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Review

Alzheimer's Disease Prevention - A Review of Modifiable Risk Factors and the Role of Dietary Supplements

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Abstract

Alzheimer's disease is a prevalent age-related medical problem world-wide for which there is no cure. Over the past few decades, researchers have identified 14 potentially modifiable risk factors for this disease. They include physical inactivity, unhealthy diet, and cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus and smoking. It is estimated that a third of Alzheimer's disease cases can be prevented by addressing risk factors at an earlier age. In addition, available data suggest that some dietary supplements may be helpful in preventing or treating dementia, though further high quality studies are needed.

Keywords: Dementia prevention; Dietary supplements; Modifiable risk factors; Prevention of Alzheimer's disease

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Introduction

Alzheimer's Disease (AD) is a prevalent age-related health care problem for which no curative treatment is available. It is estimated that approximately 45 million people in the world suffer from dementia. AD accounts for the vast majority (up to 80%) of dementia cases [1]. Systematic reviews of population-based studies have shown evidence of decreasing prevalence of dementia in Europe and North America over the past 2-3 decades [2]. This observed decline is likely related to improved control of cardiovascular risk factors and to higher rates of early-life educational achievement. This evidence strengthens the belief that age-related dementia can be preventable. It is estimated that a third of AD cases are potentially ascribable to modifiable risk factors [3].

The World Health Organization regards dementia prevention as a public health priority [4]. Improved understanding of preventive strategies could help abate the enormous socioeconomic burden of this disease and make a significant difference in the lives of millions of people worldwide [5,6]. In this review, we focus our discussion around the potentially modifiable risk factors for AD. We comment on available evidence-based strategies for possible AD prevention. In addition, we review the literature regarding the role of dietary supplements in the prevention of AD.

Risk Factors for Alzheimer's Disease

Modifiable: Physical inactivity; mental inactivity; unhealthy diet; hypertension; diabetes mellitus; hyperlipidemia; smoking; obesity; traumatic brain injury; sleep disorders; depression; chronic periodontitis; hearing loss; herpes viral infection.

Non-modifiable: Age and Genetics.

Modifiable risk factors

Physical inactivity

As shown in human studies, physical exercise has important benefits to the cerebral structure and function. It promotes neuroplasticity or brain malleability which is the brain's ability to modify itself when adjusting to environmental changes [7]. Physical exercise helps maintain brain volume including gray matter volume in the frontal and hippocampal regions [8,9]. It promotes increased levels of neurotrophic factors namely peripheral Brain-Derived Neurotrophic Factor (BDNF). This effect has been observed in at least five randomized controlled trials involving elderly patients who participated in moderate-intensity exercise training [10]. BDNF stimulates brain cells to grow and survive. In addition, this neurotrophic factor induces brain cells to create compensatory mechanisms when facing insults such as disease or injury. Moreover, physical exercise improves cerebral blood flow and the transport of vital ingredients to brain cells.

We will briefly discuss the results of a few studies which highlight the importance of physical exercises in the prevention of dementia: Physical exercise is associated with enhanced cognitive abilities and reduced risk of developing dementia in the elderly. A recent meta-analysis examined the effects of exercise training on cognitive function in individuals considered at risk of or who have AD [11]. This analysis included 1,145 subjects from nineteen studies with a mean age of 77. Participants were considered at risk of AD if they had Mild Cognitive Impairment (MCI), a genetic risk such as apolipoprotein E4 allele, or a parent diagnosed with AD. On average, the interventions consisted of moderate intensity physical exercises, mainly aerobic type, 45 minutes per session, 3 days per week, for 18 weeks. The results indicate meaningful improvements in cognitive function with aerobic exercise training. The authors conclude that exercise training may slow the gradual cognitive decline that is normally expected in these individuals. More specifically, this study identifies aerobic exercise as being superior to other exercise modalities in preserving cognitive function [12] (Table 1).

The best time in life for obtaining the most protective brain benefits from physical activity remains unclear. Midlife appears to be a vulnerable period when the effects of cardiovascular risk factors contribute to the development of dementia in later life [6,13]. Investigators from Sweden recently published the results of their study evaluating the association of midlife cardiovascular fitness and dementia. It was a 44-year longitudinal population study in Swedish women. They concluded that high cardiovascular fitness in midlife appears to reduce the risk of developing dementia in later life [14] (Table 1).

Interestingly, physical activity appears to confer better neurocognitive protection to individuals considered at risk of developing AD such as APOE-epsilon 4 allele carriers [15]. Hippocampal atrophy is a typical brain imaging finding of AD which gradually worsens with disease progression. It may also be associated, to a lesser degree, with normal aging. Erickson et al., in 2011 showed the effectiveness of physical activity in improving hippocampal volume as well as cognitive function in healthy older adults [16]. Another study in 2014 evaluated 97 healthy older adults with brain MRI scans at baseline and following 18-month-long physical activity training. Participants were involved in either Low intensity Physical Activity (Low PA) or High intensity Physical Activity (High PA). Individuals who had the APOE-epsilon 4 allele received the high risk status. The study participants were divided into four distinct intervention groups: Low Risk/High PA, Low Risk/Low PA, High Risk/High PA and High Risk/Low PA. The follow-up brain MRI scans revealed a 3% decrease (worsening) in hippocampal volume in the High Risk/Low PA group but was unchanged in the High Risk/High PA and other two groups. The results suggest that physical activity may help decrease hippocampal atrophy in individuals at higher genetic risk of developing AD [15] (Table 1).

Unhealthy diet

Certain dietary practices have been increasingly recognized as effective measures in the prevention of cognitive decline. Most observational studies have linked the Mediterranean Diet (MD) to a lower incidence of all-cause dementia [17]. This diet may provide brain protection by reducing oxidative stress and inflammation [18]. The MD is characterized by a high intake of fruits, vegetables, legumes, nuts, seeds, beans, whole grains, fish with omega-3 fatty acids (salmon, tuna and mackerel) and olive oil. Poultry, dairy products, eggs and wine are consumed in moderation. The MD is typically low in sources of saturated fats such as red meat and butter [19]. A systematic review of the literature in 2016, concluded that adherence to the MD is associated with improved cognitive function. Nevertheless, the authors cautioned that most of the data originated from epidemiologic studies and not from controlled trials [20].

