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How Do Modifiable Risk Factors Impact the Progression of Alzheimer's Disease?

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Abstract

Alzheimer's disease remains a significant health burden that affects millions in the United States. This research pursued to shed light on the modifiable risk factors and help individuals at high risk for Alzheimer's disease minimize the chances of cognitive decline. A search of literature was conducted on databases such as PubMed, Google Scholar, and Medline. Randomized control trials, longitudinal studies, systematic reviews, and meta-analyses were identified and included in the paper. The modifiable risk factors that play a role in the onset and progression of Alzheimer's disease include stress, inadequate physical exercise, lack of sleep hygiene, and lack of social engagement. However, in the studies that focused on modifying these factors, results showed an improved cognitive performance. Other modifiable factors such as alcohol and dietary intake, including omega-3 fatty acids and carotenoid-rich foods, were found to slow cognitive decline. Additionally, the MIND, DASH, and the Mediterranean diet are recommended for high-risk patients. The general implication of these findings is that modifying these risk factors for high-risk patients can lead to better cognitive performance and slow AD progress. Future studies can focus on conducting longitudinal factors such as alcohol intake due to the inconsistent findings documented in this research. The burden of Alzheimer's disease can be reduced nationwide by effectively addressing these modifiable risk factors.

Introduction

Alzheimer's disease (AD) presents a significant healthcare burden for the United States. Over 6.2 million Americans age 65 and older currently live with AD. The number of people with AD is estimated to increase to 12.7 million people by 2050.[1] It is the most common cause of dementia and affects more women than men. While the cause of AD remains unknown, multiple non-modifiable and modifiable factors are associated with its development. The most noteworthy risk factors include old age, family history, and carrying the APOE-e4 gene.[1] There are additional risk factors that are modifiable but can increase the risk of AD development. Amongst these factors include lifestyle modifications such as changes in stress management, dietary intake, sleep, and exercise that can reduce one's risk for AD. In addition, it has been found that persons with a past medical history of cardiovascular disease risk factors such as HTN, diabetes mellitus, and traumatic brain injuries are more prone to AD. However, other modifiable risk factors such as more formal years of education and remaining socially and cognitively engaged may reduce the risk of AD.[1] Since cognitive impairment increases with the progression of AD, it is important to identify the relationship between modifiable risk factors and AD. According to Wang et al,[2] these interventions effectively manage AD, but current evidence to support this assertion is still low. Therefore, healthcare providers can utilize these interventions to improve outcomes for AD patients.

Since there is no cure for AD, current treatment focuses on memory retention, cognitive and physical functioning, and slowing the condition's progression. The increasing prevalence of AD among older people underlines the need for increased awareness about modifiable risk factors. Therefore, understanding these risk factors can better facilitate the management of this disease. Ultimately, this research intends to help individuals at high risk for AD prevent and

minimize their chances of cognitive decline by shedding light on the following modifiable risk factors discussed in this work. The research question for this paper is, "In Alzheimer's disease, how does modifying risk factors impact clinical progression?" The article is outlined as follows. First, a background on the modifiable risk factors and then literature surrounding their impact of AD progression. This paper will conclude with a discussion of recommendations and future research directions based on the current literature.

Background

Pathophysiology

Alzheimer's disease (AD) is a progressive neurodegenerative disease that commonly leads to dementia. Since the exact causes of AD are not fully understood, there are proposed theories of the pathogenesis of AD. One of the most influential theories known is the amyloid cascade hypothesis and the Tau hypothesis. The amyloid hypothesis proposes that the abnormal accumulation of the amyloid-beta (Aβ) protein leads to the extracellular formation of neuritic plaques. In contrast, the tau hypothesis suggests an intracellular accumulation of the tau protein due to the hyperphosphorylation from the Aβ aggregation leading to the formation of neurofibrillary tangles. Though it is unknown, it is frequently believed that the Aβ aggregation is the initial pathological event in AD and triggers the subsequent cascade of events such as the neurofibrillary tangles, an abnormal accumulation of tau. This causes tau to detach from microtubules and form threads that eventually tangle inside neurons. Additionally, these changes lead to blockage of the neuron's transport system, harming synaptic communication.[3] Thus, understanding the AD disease process can help implement better interventions for modifiable risk factors.

Clinical Features

Given that AD has a very slow progression, its clinical manifestations present much later than the initial pathological changes in the brain. This results in a long preclinical stage that often lasts up to 20-30 years before signs and symptoms of cognitive impairment appear. In the typical presentation of AD, the age of onset is 65 and older. Following the preclinical stage, some of the earlier manifestations of AD are impairment in executive function, judgment, and most significant, memory. For a clinical diagnosis of AD, the cardinal symptom of memory impairment must be present. Memory deficits are frequently the most common initial symptom of AD. The type of memory impairment typically follows a distinctive pattern such that the episodic memory is impacted first, and then procedural memory is affected later in the disease. As the disease progresses, Alzheimer's patients are faced with behavioral and psychological symptoms such as social disengagement, irritability, and apathy.

Diagnostics

AD is typically high in suspicion when a patient of older age presents with a progressive memory decline. However, before working up AD in particular, it is important to rule out other changeable causes of dementia. A patient presenting with initial AD symptoms would first undergo various neuropsychological tests followed by lab testing to dismiss adjustable causes of dementia such as vitamin B12 deficiency or hypothyroidism. Healthcare professionals can use various approaches to confirm AD diagnosis. Family members are asked about changes in behavior and personality and then conduct memory, attention, language, and problem-solving tests. Additionally, the doctor will conduct blood and urine tests to identify other possible causes of the problem. Lastly, computed tomography, magnetic resonance imaging, along with positron emission tomography are executed to exclude other possible causes of AD symptoms.[4] Overall, these tests help doctors determine the presence of AD and its current progression.

