 7

Smith PJ, Blumenthal JA, Babyak MA, Craighead L, Welsh-Bohmer KA, Browndyke JN, Strauman TA, Sherwood A (2010) Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. Hypertension 55(6):1331–1338

Sofi F, Abbate R, Gensini GF, Casini A (2010) Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am J Clin Nutr 92(5):1189–1196

Song J, Xu H, Liu F, Feng L (2012) Tea and cognitive health in late life: current evidence and future directions. J Nutr Health Aging 16(1):31–34

Squitti R (2012) Copper dysfunction in Alzheimer's disease: from meta-analysis of biochemical studies to new insight into genetics. J Trace Elem Med Biol 26(2–3):93–96

Stankiewicz JM, Brass SD (2009) Role of iron in neurotoxicity: a cause for concern in the elderly? Curr Opin Clin Nutr Metab Care 12(1):22–29

Swaminathan A, Jicha GA (2014) Nutrition and prevention of Alzheimer's dementia. Front Aging Neurosci 6:282

Takasaki J, Ono K, Yoshiike Y, Hirohata M, Ikeda T, Morinaga A et al (2011) Vitamin A has anti-oligomerization effects on amyloid-β in vitro. J Alzheimers Dis 27(2):271–280

Tangney CC, Li H, Wang Y, Barnes L, Schneider JA, Bennett DA, Morris MC (2014) Relation of DASH-and Mediterranean-like dietary patterns to cognitive decline in older persons. Neurology 83(16):1410–1416

Ventriglia M, Brewer GJ, Simonelli I, Panetta V, Bucossi S, Squitti R (2012) Copper in Alzheimer's disease: a meta-analysis of serum, plasma, and cerebrospinal fluid studies. J Alzheimers Dis 30(4):981–984

Wang Y, Ho CT (2009) Polyphenolic chemistry of tea and coffee: a century of progress. J Agric Food Chem 57(18):8109–8114

Williams JW, Plassman BL, Burke J, Holsinger T, Benjamin S (2010) Preventing Alzheimer's disease and cognitive decline. Evid Rep Technol Assess 193(1):1–727

World Health Organisation (WHO) (2012) Mental Health: dementia: a public health priority. http://www.who.int/mental_health/publications/dementia_report_2012/en/

Yamada M, Kasagi F, Sasaki H, Masunari N, Mimori Y, Suzuki G (2003) Association between dementia and midlife risk factors: the radiation effects research foundation adult health study. J Am Geriatr Soc 51(3):410–414

Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT, Norton MC, Breitner JC (2004) Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County study. Arch Neurol 61(1):82–88