The PRIMED-NAVARRA study is the largest randomized clinical trial to date assessing the effects of the MD on cognition [21]. This study evaluated 522 participants, mean age 74 years, who were considered at high risk for vascular disease. Individuals were randomly assigned to one of three diet groups: MD supplemented with extra-virgin olive oil, MD supplemented with mixed nuts or low-fat control diet. The authors administered neuropsychological testing at baseline and after a mean follow-up of 6.5 years. Participants who adopted the two types of the MD had significantly higher mean scores on follow-up neuropsychological testing (Table 2).

Valls-Pedret et al., investigated whether a MD supplemented with either extra virgin olive oil or mixed nuts affects cognitive function compared with regular diet. This study evaluated 447 cognitively normal older patients at high cardiovascular risk. At the end of 4 years, the two MD groups showed improved cognitive function compared to the control group [22] (Table 2). The MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet is a hybrid of the Mediterranean and the DASH (Dietary Approaches to Stop Hypertension) diets. This diet emphasizes the increased consumption of berries as well as green leafy vegetables (such as collard greens, spinach, and kale). The MIND diet does not specify increased consumption of fruits, potatoes, dairy, or more than one fish meal per week [23]. The MIND diet study was a prospective trial investigating the relations of three distinct diets and the risk of developing AD [24]. The authors evaluated 923 participants who were following either the MIND, the DASH or the Mediterranean diet. This five-year-long study showed that high adherence to all three diets was associated with a reduced AD risk. Notably, even moderate adherence to the MIND diet was associated with a decreased AD risk [24] (Table 2).

	Gregory A. Panza et al.,	Helena Horder et al.,	J. Carson Smith et al.,
Number of participants	1,145, most of them at risk of AD	191 (women)	97
Mean age	77	50	72
Study design	Meta-analysis	Longitudinal, observational, cohort	Longitudinal, cohort
Intervention	Controlled studies that included a physical exercise intervention	Evaluation of cardiovascular fitness in midlife	High-physical exercise intervention
Control group	Nondiet, nonexercise, group	Lower cardiovascular fitness	Low-physical exercise group
Outcomes	Change in cognitive performance	Change in cognitive performance	Change in hippocampal volume
Findings	Exercise training may delay the decline in cognitive function	High cardiovascular fitness in midlife is associated with decreased risk of subsequent dementia	Increased physical exercise may help decrease hippocampal atrophy in individuals at high risk of AD

Table 1: Summary of studies on the effects of physical exercise on cognitive function.

	Martinez-Lapiscina et al., (PRIDIMED-NAVARRA study)	Valls-Pedret et al.,	Morris et al.,
Number of participants	522	447	923
Mean age	74	67	81
Study design	Parallel-group, randomized	Parallel-group, randomized	Prospective, observational
Intervention	Dietary (MD, 2 sub-types)	Dietary (MD, 2 sub-types)	Dietary (MIND, DASH, or MD)
Control group	Low-fat diet	Regular diet	n/a
Outcomes	Change in cognitive performance	Change in cognitive performance	Change in cognitive performance
Findings	My may improve cognition	My may improve cognition	High adherence to all 3 diets may improve cognition Moderate adherence to the MIND diet may improve cognition

Table 2: Summary of studies on the effects of dietary changes on cognitive function.

Mental inactivity

Epidemiological studies have suggested a reduced risk of developing AD in individuals with higher educational/occupational attainment as well as higher exposure to stimulating social environments [25]. These individuals develop the so-called "cognitive reserve" which helps them maintain normal cognitive function for longer when their brains are undergoing structural changes related to AD. It is plausible that intellectual activities create cognitive reserve by promoting neurogenesis [26] and stimulating neurotrophic factors such as peripheral Brain-Derived Neurotrophic Factor (BDNF). As mentioned earlier, BDNF provides brain protection by promoting neuroplasticity as a compensatory reaction to brain insults [27]. A prospective, population-based cohort study in 2017 evaluated the association of mentally stimulating activities in old age with neurocognitive function. The authors followed 1929 cognitively normal individuals 70 years or older for 4 years. Participants who engaged in various intellectual activities including regular computer use, craft activities, social activities and playing games showed significant decreased risk of new-onset mild cognitive impairment [28].

Vascular Risk Factors: Hypertension, Hyperlipidemia, Diabetes, Smoking, Obesity

Observational studies over the years have shown a link between vascular risk factors and AD. Hypertension, hyperlipidemia, diabetes, obesity and smoking, alone or in combination, can cause damage to the cerebral blood vessels and might contribute to the development of AD. A recent original investigation concluded that having vascular risk factors in midlife contributes to brain amyloid deposition in late-life [29]. This prospective cohort study evaluated 346 participants without dementia, mean age of 52, for vascular risk factors including hypertension, diabetes, total cholesterol >200 mg/dL, current smoking and BMI >30. Positron Emission Tomography (PET) was used to detect brain amyloid deposition in late-life, mean age of 76. The results revealed a clear association between an increasing number of vascular risk factors in midlife, but not in late-life, and elevated brain amyloid deposition [29].

Hypertension

High blood pressure appears to contribute to dementia by damaging the brain blood vessels and causing a disruption of the blood-brain barrier. This may lead to protein extravasation and accumulation of amyloid B in the brain tissue [30].

Diabetes mellitus

Diabetes Mellitus has been linked to an increased risk of dementia, including AD [31,32]. Brain dysfunction in the setting of diabetes appears related to increased inflammation and oxidative stress leading to accelerated brain ageing [33]. In addition, hyperinsulinemia may increase amyloid deposition in the brain by impairing its brain clearance mechanisms [34].

Hyperlipidemia

Hyperlipidemia is a well-established risk factor for cerebral vascular disease and has also been associated with AD [35,36]. A recent study from the University of Cambridge identified a specific microscopic pathway by which cholesterol acts as a major catalyst in the accumulation of amyloid-beta protein in the brain [37]. This newly discovered pathway in the brain could represent a target for potential treatments for AD. It is worth mentioning that lipid-lowering therapies such as the Statin drugs have not yet been shown to lower the risk for AD.