Management

Active management of AD involves pharmacological and non-pharmacological interventions. The medications sanctioned by the FDA for AD treatment are rivastigmine, galantamine, donepezil, memantine, and memantine combined with donepezil. However, these medications are not curative; rather, they are used to slow down the neuronal damage caused by AD.[1] Apart from these interventions, non-pharmacologic therapies are initiated for AD to ensure improvement in cognitive function and quality of life (QoL). Interventions such as computerized memory training, listening to music, physical exercise, and special lighting are often utilized. According to Wang et al,[2] music therapy improves cognitive function and mental well-being. Additionally, regular physical activity decreases cognitive declines and reduces the risk of AD.[2] Therefore, once a patient is diagnosed with AD, these interventions are utilized to slow its progression and reduce cognitive decline.

Lifestyle Modification

Stress Management

The relationship between stress and AD is documented in various studies. Firstly, Hoeijmakers et al[5] examine whether stress in early life increases vulnerability for AD. The authors summarize information from preclinical literature with a specific focus on biological substrates that mediate the relationship between these two conditions. Early-life stress elevated glucocorticoid levels and corticotropin release factor signaling. Additionally, stress increases amyloid and tau pathology and reduces synaptic connectivity and hippocampal neurogenesis, which leads to cognitive decline due to less cognitive reserve. These findings indicate that stress experienced particularly in one's childhood may hinder healthy aging and modify AD development. Other studies corroborate these findings. Caruso et al[6] indicate that elevated

glucocorticoid levels from high-stress levels can trigger cellular, molecular, and behavioral imbalances that resemble the pathological features of AD. In particular, stress enhances the amyloid ß precursor protein and tau phosphorylation that were previously noted as major contributory factors to the development of AD by causing synaptic dysfunction and neuronal death.[6] Thus, stress increases vulnerability to AD.

In another study, Quanes and Popp[7] reviewed the literature to document how high cortisol levels enhance the threat of dementia and AD. This study indicates that enhanced cortisol levels are connected with poor mental functioning, lower episodic memory, executive functioning, and social cognition. The authors conclude that elevated cortisol levels have detrimental effects on cognition and lead to AD.[7] In another study, Justice[8] examines the relationship between stress and AD. The findings from this article indicate that stress exacerbates AD pathogenesis. Moreover, AD can also lead to stress as it disrupts neural circuits that mediate stress responses.[8] The link between these two conditions is demonstrated in these studies. Stress management through different strategies is included in the discussion section. Therefore, stress management is essential to prevent cognitive decline and possible AD development.

Dietary Intake

Omega-3

Omega-3 fatty acids have demonstrated effectiveness in enhancing memory functions in patients diagnosed with AD. Marti and Fortique[9] conducted a systematic review of fourteen RCTs to determine the effectiveness of this intervention in cognitive function. The results from this review show that omega-3 fatty acids can improve individual domains of cognitive function such as working memory, executive function, perceptual speed, and verbal memory. The systematic review concludes that of the fourteen studies, ten of them showed a positive outcome

in that omega-3 supplementation might improve cognitive function.[9] Of the remaining studies showed no positive outcome, it was found that the participants in those studies had an average younger age than the ones that had a positive outcome. Another study by Nolan et al[10] attempted to demonstrate the potential benefits of combining omega-3 fatty acids with Xanthophyll carotenoids. The study included three experiments that focused on patients with mild and moderate AD and those free from the condition. The first group was given Xanthophyll carotenoids only supplementation, the second group was given Xanthophyll carotenoids and fish oil, while the third group of participants without AD received Xanthophyll carotenoids. Similar to Marti and Fortique9, the findings show that participants in the second group had positive cognition outcomes from the additional supplementation of omega-3. However, the authors conclude that more scientific evidence is needed to confirm this significant observation.[10] The findings from this study indicate that omega-3 fatty acids consumption can decrease cognitive decline associated with AD.

While omega-3 fatty acids are effective; some studies indicate that it does not entirely improve cognitive function. In a systematic review of seven studies, Canada et al[11] found that omega-3 fatty acids are beneficial during disease onset. The effectiveness of these supplements at this stage is due to slight impairment in cognitive function. However, there is no sufficient evidence to support omega-3 supplementation in severe AD cases. 9 In another systematic review and meta-analysis, Araya-Quintanilla et al[12] examine whether there is sufficient scientific evidence to support omega-3 supplementation in patients with AD. The study includes six randomized controlled trials (RCTs). Contrary to study,[9] the results from this paper show that there is still a lack of consistent evidence that supports omega-3 supplementation.12 Omega-3 supplementations can be used during the early stages of AD to prevent the decline in cognitive

function. While this intervention can slow cognitive decline, this evidence indicates that it is only effective in earlier stages of AD.

Carotenoid-rich Foods

Carotenoids rich-food are effective for reducing cognitive decline connected to AD. In the study by Nolan et al,[10] the researchers found that combining carotenoids with omega-3 enhanced cognitive outcomes for AD patients. These findings are upheld in a recent meta-analysis of RCTs by Davonelli et al,[13] examining the relationship between carotenoids and cognitive outcomes. The analysis included 9 studies with a total of 4402 participants ranging between 45 to 78 years. Though the results from this study indicate that carotenoids enhanced cognitive outcomes for the participants, the findings were geared more towards healthy subjects than those with dementia or AD.[13] Additionally, Lakey-Beitia[14] examines how the chemistry and structure of carotenoid compounds act against Aβ aggregation. The findings indicate that carotenoids possess dominant anti-amyloidogenic molecules that can prevent AD by inhibiting Aβ aggression. Similar to Nolan's study, these findings support the view that carotenoids effectively avert cognitive decline in patients with AD.

Furthermore, Beydoun et al[15] evaluate longitudinal data from 1251 participants to determine the effects of carotenoids, vitamins A, C, and Eon favorable cognitive outcomes. The results show that an interaction between vitamins A, C, and carotenoids was not consistent and rather found that carotenoids and vitamin E are linked to positive outcomes in the memory performance.[15] Another study by Tan and Norhaizan[16] tried to establish the effectiveness of carotenoids in preventing age-related diseases. The findings show that carotenoids reduce oxidative stress and promote healthy aging by slowing the progress of age-related diseases.[16]

Ultimately, through these various studies, it is evident that the role of carotenoids is pivotal in the prevention of AD by enhancing an individual's cognitive outcomes.

Mediterranean and DASH Diet

Some of the most common modifiable risk factors, such as type II diabetes, hypertension, and obesity, can be reduced by changes in one's dietary patterns. Miranda et al[17] examine how the Mediterranean diet consisting of fruits, vegetables, olive oil, and moderate wine intake can prevent AD. Through these foods, one gets vitamins, polyphenols, and unsaturated fatty acids that reduce oxidative stress. Another important role of this diet highlighted by Miranda et al[17] is that it possesses an anti-inflammatory effect inhibiting the pathogenesis of AD. As a result, the Mediterranean diet improves AD risk factors by slowing the progression of this condition.[17] Another study by Van de Brink[18] established that the Mediterranean and the Dietary approaches to Stop Hypertension (DASH) were associated with less cognitive decline and could lower the risk of developing AD. Moreover, the review found that adherence to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) was linked to better cognitive performance.[17] The evidence from these studies supports the view that both the Mediterranean and DASH diets can slow cognitive decline and decrease the possibility of AD. Patients should be encouraged to adhere to these diets to modify risk factors and promote better cognitive outcomes.

Cherian et al[19] also examine how the MIND diet can slow cognitive decline after stroke. The study included 106 participants with a clinical history of stroke. The MIND diet components comprised whole grains, leafy greens, vegetables, beans, nuts, lean meats, and poultry. The participants were also expected to reduce consumption of cheese, butter, fried foods, and sweets. The results show that participants had a slower global cognitive decline rate. The authors conclude that adherence to the MIND diet is linked to slow cognitive decline through these

results. In another study, Berendsen et al[20] examined how long-term adherence to the MIND diet was related to cognitive function and decline among American women. The study included 16,058 women aged 70 and over. The findings from this study show that adherence to the MIND diet was linked to better verbal memory but not cognitive decline. The authors recommend the need for more studies to confirm the effectiveness of the MIND diet on slowing cognitive decline.[20] Overall, the diet is an effective intervention for slowing AD progression.

Alcohol

The relationship between alcohol consumption and AD has been researched in several studies. In particular, an observational study conducted by Andrews et al[21] shows that light-to-moderate alcohol consumption decreases the risk of AD. However, this study utilized two-sample Mendelian randomization (MR) approach to analyze how alcohol consumption dependence and alcohol use disorder were linked to late-onset AD. The findings from the study demonstrated that alcohol consumption was linked to earlier onset of AD while alcohol dependence was linked to delayed age of onset survival. This delayed onset was associated with survivor bias in the study. 21 Some of the findings from this study are corroborated by Venkataraman et al[22] in a literature review propose that alcohol adds to the cognitive burden of dementia. Indeed, alcohol misuse and dependence cause cognitive impairment.[22] These results confirm that the level of alcohol intake determines the rate of cognitive decline and can contribute to AD.

At the same time, Topiwala et al[23] examined the relationship between moderate alcohol consumption and cognitive decline. The researchers adopted a longitudinal study that comprised 550 men and women who were not alcohol dependent. Through a 30-year follow-up, the results showed that high alcohol consumption was linked to adverse brain outcomes. Light drinking did

not offer the participants any protective effects. The study concluded that alcohol consumption even at moderate levels can lead to adverse brain outcomes. For instance, persons consuming over 30 units weekly had the highest risk of cognitive decline, while those consuming 14-21 units showed right-sided hippocampal atrophy. Moreover, light drinkers (1-7 units per week) did not have any protective effects against cognitive decline compared to abstainers.[23] However, results from a study by Zhang et al[24] indicate that low to moderate alcohol consumption is linked to better global cognition scores. However, these findings appear stronger among white participants than blacks. The racial differences in this study limit the generalization of the findings to other populations. The question of alcohol consumption and AD need more research with the inclusion of more participants. For example, diverse participants such as Blacks, Hispanics, Native Americans, and Asian Americans can be included in future studies to help predict the link between alcohol consumption and AD. Therefore, the relationship between alcohol and AD needs further examination.

Sleep Hygiene

Emerging evidence has linked the lack of sleep hygiene to the risk of AD. Burke et al[25] study examined whether sleep medication could offer protection against AD and whether APOE e4 carriers that showed signs of sleep disturbance were at an increased risk of AD. A secondary analysis of data from the National Alzheimer's Coordinating Center was conducted. The results showed that sleep disturbance is linked to eventual AD development. However, sleep medication was found to mediate this relationship. Additionally, APOE e4 carriers had a significant risk of AD. Similarly, Sabia et al[26] examined how sleep duration was related to the risk of dementia; it was found that lower sleep duration was linked to increased dementia risk. Notably, the 25-year follow-up study indicated that people with a normal sleep duration of more than seven hours had

a lower risk of dementia.[26] These findings underline the positive link between sleep and AD. People should be encouraged to observe better sleep hygiene to lower their risk of dementia.