Smoking

Cigarette smoking has been increasingly recognized as a modifiable risk factor for AD [38]. Interestingly, some studies published in 1994 or before signaled to a possible protective role of chronic cigarette smoking against the development of AD. A meta-analysis in 2010 concluded that only the tobacco industry funded studies were associated with a decreased risk [38]. Otherwise, this meta-analysis and other subsequent studies indicated an association between cigarette smoking and increased risk for AD [39,40]. Cigarette smoking adversely affects the brain by causing a state of chronic oxidative stress which may trigger pathophysiological changes of AD [41].

Obesity

Obesity, defined as Body Mass Index (BMI) >30 kg/m^2, in midlife is considered a risk factor for AD [42]. Obesity may increase the risk of AD by itself or by leading to other known risk factors such as hypertension, diabetes and hyperlipidemia. According to studies, adipose tissue secretes pro-inflammatory cytokines and causes chronic local and systemic inflammation [43]. Chronic brain inflammation leads to abnormal cerebral insulin action which may contribute to amyloid B and tau protein accumulation [44].

Traumatic brain injury

For many years, moderate to severe traumatic brain injury, has been considered a risk factor for earlier onset AD [45,46]. Traumatic brain injury may increase dementia risk by causing brain atrophy, white matter degeneration and neuroinflammation. A recent retrospective study examined the association between traumatic brain injury severity and dementia diagnosis. The authors found a 2-fold increase in dementia diagnosis associated with mild traumatic brain injury without loss of consciousness [47]. This finding highlights the importance of proper brain protection against trauma in at risk situations including the practice of contact sports.

Sleep disorders

Sleep disorders are known for disturbing memory consolidation processes in the brain and therefore leading to learning difficulties [48]. It is also known that individuals who suffer from sleep disorders are more likely to receive a diagnosis of AD [49]. To this date, it is unclear whether abnormal sleep patterns play a causal role in the pathophysiology of AD or whether they represent early clinical manifestations of this degenerative brain disorder [50]. A systematic review and meta-analysis in 2016 quantified an "average" magnitude of the association between sleep disorders and AD [51]. According to this meta-analysis, individuals with sleep disorders are 1.68 times more likely to have cognitive impairment and/or AD. Their findings suggest that 15% of AD cases may be attributed to sleep problems.

Depression

AD is often accompanied by major depressive disorder [52] and the appearance of depressive symptoms in older age may represent a prodromal manifestation of dementia [53]. In addition, studies have shown that major depressive disorder in mid-life is considered an independent risk factor for AD [54]. The exact mechanism of this association is unknown but may be related to raised cytokines, increased brain inflammation and aberrant hypothalamic pituitary axis function [55].

Chronic periodontitis

Studies have linked chronic periodontitis to several inflammatory conditions, cardiovascular disease [56] and neurodegenerative disease [57]. Chronic periodontitis is associated with increased levels of pro-inflammatory markers including C-reactive protein [58]. It may play a role in the pathogenesis of AD by increasing brain inflammation and triggering vascular dysfunction. A retrospective cohort study in 2017 demonstrated that 10-year chronic periodontitis exposure increased the risk of developing AD by 1.7 [59]. These results call attention to the need for improved prevention and treatment of periodontal disease.

Hearing loss

Hearing impairment has been increasingly considered as a risk factor for AD [60,61]. The mechanisms of this association are unclear but may relate to social isolation which is a known contributor to dementia. Hearing loss has also been shown to adversely affect cognition by diverting cognitive resources from working memory toward improved auditory processing [62]. A systematic review in 2017 evaluated an association between hearing loss and dementia. The several studies in this review utilized different evaluation methods but they all demonstrated a link between hearing loss and dementia in older adults [63]. High-quality prospective studies are needed to confirm this association. In the meantime, we should continue efforts to detect and treat hearing impairment for improved socialization and quality of life as well as for possible prevention of cognitive decline.

Viral infection

Recent studies suggest a link between brain infection with herpesviruses and AD [64-66]. Investigators detected more signs of active viral infection in postmortem brains of individuals who had AD compared to controls [64]. Herpes viral infection appears to trigger an accelerated deposition of beta amyloid protein in the brain as a protective measure against viral cell damage [65]. A retrospective cohort study from Taiwan in 2018 investigated the association between herpes simplex viral infection and dementia as well as the possible effects of anti-herpetic medications in attenuating this risk. The results suggest that patients with herpes simplex viral infection may have a 2.56-fold increased risk of dementia. Notably, the use of anti-herpetic medications was associated with a decreased risk of dementia [67]. More research is needed to clarify the relationship between herpesviruses and AD and the role of antiviral medications.

Dietary Supplements for Alzheimer's Disease Prevention

Vitamins

Vitamin D

Several recent meta-analyses and systematic reviews have confirmed the association between low vitamin D levels and an increased risk for dementia, poor cognitive performance, and cognitive decline [68-71]. In one meta-analysis, a decreased risk of dementia was seen at serum levels of at least 25ng/ml [68]. In another, patients with serum levels below 20ng/ml had a 21% higher risk of developing Alzheimer's disease than did those with higher levels [71]. While epidemiologic data do seem to support vitamin D's role in the prevention of dementia, interventional studies have been sparse and have failed to show a benefit with supplementation [69]. Clinicians can advise their patients that until further studies are done, maintaining a vitamin D level of at least 20ng/ml may be helpful in reducing their risk of AD and dementia.

Vitamin E

While a 2017 Cochrane systematic review found no evidence that vitamin E improves cognition or prevents progression to dementia in patients with MCI, some earlier studies did have positive findings [72]. A 1997 RDBPCT found that in patients with moderately severe AD, 2000 IU/day of vitamin E delayed disease progression [73]. A later study showed that when patients with mild to moderate AD were given the same dose of vitamin E, they retained their ability to perform ADLs 6 months longer than those given placebo [74]. Providers can inform their patients that vitamin E may be helpful in delaying disease progression and functional decline in those with AD, but it does not appear to prevent progression in those with MCI.