At the same time, other studies [27,28] have affirmed the positive link between lack of sleep and AD. Westwood[27] conducted a self-reported study comprising 2457 men and women to determine the relationship between sleep duration and early neurodegeneration. The findings indicate that prolonged sleep is a possible marker of neurodegeneration. These results can be used to identify people at higher risk of progressing to clinical dementia. In another study, Brzecka[28] link sleep disorders to AD, describing how sleep disturbance causes circadian fluctuations in amyloid- β concentration in the interstitial brain fluid.[28] The accumulating evidence suggests that sleep disturbance can lead to cognitive decline and AD development. Sabia et al[26] note that having at least seven hours of sleep each day can reduce the risk of AD. Therefore, individuals at risk of AD should be advised to observe appropriate sleep hygiene to minimize progressive cognitive decline.

Physical Activity and Exercise

Physical activity and exercise are protective against various chronic diseases. Several studies have been conducted to determine how physical exercise is beneficial in slowing AD progress. The efficacy of physical exercise has been examined in RCTs [29,30] in patients with AD. Fonte et al[29] conducted a study to determine how physical exercise was effective for AD and mild cognitive impairment (MCI). The results suggest that constant physical exercise is linked to the mitigation of cognitive decline. However, it is only effective when constantly applied and not periodically.[29] In another RCT, Cox et al[30] examined how physical exercise is beneficial for older patients at risk of AD. The study involved participants above 60 years with MCI or subjective memory complaints. Physical activity was associated with benefits such as leg

strength and better fat mass distribution. These benefits reduced cardiovascular risk, which in return minimized cognitive decline. Exercises such as walking, cycling, and swimming are often designed by considering health problems and other limitations.[30] Additionally, moderate-intensity aerobic physical activity is also recommended for AD patients.[32] Physical exercise is a useful intervention to slow cognitive decline in patients with AD.

Various meta-analyses and systematic reviews have also underlined the efficacy of physical exercise for older persons with AD. Cunningham et al[31] performed a systematic review and meta-analysis to establish the effect of physical exercise on older adults. The study included 24 studies that focused on older adults above 60 years. Results indicated that physical exercise for these older adults reduced cardiovascular and cancer risk. Additionally, the risk of AD, dementia and depression was also reduced through physical exercise. The articles included in this study showed that the QoL and cognitive function of the participants improved significantly as a result of physical activity. Similarly, Jia et al[32] conducted a meta-analysis that supports these findings. The meta-analysis included 13 RCTs comprising 673 participants diagnosed with AD. Physical activity interventions in each of these studies resulted in significant cognitive improvements. Moreover, the frequency of interventions did not result in a significant difference in the cognitive improvements.[32] These reviews and meta-analyses support the notion that physical activity slows cognitive decline for patients with AD and those at-risk.

Medical Comorbidities

Hypertension

The link between hypertension (HTN) and AD has been discussed in various studies. Lennon et al[33] conducted a systematic review and meta-analysis to establish the link between midlife HTN and AD. While the authors found 3426 publications addressing the issue, only

seven were eligible based on their meticulous design. The findings showed a significant association between HTN and AD. Midlife systolic HTN increased the risk of AD by 18-25%, while diastolic HTN was not linked to AD. Another systematic review and meta-analysis by Hughes et al[34] established how antihypertensive therapy lowered the risk of dementia and HTN. The authors included 12 trials comprising 92,135 participants in this study. The results indicated that lowering blood pressure through antihypertensive therapy led to a lower risk of dementia and cognitive impairment.[34] The results from these two studies support the assertion that HTN increases the risk of AD. Controlling HTN through pharmacological and non-pharmacological interventions is necessary to slow the cognitive decline associated with AD. Patients diagnosed with HTN should be advised to adhere to treatment to reduce the risk of AD in old age. Additionally, adherence to HTN management among AD patients should be encouraged to improve outcomes.

Diabetes Mellitus

The link between diabetes mellitus (DM) and the risk of AD is still a debate. However, several studies have sought to determine the link between the two medical conditions. Hersi et al[35] conducted a systematic review to determine the risk factors linked to the onset and progression of AD. The review included 65 studies published between 2010 and 2012. The evidence from these articles indicates that DM increases the risk of AD onset and progression. In another study conducted by Hayden,[36] type 2 diabetes mellitus (T2DM) increased the risk of late-onset AD. T2DM increases exposure of the brain's neurovascular unit through ultrastructural remodeling. This tips the balance of the brain and increases the risk of late-onset AD.[36] An emphasis on insulin adherence can help patients with DM manage symptoms effectively while reducing the risk of AD onset and progression.

Head Trauma

Several studies have linked head trauma to the increased risk of AD. Zhang et al[37] conducted a meta-analysis of cohort studies to determine the relationship between traumatic brain injury (TBI) and the risk of AD. The researchers analyzed 17 studies that focused on the relationship between head trauma and AD. The results from this study indicate that the risk of AD was enhanced among individuals with traumatic brain injury. Indeed, moderate and severe traumatic brain injury was linked to an increased risk of AD. Similarly, LoBue et al[38] support these findings by underlining the connection between brain injury and earlier age of onset of AD. The findings showed that individuals with TBI and Apoe4 carriers had the earliest mean age of AD. TBI was associated with increased cognitive decline regardless of Apoe4 and gender.[37] Lastly, Tolppanen et al[39] conducted a case-control study to determine the association between head injuries and AD. The study was conducted among 70,719 community dwellers diagnosed with clinical AD in Finland. The findings showed a strong association between head or brain injury in the AD disease process.[39] Head trauma can increase AD progression. Interventions to slow the progress of these conditions should focus on individuals with a history of head trauma.

Psychosocial Factors

Social Engagement

Social engagement (SE) is linked to significant health benefits such as reduced rates of mortality and reduced risk of depression. The link between social engagement and AD has been discussed in various studies. Zhou et al[40] determine how SE and its change are linked to dementia risk. The longitudinal study was conducted in a 9-year follow-up and involved 7511 older Chinese adults over 65 years. The results indicated that enhanced SE was linked with lower risk dementia. Moreover, participants with lower levels of SE were at a higher risk of dementia.

Notably, during the 9-year follow-up, 338 persons among the participants developed dementia.40 These findings are corroborated by Biddle et al,[41] who examines the relationship between SE and Amyloid-β-related cognitive decline. The study was also longitudinal and included 217 community-dwelling cognitively normal adults. The findings showed that the level of SE determined the risk of cognitive change among high-risk individuals. So lower SE was seen as a marker of neurocognitive vulnerability in older adults. Spending time with family, friends, and community groups increases social engagement and help older adults remain active.[41] Older adults should be encouraged to remain socially active to slow the cognitive decline associated with AD.

Apart from longitudinal studies, systematic reviews and meta-analyses have found positive links between SE and AD. In a systematic review of sixty-five studies, Hersi et al[35] established an association between SE and AD. Notably, evidence suggested that lower SE was associated with an increased risk of AD. The results from the review indicate that lower SE, poor social networks, and loneliness increase the risk of AD. For example, widowhood, being single, or living alone enhanced the risk of AD.[35] These findings on loneliness are supported by Sundstrom et al,[42] who examined whether loneliness increased the risk of dementia and AD. The study included 1,905 participants with a follow-up time of 20 years. During the study period, 428 developed dementia, 221 developed AD, 157 had vascular dementia, while 50 had other types of dementia. These results indicate that loneliness is a significant risk factor for AD. The authors note that any subjective reports of loneliness among the elderly should not be ignored.[43] Thus, the level of social engagement can enhance or reduce the rate of AD progression.

While these studies underline the link between loneliness and AD, a systematic review and meta-analysis by Penninkilampi et al[43] arrived at different findings. The study attempts to

determine the connection between SE, loneliness, and the risk of dementia. Poor SE was found to increase the risk of dementia, while good SE was protective. SE engagement indices such as poor social support the poor social network increased the risk of dementia. However, the relationship between loneliness and dementia was insignificant. The authors encourage implementing interventions that target social isolation and lack of SE to prevent dementia.[43] Healthcare professionals caring for older adults should encourage them to remain socially active as this is protective against AD.

Cognitive Reserve

Cognitive reserve (CR) refers to the brain's capacity to retain cognition despite underlying cerebral damage. Van Loenhoud et al[44] tries to determine the relationship between CR and clinical progress across the AD spectrum. The study included 839 participants who were Aβ positive. 175 participants had normal cognition, 437 had MCI, and 227 had AD dementia. These participants were followed for 24 months. The results indicate that among Aβ-positive participants, a higher CR decreased clinical progress of AD. However, higher amounts of Aβ inevitably increased the rate of cognitive decline among individuals with dementia.[44] In another study, Soldan et al[45] establish whether the level of CR and AD biomarkers modified the change in cognition. Notably, higher CR was linked to enhanced cognitive performance. Nevertheless, these higher rates did not modify the rate of cognition change. Moreover, higher CR was linked to quicker cognitive decline after symptom commencement of MCI.[45] The results show that CR mediates the connection between pathology and cognitive function. CR can delay symptom onset but will not reduce the rate of cognitive decline.

Depression and Anxiety

Depression and anxiety are established risk factors in AD. Eijansantos et al[46] examine the relationship between a history of psychiatric disease and AD. The study involved 1500 AD patients with depression, anxiety, PTSD, bipolar, and schizophrenia. The results indicated that patients with depression and anxiety had a slightly younger-onset than others. The authors conclude that the diagnosis of depression and anxiety possess additive impacts on AD pathology. Thus, Similarly, Santabarbara et al[47] performed a meta-analysis of cohort studies to determine the link between anxiety and all-cause dementia. The analysis included eight studies comprising 29,608 participants. The results indicate that anxiety was linked to an increased risk of all-cause dementia. The authors note that treatment of anxiety can reduce the incidence of dementia.48 Another study by Canton-Habas[48] focuses on depression as a risk factor for dementia and AD. The case-control study involved 125 controls. The findings showed that depression increased the risk of AD which underlines the need for effective interventions to address these conditions early.

Additionally, Almeida et al[49] investigated whether antidepressant use among patients with depression reduces the risk of dementia. The study involved 4922 cognitively healthy men and women and was conducted for 14-years. The results indicated that antidepressant use did not decrease the risk of dementia. The relationship between dementia and depression was only evident during the first five years of follow-up. Additionally, older men with a history of dementia had a higher susceptibility for dementia. The authors concluded that depression is a marker of dementia and not necessarily a modifiable factor.[47] Other treatment alternatives should be considered for individuals diagnosed with depression and anxiety.

Methods

A systematic search of the literature was conducted on various databases. These databases include Google Scholar, PubMed, and Medline. Search terms utilized include modifiable risk factors of Alzheimer's disease. Other terms are stress and AD, diet intake and AD, and psychosocial risk factors for AD. Additionally, search results were limited to the last five years. The articles retrieved include those published in English and those translated from other languages such as Spanish. Moreover, the articles retrieved included meta-analyses, systematic reviews, randomized control trials, reviews, and longitudinal studies. Studies published beyond the last five years and expert opinions were excluded from the literature review.

Discussion

The expected increase in the prevalence of AD in the U.S.1 underlines the need to example how modifiable factors affect its clinical progression. The main purpose of the literature review is to analyze how modifiable risk factors impact AD's progress. This review found that some modifiable risk factors can accelerate AD progression while others have the potential to slow the progression of AD. The review focused on stress, diet, alcohol, sleep hygiene, physical activity, and social engagement. Thus, this section discusses these factors and what healthcare professionals can do to slow AD progression.