B-Vitamins

While a 2017 meta-analysis failed to show that B-vitamins improve cognition in patients with dementia, earlier studies have been more promising [75]. Supplementation with vitamins B12, B6 and folic acid has been found to decrease cerebral atrophy in cortical regions known to be specifically vulnerable in AD [76]. This effect, however, was only seen in patients with high homocysteine levels at baseline. Similarly, supplementing with these three B-vitamins decreased cognitive decline in patients with MCI and elevated homocysteine levels

[77]. Interestingly, some data show that omega-3 fatty acids are a necessary co-requisite in achieving these cognitive benefits. In patients with MCI who also had low omega-3 fatty acid levels, B-vitamin treatment failed to slow cognitive decline [78]. Similarly, B-vitamin supplementation reduced brain atrophy only in patients with high levels of omega-3 fatty acids [79]. While the data is mixed, the take-home message seems to be that in patients with low to low-normal B12 levels and/or high homocysteine levels, supplementing B12, possibly in combination with folic acid and B6, may help preserve cognitive function, particularly when intake of omega-3 fatty acids is optimal.

Botanicals

Ginkgo biloba

While studies have been inconsistent and often plagued by industry sponsorship, a recent overview of systematic reviews found that *Ginkgo biloba* did have positive effects on cognitive performance, ADLs and clinical global impression in patients with dementia [80-82]. This herb, however, does not seem to be effective for prevention [83]. If patients with established dementia do choose to try *Ginkgo*, providers should recommend the use of at least 200mg per day for at least 22 weeks before determining efficacy [82].

Green tea

Several studies have found a significantly decreased incidence of dementia with green tea consumption [84,85]. This effect seems to be particularly notable in those at an increased risk of developing AD [86]. Among carriers of the ApoE4 gene, regular tea consumption (green, black, and oolong) reduced the risk of cognitive decline by 86% [86]. Green tea consumption, however, does not seem to improve cognition among those who are already cognitively impaired [87]. If patients enjoy drinking green tea, clinicians can encourage them to continue as it may have a protective effect, particularly for those at an increased risk for developing AD.

Resveratrol

Resveratrol has been postulated to improve cognition by optimizing circulation in the brain [88]. Studies in animals have been promising. In rodent models of AD, resveratrol was found to have a neuroprotective effect, improving memory and decreasing amyloid burden in the brain [89]. When studied clinically, results have been mixed. One randomized, placebo-controlled trial did show that resveratrol supplementation modestly improved cognitive performance and memory in healthy postmenopausal women, but other studies have not shown a clinical benefit to supplementation [90-92]. A recent meta-analysis concluded that resveratrol had no significant effect on cognitive performance [93]. Overall, the data for resveratrol in improving cognitive functioning is relatively weak.

Curcumin

Curcumin has well-established antioxidant and anti-inflammatory properties. *In vitro*, curcumin has been found to decrease beta-amyloid protein production and to increase its clearance [94,95]. While preclinical studies have been promising, there is currently not enough clinical evidence to recommend curcumin for the prevention or treatment of dementia. In a recent randomized, double-blind, placebo-controlled trial, curcumin had little effect on cognitive function or decline in a group of cognitively normal older adults [96]. Regarding its efficacy in dementia treatment, a 2014 systematic review found insufficient evidence to support its use in patients with AD [97]. Study authors have noted poor oral bioavailability, underpowered studies and insufficient follow-up periods as limiting factors [97]. Clinicians should advise their patients that while preclinical evidence is promising, additional studies are needed to further evaluate clinical effects.

Other dietary supplements

Omega-3 fatty acids

Fish and omega-3 fatty acids have also been studied on their own for their role in preventing dementia. In a recent meta-analysis, higher fish intake was associated with a 36% reduced risk of AD [98]. A 1 serving per week increase in fish consumption has been associated with a 7% decrease in the risk of AD and a 5% decrease in the risk of dementia [99]. Similarly, a 0.1g per day increase in consumption of the omega-3 fatty acid, DHA (but not EPA), was associated with a 14% decreased risk of dementia and a 37% decreased risk of AD [99]. Taken in aggregate, these data suggest that higher dietary intakes of fish and possibly fish oil supplements, may lower the risk of AD. If a fish oil supplement is used, the DHA component may be more beneficial than the EPA component.

Acetyl-L-Carnitine

A meta-analysis of placebo-controlled trials found that when given to patients with MCI or early AD, acetyl-l-carnitine had positive effects on both clinical and psychometric scales [100]. Severity and stage of dementia appear to be important determinants of response to this supplement. A Cochrane systematic review evaluating acetyl-l-carnitine for patients with dementia that was not limited to mild forms or early onset showed that acetyl-l-carnitine had a positive effect on clinical global impression, but not on other objectively measured outcomes [101]. Acetyl-l-carnitine may be modestly beneficial for those with mild, early onset dementia.

Phosphatidylserine

Multiple placebo-controlled trials have shown that bovine cortex-derived phosphatidylserine is effective in treating dementia and age-related cognitive decline [102-106]. This form of animal-derived phosphatidylserine, however, is no longer available given safety concerns, namely contamination and transmission of diseases such as Bovine Spongiform Encephalopathy. Plant-derived phosphatidylserine has also been evaluated and while results were promising in a very small preliminary study, a larger follow up study failed to find a beneficial effect [107,108]. When used in combination with DHA or phosphatidic acid, however, cognitive performance was improved in elderly patients with memory impairment or AD [109,110]. Clinicians can advise their patients that there is currently not enough evidence to recommend plant-derived phosphatidylserine on its own for cognitive impairment. If this supplement is tried, a product that combines phosphatidylserine with DHA or phosphatidic acid should be utilized.

Choline

Certain forms of choline have been found to be helpful in patients with AD. Choline alfoscerate (alpha GPC) at a dose of 400mg TID has been found to improve cognition and global function in patients with mild to moderate AD when used over a period of 6 months [111].