Impact of Stress Management and the Progression of AD

The findings from the literature review show that stress plays a critical role in AD progression. Stress is positively linked to the onset of AD.[5,6,7,8] In their summary of pre-clinical literature, Hoeijmakers et al[5] established that stress plays a role in disturbing glucocorticoid levels and corticotrophin release. Indeed, the summary by these authors indicates that stress

intensifies cognitive decline as people who experienced stress in early life have a less cognitive reserve (CR). Other studies [44, 45] have found that CR mediates AD pathology and cognitive function. Yet another study by Caruso et al[6] found that stress results in cellular, molecular, and behavioral imbalances that reflect AD features. Notably, stress can lead to synaptic dysfunction and neuronal death that is linked to AD. The results from this study highlight the critical role that stress plays in AD progress. Individuals who experience early-life stress are likely to experience an earlier onset of AD.

Each of these studies shows that stress plays a significant role in AD progression. Any reports of stressors should not be ignored by healthcare providers but documented adequately to initiate interventions. These interventions can ensure that onset of AD is delayed, or its progress slowed. The interventions to address stress include physical exercise and mediation. These interventions should be encouraged for patients that report any symptoms of stress. The conclusion from the review of these studies is that stress management is an effective strategy to slow and delay AD progression. The lack of effective stress management leads to exacerbation of AD symptoms.

Impact of Dietary Intake of the Progression of AD

The review indicated that maintaining a healthy diet is linked to slowing AD progression. Various studies [9, 10, 11, 12] established that omega-3 fatty acids enhance cognitive functions. Omega-3 fatty acids can provide benefits such as improved working memory, executive function, and verbal memory. The omega-3 fatty acids can be provided to those at risk of AD or those diagnosed with the condition to slow cognitive decline. Combining these foods with carotenoids has also shown significant efficacy in patients with AD. For example, Nolan et al[10] found that Xanthophyll carotenoids combined with omega-3 fatty acids resulted in improved

cognitive outcomes for patients with mild and moderate AD.[10] However, the findings from this study are only experimental. Conducting more studies such as systematic reviews and meta-analyses can provide stronger evidence linking this dietary intake to improved cognitive outcomes. Generally, these foods effectively slow the cognitive decline in AD patients by improving memory functions.

While omega-3 fatty acids are considered effective, other studies [11, 12] present differing evidence. Canada et al[11] established that omega-3 fatty acids are only impactful during AD onset due to slight cognitive impairment. These findings are substantiated by Araya-Quintanilla et al,[12] who notes that evidence on omega-3 fatty acids supplementation is still inconsistent. However, due to some studies underlining the efficacy of omega-3 fatty acids, this diet should continue to be recommended for patients at risk of AD or those with clinically diagnosed AD. More studies supporting the effectiveness of omega-3 fatty acids are needed to enhance dietary care for AD patients.

Apart from omega-3 fatty acids, patients with AD are often advised to take carotenoid-rich foods or supplements. Carotenoid-rich foods include yams, kale, spinach, watermelon, bell peppers, and tomatoes. Some studies [13,14] have shown that carotenoid-rich foods can slow the progression of AD. Davonelli et al[13] found that carotenoid-rich foods improved cognitive outcomes among patients with AD. The majority of the participants in the study included in the meta-analysis13 reported improved memory functions due to taking a carotenoid-rich diet. Additionally, another study by Lakey-Beitia[14] confirms that the chemical structure of carotenoid compounds can prevent AD. However, this finding needs to be confirmed in more studies to provide clinical evidence that supports carotenoid effectiveness.

Another study by Beydoun et al[15] recommended combining carotenoids with vitamin E to improve memory performance. This study's findings indicate that participants who received this vitamin E and carotenoids had improved cognitive outcomes. However, the interaction between vitamins A and C and carotenoids still needs more inquiry. Yet another study by Tan and Norhaizan[16] found that taking carotenoid-rich foods as preventive against age-related diseases. The findings indicate that carotenoids are effective in decreasing oxidative stress and promoting healthy aging. The major implication from the results in these studies is that carotenoids should always be a consideration for patients diagnosed with AD or those at an enhanced risk of developing the condition.

Diet is also an effective intervention for the management of AD risk factors such as T2DM and HTN. Miranda et al[17] demonstrate that patients who take the Mediterranean diet experienced slow AD progress in one study. Other diets such as DASH and MIND are also recommended for patients with AD. Van de Brink[18] provides evidence that links these diets to improved cognitive performance. Additionally, Cherian et al. 19 established that the MIND diet slows cognitive decline after stroke. The dietary guidelines include increasing the consumption of whole greens, beans, lean meats, and poultry while reducing the consumption of fried foods, cheese, and sweets. While these dietary guidelines are beneficial, their effectiveness is significantly reliant on patient adherence. Notably, Berendsen et al[20] found that long-term adherence to the MIND diet among American women improved cognitive performance. Nevertheless, the findings show that while MIND improves cognitive performance, it was not linked to slower cognitive decline. Thus, these diets can be recommended to impact risk factors and slow AD progression.

Impact of Alcohol on the Progression of AD

Alcohol is a major risk factor for chronic diseases such as hypertension. The link between alcohol and AD progression has been examined in various studies, as shown in the literature review. Several studies [21, 22] have linked alcohol consumption to AD. Andrews et al[21] found that alcohol consumption results in the early onset of AD. This assertion is supported by Venkaraman et al,[22] which established that alcohol use, misuse, and dependence contribute to cognitive impairment. Similar conclusions are shared by Topiwala et al,[23] who conducted a 30-year follow-up and found that excessive alcohol consumption was linked to adverse cognitive outcomes. One of the most significant findings from this study is that even light drinking contributed to poor cognitive outcomes. However, findings in other studies [24,35] have shown that light-to-moderate consumption decreases the risk of AD onset. The findings from these studies [21,22,23,24,35] are conflicting on the impact of alcohol intake on AD progression. Nevertheless, due to the contributing aspect of alcohol to chronic diseases such as hypertension, it is essential to moderate consumption. More clinical studies are necessary to provide substantial evidence on the link between alcohol intake and AD.