This supplement, when taken with donepezil, also decreased mood symptoms in this patient population [112]. A 2010 meta-analysis found that another form of choline (CDP choline) has positive effects on several cognitive domains [113]. In recent studies, CDP choline improved cognition and slowed progression of dementia when used in conjunction with acetylcholinesterase inhibitors [114,115].

Spermidine

Spermidine is a natural polyamine whose intracellular concentration declines in the human brain with ageing [116]. This substance presumably preserves memory performance by regulating neural mechanisms in the brain [117]. A recent randomized, placebo-controlled, double-blind trial from Germany evaluated the impact of spermidine on memory performance in 30 older adults at risk for dementia [117]. This 3-month-long trial showed improved memory performance in the spermidine group compared to the placebo group. Based on the positive results of this small trial, spermidine supplementation shows promise for the treatment of age-related cognitive impairment and warrants further investigation.

Summary

The identification of these 14 potentially modifiable risk factors for Alzheimer's disease should prompt us to create and implement more effective measures for their prevention and/or treatment. By doing so, we may not only decrease the burden of each risk factor in isolation but may achieve 1/3 reduction of Alzheimer's disease cases. Regarding dietary supplements, the available data suggest that some of them may be helpful in preventing and/or treating dementia, though further high quality studies are needed.

References

1. Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, et al. (2015) The global impact of dementia: An analysis of prevalence, incidence, cost and trends. World Alzheimer's Report, Alzheimer's Disease International, London, UK.
2. Qiu C, Fratiglioni L (2018) Aging without Dementia is Achievable: Current Evidence from Epidemiological Research. J Alzheimers Dis 62: 933-942.
3. Crous-Bou M, Minguillón C, Gramunt N, Luis Molinuevo J (2017) Alzheimer's disease prevention: From risk factors to early intervention. Alzheimers Res Ther 9: 71.
4. World Health Organization, Alzheimer's Disease International (2012) Dementia: A Public Health Priority. WHO, Geneva, Switzerland. Pg no: 112.
5. Daviglus ML, Bell CC, Berrettini W, Bowen PE, Connolly ES Jr, et al. (2010) National Institutes of Health State-of-the-Science Conference statement: Preventing alzheimer disease and cognitive decline. Ann Intern Med 153: 176-181.
6. Barnes DE, Yaffe K (2011) The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 10: 819-828.
7. Erickson KI, Kramer AF (2009) Aerobic exercise effects on cognitive and neural plasticity in older adults. Br J Sports Med 43: 22-24.
8. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, et al. (2006) Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci 61: 1166-1170.
9. Erickson KI, Miller DL, Weinstein AM, Akl SL, Banducci S (2012) Physical activity and brain plasticity in late adulthood: a conceptual and comprehensive review. Ageing Res 3: 6.
10. Coelho FG, Gobbi S, Andreatto CA, Corazza DI, Pedroso RV, et al. (2013) Physical exercise modulates peripheral levels of Brain-Derived Neurotrophic Factor (BDNF): A systematic review of experimental studies in the elderly. Arch Gerontol Geriatr 56: 10-15.
11. Panza GA, Taylor BA, MacDonald HV, Johnson BT, Zaleski AL, et al. (2018) Can Exercise Improve Cognitive Symptoms of Alzheimer's Disease? J Am Geriatr Soc 66: 487-495.
12. Etnier JL, Nowell PM, Landers DM, Sibley BA (2006) A meta-regression to examine the relationship between aerobic fitness and cognitive performance. Brain Res Rev 52: 119-130.
13. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C (2014) Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. Lancet Neurol 13: 788-794.
14. Horder H, Johansson L, Guo X, Grimby G, Kern S, et al. (2018) Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women. Neurology: 1-9.
15. Smith JC, Nielson KA, Woodard JL, Seidenberg M, Durgerian S, et al. (2014) Physical activity reduces hippocampal atrophy in elders at genetic risk for Alzheimer's disease. Front Aging Neurosci: 6: 61.
16. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, et al. (2011) Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci USA 108: 3017-3022.
17. Dai J, Jones DP, Goldberg J, Ziegler TR, Bostick RM, et al. (2008) Association between adherence to the Mediterranean diet and oxidative stress. Am J Clin Nutr 88: 1364-1370.
18. Chrysohoou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C (2004) Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: The ATTICA Study. J Am Coll Cardiol 44: 152-158.
19. Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, et al. (1995) Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr 61: 1402-1406.
20. Petersson SD, Philippou E (2016) Mediterranean diet, cognitive function, and dementia: A systematic review of the evidence. Adv Nutr 7: 889-904.
21. Martínez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, et al (2013) Mediterranean diet improves cognition: The PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry 84: 1318-1325.
22. 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: 1094-1103.
23. Morris MC, Tangney CC, Wang Y, Sachs F, Barnes LL, et al. (2014) MIND diet score more predictive than DASH or Mediterranean diet scores. Alzheimer's & Dementia 10: 166.
24. Morris MC, Tangney CC, Wang Y, Sacks F, Bennett DA, et al. (2015) MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimers Dement 11: 1007-1014.
25. Stern Y (2012) Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol 11: 1006-1012.
26. Brown J, Cooper-Kuhn CM, Kemperman G, van Praag H, Winkler J, et al. (2003) Enriched environment and physical activity stimulate hippocampal but not olfactory bulb neurogenesis. Eur J Neurosci 17: 2042-2046.
27. Van Praag H, Kempermann G, Gage FH (2000) Neural consequences of environmental enrichment. Nat Rev Neurosci 1: 191-198.

28. Krell-Roesch J, Vemuri P, Pink A, Roberts RO, Stokin GB, et al. (2017) Association Between Mentally Stimulating Activities in Late Life and the Outcome of Incident Mild Cognitive Impairment, With an Analysis of the APOE ε4 Genotype. JAMA Neurol 74: 332-338.

29. Gottesman RF, Schneider ALC, Zhou Y, Coresh J, Green E, et al. (2017) Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition. JAMA 317: 1443-1450.

30. Deane R, Wu Z, Zlokovic BV (2004) RAGE (yin) versus LRP (yang) balance regulates alzheimer amyloid beta-peptide clearance through transport across the blood-brain barrier. Stroke 35: 2628-2631.

31. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P (2006) Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 5: 64-74.

32. Cheng G, Huang C, Deng H, Wang H (2012) Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Intern Med J 42: 484-491.

33. Muriach M, Flores-Bellver M, Romero FJ, Barcia JM (2014) Diabetes and the Brain: Oxidative Stress, Inflammation, and Autophagy. Oxid Med Cell Longev 102158: 9.

34. Farris W, Mansourian S, Chang Y, Lindsley L, Eckman EA, et al. (2003) Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain *in vivo*. Proc Natl Acad Sci USA 100: 4162-4167.

35. Bu G (2009) Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. Nat Rev Neurosci 10: 333-344.

36. Kim J, Basak JM, Holtzman DM (2009) The role of apolipoprotein E in Alzheimer's disease. Neuron 63: 287-303.

37. Habchi J, Chia S, Galvagnion C, Michaels TCT, Bellaiche MMJ, et al. (2018) Cholesterol catalyses Aβ42 aggregation through a heterogeneous nucleation pathway in the presence of lipid membranes. Nat Chem 10: 673-683.

38. Cataldo JK, Prochaska JJ, Glantz SA (2010) Cigarette smoking is a risk factor for Alzheimer's Disease: an analysis controlling for tobacco industry affiliation. J Alzheimers Dis 19: 465-480.

39. Rusanen M, Rovio S, Ngandu T, Nissinen A, Tuomilehto J (2010) Midlife smoking, apolipoprotein E and risk of dementia and Alzheimer's disease: a population-based cardiovascular risk factors, aging and dementia study. Dement Geriatr Cogn Disord 30: 277-284.

40. Rusanen M, Kivipelto M, Quesenberry CP Jr, Zhou J, Whitmer RA (2010) Heavy smoking in midlife and long-term risk of Alzheimer disease and vascular dementia. Arch Intern Med 171: 333-339.

41. Durazzo TC, Mattsson N, Weiner MW, Alzheimer's Disease Neuroimaging Initiative (2014) Smoking and increased Alzheimer's disease risk: a review of potential mechanisms. Alzheimers Dement 10: 122-145.

42. Alford S, Patel D, Perakakis N, Mantzoros CS (2018) Obesity as a risk factor for Alzheimer's disease: Weighing the evidence. Obesity Reviews 19: 269-280.

43. Gregor MF, Hotamisligil GS (2011) Inflammatory mechanisms in obesity. Annu Rev Immunol 29: 415-445.

44. Kleinridders A, Ferris HA, Cai W, Kahn CR (2014) Insulin action in brain regulates systemic metabolism and brain function. Diabetes 63: 2232-2243.

45. National Academies Press (2009) Long-term Consequences of Traumatic Brain Injury. National Academies Press, Washington DC, USA. Vol 7: 381.

46. Perry DC, Sturm VE, Peterson MJ, Pieper CF, Bullock T, et al. (2016) Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. J Neurosurg 124: 511-526.

47. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, et al. (2018) Association of Mild Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in US Military Veterans. JAMA Neurol 75: 1055-1061.

48. Havekes R, Vecsey CG, Abel T (2012) The impact of sleep deprivation on neuronal and glial signaling pathways important for memory and synaptic plasticity. Cell Signal 24: 1251-60.

49. Lobo A, López-Antón R, de-la-Cámara C, Quintanilla MA, Campayo A, et al. (2008) Non-cognitive psychopathological symptoms associated with incident mild cognitive impairment and dementia, Alzheimer's type. Neurotox 14: 263-272.

50. Palma JA, Urrestarazu E, Iriarte J (2013) Sleep loss as risk factor for neurologic disorders: A review. Sleep Med 14: 229-236.

51. Bubu OM, Brannick M, Mortimer J, Umasabor-Bubu O, Sebastião YV, et al. (2017) Sleep, Cognitive impairment, and Alzheimer's disease: A Systematic Review and Meta-Analysis. Sleep 40.

52. Benoit M, Berrut G, Doussaint J, Bakchine S, Bonin-Guillaume S, et al. (2012) Apathy and depression in mild Alzheimer's disease: a cross-sectional study using diagnostic criteria. J Alzheimer's Dis 31: 325-334.

53. Heser K, Tebarth F, Wiese B, Eisele M, Bickel H, et al. (2013) Age of major depression onset, depressive symptoms, and risk for subsequent dementia: results of the German study on Ageing, Cognition, and Dementia in Primary Care Patients (AgeCoDe). Psychol Med 43: 1597-1610.

54. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D (2006) Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry 63: 530-538.

55. Herbert J, Lucassen PJ (2016) Depression as a risk factor for Alzheimer's disease: Genes, steroids, cytokines and neurogenesis - What do we need to know? Front Neuroendocrinol 41: 153-171.

56. Teles R, Wang CY (2011) Mechanisms involved in the association between periodontal diseases and cardiovascular disease. Oral Dis 17: 450-461.

57. Liu TC, Sheu JJ, Lin HC, Jensen DA (2013) Increased risk of parkinsonism following chronic periodontitis: a retrospective cohort study. Mov Disord 28: 1307-1308.

58. Paraskevas S, Huizinga JD, Loos BG (2008) A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J Clin Periodontol 35: 277-290.

59. Chen CK, Wu YT, Chang YC (2017) Association between chronic periodontitis and the risk of Alzheimer's disease: a retrospective, population-based, matched-cohort study. Alzheimers Res Ther 9: 56.

60. Lin FR, Metter EJ, O'Brian RJ, Resnick SM, Zonderman AB, et al. (2011) Hearing loss and incident dementia. Arch Neurol 68: 214-220.

61. Deal JA, Sharrett AR, Albert MS, Coresh J, Mosley TH, et al. (2015) Hearing impairment and cognitive decline: A pilot study conducted within the atherosclerosis risk in communities neurocognitive study. Am J Epidemiol 181: 680-690.

62. Campbell J, Sharma A (2013) Compensatory changes in cortical resource allocation in adults with hearing loss. Front Syst Neurosci 7: 71.