Impact of Sleep Hygiene of the Progression of AD

Proper sleep hygiene ensures that the body maintains sufficient rest. Lack of sleep hygiene has been linked to AD. Burke et al[25] established that sleep disturbance was linked to the early onset of AD. These findings are corroborated by Sabia et al,[26] who notes that maintaining a sleep duration of at least seven hours had protective effects against AD. Additionally, for people at risk of developing AD, prolonged sleep has been underlined as a marker for cognitive decline.[27] Lastly, Brzecka[28] found a link between sleep disturbance and AD. The findings from each of these studies indicate that lack of adequate sleep hygiene is a significant risk factor that

can contribute to AD progression. Interventions for patients diagnosed with sleep disorders are necessary to prevent cognitive decline and delay AD onset.

Impact of Physical Exercise of the Progression of AD

Physical exercise is linked to significant health benefits. In AD, physical exercise has been shown to slow cognitive decline. Fonte et al[29] suggest that constant physical exercise can mitigate cognitive decline in AD patients. Another study by Cox et al[30] established that physical exercise for older adults diagnosed with AD reduced cardiovascular risk and decreased cognitive decline. Also, Cunningham et al[31] established that cardiovascular and dementia risk was significantly reduced through adequate physical exercise. Another study by Jie et al[32] established that physical exercise led to cognitive improvements in patients diagnosed with AD. The major implication of these findings is that physical exercise is recommendable for patients diagnosed with AD. These exercises can be individualized depending on the patient's diagnosis.

Impact of Social Engagement on the Progression of AD

Another modifiable protective risk factor is social engagement SE. Enhanced levels of social interactions have been found to reduce the risk of AD. Zhou et al[40] established that older adults with high SE had a lower risk of developing dementia. Moreover, Biddle et al[41] showed that cognitive change in some older adults was linked to the level of SE. Hersi35 found a direct link between lower levels of SE to increased risk of AD. Older adults who had a poor social network experience loneliness leading to a significant cognitive decline.43 Other contributing factors include loss of partners and being single. Maintaining active social networks can ensure that the progression of AD is slowed. Healthcare providers should encourage patients to maintain active interactions with friends and family to reduce AD progression.

Management of High-Risk Patients for AD

The literature review has shown that various strategies can manage patients at high risk of AD. The first effective stress management strategy is to implement stress management interventions for patients at risk of AD. Through effective management of stress, the progression of AD will be slower as the patient will maintain better cognitive function. Additionally, persons who experience early-life stress should be prioritized for these interventions as they are at high risk for AD.[15] The stress management techniques can be combined with other interventions to ensure effectiveness in AD prevention.

Apart from stress, interventions for patients at high risk should focus on dietary intake. Consuming omega-3 fatty acids, vitamin E, and a carotenoid-rich diet should be recommended for patients due to their protective effects against cognitive decline.[10,13,14,15] The diet can be developed by working collaboratively with dieticians to ensure that patient meals are individualized. Moreover, aspects such as cultural background should be considered to ensure that the foods recommended are culturally appropriate. Additionally, diets such as DASH, MIND, and Mediterranean are effective in preventing cognitive decline.[18] Patients at high risk for AD should be put on these diets to delay the onset of AD and slow its progression. Each of these diets can improve cognitive performance and lower the AD burden.

While this literature review found conflicting evidence about the role of alcohol in AD, at-risk patients should be advised to moderate consumption. Indeed, patients consuming the Mediterranean diet are advised to take wine moderately.[17] Excessive alcohol consumption should be avoided as it is detrimental to the brain and can contribute to other risk factors such as hypertension and diabetes. Additionally, patients at high risk should be advised to maintain effective sleep hygiene of at least seven hours to prevent cognitive decline.[25 27] Closely

monitoring patients at high risk of AD is also recommended as prolonged sleep patterns may be a feature of cognitive decline.[27]

Lastly, patients at high risk for AD can be managed through adequate physical exercise and social engagement. Physical exercise helps these patients address cardiovascular risk, which is linked to AD progression. For example, Jie et al. 32 indicate that physical exercise improves cognitive health for patients diagnosed with AD. Additionally, maintaining active social networks is necessary for patients at high risk of AD. Patients such as widows or those who live alone should be encouraged to maintain active social lives as this provides some prevention against the onset of AD. These patients can be connected to social groups within their communities to ensure social engagement. Thus, physical exercise and social engagement are important risk factors that can ensure AD onset is delayed and its progression slowed.

Conclusion

Alzheimer's disease remains a significant health burden in the U.S. Various factors impact AD progression. This paper has documented how different modifiable risk factors impact AD progression. While other factors can slow or prevent AD, others accelerate the clinical progression of AD. The research conducted so far indicates that modifiable risk factors such as stress management, dietary intake, sleep hygiene, and physical activity are linked to Alzheimer's disease. Other factors such as medical and psychosocial history play a role in AD onset and progress. However, the research conducted through this literature review indicates that some of these factors can be modified to impact AD progression. Factors such as stress can be managed through effective intervention. Additionally, dietary intakes that comprise omega-3 fatty acids and carotenoid-rich foods should be recommended. The MIND, DASH, and Mediterranean diets are also effective in patients with AD or those at risk of developing the condition due to their

impact on cognitive performance. Overall, the progression of AD can be slowed by modifying these risk factors.