63. Thomson RS, Auduong P, Miller AT, Gurgel RK (2017) Hearing loss as a risk factor for dementia: A systematic review. Laryngoscope Investig Otolaryngol 2: 69-79.

64. Readhead B, Haure-Mirande JV, Funk CC, Richards MA, Shannon P, et al. (2018) Multiscale analysis of independent Alzheimer's cohorts finds disruption of molecular, genetic, and clinical networks by human herpesvirus. Neuron 99: 64-82.

65. Eimer WA, Vijaya Kumar DK, Navalpur Shanmugam NK, Rodriguez AS, Mitchell T, et al. (2018) Alzheimer's disease-associated β-amyloid is rapidly seeded by Herpesviridae to protect against brain infection. Neuron 99: 56-63.

66. Itzhaki RF, Lathe R (2018) Herpes viruses and senile dementia: First population evidence for a causal link. J Alzheimers Dis 64: 363-366.

67. Tzeng NS, Chung CH, Lin FH, Chiang CP, Yeh CB, et al. (2018) Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections-a Nationwide, Population-Based Cohort Study in Taiwan. Neurotherapeutics 15: 417-429.

68. Jayedi A, Rashidy-Pour A, Shab-Bidar S (2018) Vitamin D status and risk of dementia and Alzheimer's disease: A meta-analysis of dose-response. Nutr Neurosci 15: 1-10.

69. Goodwill AM, Szoeke C (2017) A Systematic Review and Meta-Analysis of The Effect of Low Vitamin D on Cognition. J Am Geriatr Soc 65: 2161-2168.

70. Sommer I, Griebler U, Kien C, Auer S, Klerings I, et al. (2017) Vitamin D deficiency as a risk factor for dementia: a systematic review and meta-analysis. BMC Geriatr 17: 16.

71. Shen L, Ji HF (2015) Vitamin D deficiency is associated with increased risk of Alzheimer's disease and dementia: Evidence from meta-analysis. Nutr J 14: 76.

72. Farina N, Isaac MG, Clark AR, Rusted J, Tabet N (2012) Vitamin E for Alzheimer's dementia and mild cognitive impairment. Cochrane Database Syst Rev 11: CD002854.

73. Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, et al. (1997) A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med 336: 1216-1222.

74. Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, et al. (2014) Effect of vitamin E and memantine on functional decline in Alzheimer disease: The TEAM-AD VA cooperative randomized trial. JAMA 311: 33-44.

75. Zhang DM, Ye JX, Mu JS, Cui XP (2017) Efficacy of Vitamin B Supplementation on Cognition in Elderly Patients With Cognitive-Related Diseases. J Geriatr Psychiatry Neurol 30: 50-59.

76. Douaud G, Refsum H, de Jager CA, Jacoby R, Nichols TE, et al. (2013) Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. Proc Natl Acad Sci USA 110: 9523-9528.

77. de Jager CA, Oulhaj A, Jacoby R, Refsum H, Smith AD (2012) Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. Int J Geriatr Psychiatry 27: 592-600.

78. Oulhaj A, Jernerén F, Refsum H, Smith AD, de Jager CA (2016) Omega-3 Fatty Acid Status Enhances the Prevention of Cognitive Decline by B Vitamins in Mild Cognitive Impairment. J Alzheimers Dis 50: 547-557.

79. Jernerén F, Elshorbagy AK, Oulhaj A, Smith SM, Refsum H, et al. (2015) Brain atrophy in cognitively impaired elderly: the importance of long-chain ω-3 fatty acids and B vitamin status in a randomized controlled trial. Am J Clin Nutr 102: 215-221.

80. Birks J, Grimley Evans J (2007) *Ginkgo bilob*a for cognitive impairment and dementia. Cochrane Database Syst Rev: CD003120.

81. Hyde AJ, May BH, Dong L, Feng M, Liu S, et al. (2017) Herbal medicine for management of the behavioural and psychological symptoms of dementia (BPSD): A systematic review and meta-analysis. J Psychopharmacol 31: 169-183.

82. Yuan Q, Wang CW, Shi J, Lin ZX (2017) Effects of *Ginkgo biloba* on dementia: An overview of systematic reviews. J Ethnopharmacol 195: 1-9.

83. Charemboon T, Jaisin K (2015) *Ginkgo biloba* for prevention of dementia: A systematic review and meta-analysis. J Med Assoc Thai 98: 508-513.

84. Tomata Y, Sugiyama K, Kaiho Y, Honkura K, Watanabe T, et al. (2016) Green Tea Consumption and the Risk of Incident Dementia in Elderly Japanese: The Ohsaki Cohort 2006 Study. Am J Geriatr Psychiatry 24: 881-889.

85. Noguchi-Shinohara M, Yuki S, Dohmoto C, Ikeda Y, Samuraki M, et al. (2014) Consumption of green tea, but not black tea or coffee, is associated with reduced risk of cognitive decline. PLoS One 9: 96013.

86. Feng L, Chong MS, Lim WS, Gao Q, Nyunt MS, et al. (2016) Tea Consumption Reduces the Incidence of Neurocognitive Disorders: Findings from the Singapore Longitudinal Aging Study. J Nutr Health Aging 20: 1002-1009.

87. Ide K, Yamada H, Takuma N, Kawasaki Y, Harada S, et al. (2016) Effects of green tea consumption on cognitive dysfunction in an elderly population: a randomized placebo-controlled study. Nutr J 15: 49.

88. Evans HM, Howe PR, Wong RH (2016) Clinical Evaluation of Effects of Chronic Resveratrol Supplementation on Cerebrovascular Function, Cognition, Mood, Physical Function and General Well-Being in Postmenopausal Women-Rationale and Study Design. Nutrients 8: 150.

89. Lange KW, Li S (2018) Resveratrol, pterostilbene, and dementia. Biofactors 44: 83-90.

90. Evans HM, Howe PRC, Wong RHX (2017) Effects of Resveratrol on Cognitive Performance, Mood and Cerebrovascular Function in Post-Menopausal Women; A 14-Week Randomised Placebo-Controlled Intervention Trial. Nutrients 9: 27.

91. Köbe T, Witte AV, Schnelle A, Tesky VA, Pantel J, et al. (2017) Impact of Resveratrol on Glucose Control, Hippocampal Structure and Connectivity, and Memory Performance in Patients with Mild Cognitive Impairment. Front Neurosci 11: 105.

92. Wightman EL, Haskell-Ramsay CF, Reay JL, Williamson G, Dew T, et al. (2015) The effects of chronic trans-resveratrol supplementation on aspects of cognitive function, mood, sleep, health and cerebral blood flow in healthy, young humans. Br J Nutr 114: 1427-1437.

93. Farzaei MH, Rahimi R, Nikfar S, Abdollahi M (2018) Effect of resveratrol on cognitive and memory performance and mood: A meta-analysis of 225 patients. Pharmacol Res 128: 338-344.

94. Zhang L, Fiala M, Cashman J, Sayre J, Espinosa A, et al. (2006) Curcuminoids enhance amyloid-beta uptake by macrophages of Alzheimer's disease patients. J Alzheimers Dis 10: 1-7.

95. Shimmyo Y, Kihara T, Akaike A, Niidome T, Sugimoto H (2008) Epigallocatechin-3-gallate and curcumin suppress amyloid beta-induced beta-site APP cleaving enzyme-1 upregulation. Neuroreport 19: 1329-1333.

96. Rainey-Smith SR, Brown BM, Sohrabi HR, Shah T, Goozee KG, et al. (2016) Curcumin and cognition: a randomised, placebo-controlled, double-blind study of community-dwelling older adults. Br J Nutr 115: 2106-2113.

97. Brondino N, Re S, Boldrini A, Cuccomarino A, Lanati N, et al. (2014) Curcumin as a therapeutic agent in dementia: a mini systematic review of human studies. ScientificWorldJournal 2014: 174282.

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

99. Zhang Y, Chen J, Qiu J, Li Y, Wang J, et al. (2016) 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: 330-340.

100. Montgomery SA, Thal LJ, Amrein R (2003) Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. Int Clin Psychopharmacol 18: 61-71.

101. Hudson S, Tabet N (2003) Acetyl-L-carnitine for dementia. Cochrane Database Syst Rev: CD003158.

102. Crook TH, Tinklenberg J, Yesavage J, Petrie W, Nunzi MG, et al. (1991) Effects of phosphatidylserine in age-associated memory impairment. Neurology 41: 644-649.

103. Crook T, Petrie W, Wells C, Massari DC (1992) Effects of phosphatidylserine in Alzheimer's disease. Psychopharmacol Bull 28: 61-66.

104. Cenacchi T, Bertoldin T, Farina C, Fiori MG, Crepaldi G (1993) Cognitive decline in the elderly: a double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration. Aging (Milano) 5: 123-133.

105. Delwaide PJ, Gyselynck-Mambourg AM, Hurlet A, Ylieff M (1986) Double-blind randomized controlled study of phosphatidylserine in senile demented patients. Acta Neurol Scand 73: 136-140.

106. Engel RR, Satzger W, Günther W, Kathmann N, Bove D, et al. (1992) Double-blind cross-over study of phosphatidylserine vs. placebo in patients with early dementia of the Alzheimer type. Eur Neuropsychopharmacol 2: 149-155.

107. Schreiber S, Kampf-Sherf O, Gorfine M, Kelly D, Oppenheim Y, et al. (2003) An open trial of plant-source derived phosphatydilserine for treatment of age-related cognitive decline. Isr J Psychiatry Relat Sci 4: 302-307.

108. Jorissen BL, Brouns F, Van Boxtel MP, Ponds RW, Verhey FR, et al. (2001) The influence of soy-derived phosphatidylserine on cognition in age-associated memory impairment. Nutr Neurosci 4: 121-134.

109. Vakhapova V, Cohen T, Richter Y, Herzog Y, Korczyn AD (2010) Phosphatidylserine containing omega-3 fatty acids may improve memory abilities in non-demented elderly with memory complaints: A double-blind placebo-controlled trial. Dement Geriatr Cogn Disord 29: 467-474.

110. Moré MI, Freitas U, Rutenberg D (2014) Positive effects of soy lecithin-derived phosphatidylserine plus phosphatidic acid on memory, cognition, daily functioning, and mood in elderly patients with Alzheimer's disease and dementia. Adv Ther 31: 1247-1262.

111. De Jesus Moreno Moreno M (2003) Cognitive improvement in mild to moderate Alzheimer's dementia after treatment with the acetylcholine precursor choline alfoscerate: A multicenter, double-blind, randomized, placebo-controlled trial. Clin Ther 25: 178-193.

112. Carotenuto A, Rea R, Traini E, Fasanaro AM, Ricci G, et al. (2017) The Effect of the association between Donepezil and Choline Alphoscerate on behavioral disturbances in Alzheimer's Disease: Interim results of the ASCOMALVA trial. J Alzheimers Dis 56: 805-815.

113. García-Cobos R, Frank-García A, Gutiérrez-Fernández M, Díez-Tejedor E (2010) Citicoline, use in cognitive decline: vascular and degenerative. J Neurol Sci Dec 299: 188-192.

114. Gareri P, Castagna A, Cotroneo AM, Putignano D, Conforti R, et al. (2017) The Citicholinage Study: Citicoline Plus Cholinesterase Inhibitors in Aged Patients Affected with Alzheimer's Disease Study. J Alzheimers Dis 56: 557-565.

115. Castagna A, Cotroneo AM, Ruotolo G, Gareri P (2016) The CITIRIVAD Study: CITIcoline plus RIVAstigmine in Elderly Patients Affected with Dementia Study. Clin Drug Investig 36: 1059-1065.

116. Gupta VK, Scheunemann L, Eisenberg T, Mertel S, Bhukel A, et al. (2013) Restoring polyamines protects from age-induced memory impairment in an autophagy-dependent manner. Nat Neurosci 16: 1453-1460.

117. Wirth M, Benson G, Schwarz C, Kobe T, Grittner U, et al. (2018) The effect of spermidine on memory performance in older adults at risk for dementia: A randomized controlled trial. Cortex 109: 181-188.