Research also indicates that moderate alcohol consumption offers protection, while excessive consumption can lead to cognitive decline. Moreover, the research has established that maintaining sleep hygiene and engaging in physical exercise effectively prevent AD. Patient education about these factors is necessary to improve knowledge about AD and enhance preventive measures. Additionally, research has linked medical history factors such as hypertension, diabetes, and head trauma to AD. Patients diagnosed with these health conditions should be prioritized for interventions that slow cognitive decline. Lastly, other factors such as lack of social engagement, cognitive reserve, depression, and anxiety contribute to the onset and progress of AD. Healthcare professionals should consider these factors when caring for AD patients.

While research about the significance of modifiable risk factors is extensive, future studies can focus on several issues. More longitudinal studies can examine the role that alcohol intake plays in cognitive decline. Additionally, future studies can perform systematic reviews and meta-analyses of these studies to provide more evidence on risk factors such as dietary patterns across cultures and how they affect AD. Lastly, future studies should include patients with an early onset of AD as this will help identify common modifiable risk factors.

References

1. Alzheimer's Association. 2021 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2021;17(3). https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf
2. Wang LY, Pei J, Zhan YJ, Cai YW. Overview of meta-analyses of five non-pharmacological interventions for Alzheimer's disease. *Front Aging Neurosci*. 2020; 12:594432. Published 2020 Nov 25. doi:10.3389/fnagi.2020.594432
3. What happens to the brain in Alzheimer's disease? National Institute on Aging. https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease. Updated May 16, 2017. Accessed August 10, 2021.
4. How is alzheimer's disease diagnosed? National Institute on Aging. https://www.nia.nih.gov/health/how-alzheimers-disease-diagnosed. Updated May 22, 2017. Accessed August 10, 2021.
5. Hoeijmakers L, Lesuis SL, Krugers H, Lucassen PJ, Korosi A. A preclinical perspective on the enhanced vulnerability to Alzheimer's disease after early-life stress. *Neurobiol Stress*. 2018;8:172-185. Published 2018 Feb 23. doi:10.1016/j.ynstr.2018.02.003
6. Caruso A, Nicoletti F, Mango D, Saidi A, Orlando R, Scaccianoce S. Stress as risk factor for Alzheimer's disease. *Pharmacol Res*. 2018;132:130-134. doi:10.1016/j.phrs.2018.04.017
7. Ouanes S, Popp J. High cortisol and the risk of dementia and alzheimer's disease: a review of the literature. *Front Aging Neurosci*. 2019;11:43. Published 2019 Mar 1. doi:10.3389/fnagi.2019.00043

8. Justice NJ. The relationship between stress and Alzheimer's disease. *Neurobiol Stress*. 2018;8:127-133. Published 2018 Apr 21. doi:10.1016/j.ynstr.2018.04.002
9. Martí Del Moral A, Fortique F. Omega-3 fatty acids and cognitive decline: a systematic review. *Nutr Hosp*. 2019;36(4):939-949. doi:10.20960/nh.02496
10. Nolan JM, Mulcahy R, Power R, Moran R, Howard AN. Nutritional intervention to prevent alzheimer's disease: potential benefits of xanthophyll carotenoids and omega-3 fatty acids combined. *J Alzheimers Dis*. 2018;64(2):367-378. doi:10.3233/JAD-180160
11. Canhada S, Castro K, Perry IS, Luft VC. Omega-3 fatty acids' supplementation in Alzheimer's disease: A systematic review. *Nutr Neurosci*. 2018;21(8):529-538. doi:10.1080/1028415X.2017.1321813
12. Araya-Quintanilla F, Gutiérrez-Espinoza H, Sánchez-Montoya U, et al. Effectiveness of omega-3 fatty acid supplementation in patients with Alzheimer disease: a systematic review and meta-analysis. *Neurologia (Engl Ed)*. 2020;35(2):105-114. doi: 10.1016/j.nrl.2017.07.009
13. Davinelli S, Ali S, Solfrizzi V, Scapagnini G, Corbi G. Carotenoids and cognitive outcomes: a meta-analysis of randomized intervention trials. *Antioxidants (Basel)*. 2021;10(2):223. Published 2021 Feb 2. doi:10.3390/antiox10020223
14. Lakey-Beitia J, Kumar D J, Hegde ML, Rao KS. Carotenoids as novel therapeutic molecules against neurodegenerative disorders: chemistry and molecular docking analysis. *Int J Mol Sci*. 2019;20(22):5553. Published 2019 Nov 7. doi:10.3390/ijms20225553
15. Beydoun MA, Canas JA, Fanelli-Kuczmarski MT, et al. Association of antioxidant vitamins a, c, e and carotenoids with cognitive performance over time: a cohort study of

middle-aged adults. *Nutrients*. 2020;12(11):3558. Published 2020 Nov 20. doi:10.3390/nu12113558

16. Tan BL, Norhaizan ME. Carotenoids: How effective are they to prevent age-related diseases? *Molecules*. 2019;24(9):1801. Published 2019 May 9. doi:10.3390/molecules24091801
17. Miranda A, Gómez-Gaete C, Mennickent S. Dieta mediterránea y sus efectos benéficos en la prevención de la enfermedad de Alzheimer [Role of Mediterranean diet on the prevention of Alzheimer disease]. *Rev Med Chil*. 2017;145(4):501-507. doi:10.4067/S0034-98872017000400010
18. van den Brink AC, Brouwer-Brolsma EM, Berendsen AAM, van de Rest O. The Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets are associated with less cognitive decline and a lower risk of Alzheimer's disease-a review. *Adv Nutr*. 2019;10(6):1040-1065. doi:10.1093/advances/nmz054
19. Cherian L, Wang Y, Fakuda K, Leurgans S, Aggarwal N, Morris M. Mediterranean-Dash Intervention for Neurodegenerative Delay (MIND) diet slows cognitive decline after stroke. *J Prev Alzheimers Dis*. 2019;6(4):267-273. doi:10.14283/jpad.2019.28
20. Berendsen AM, Kang JH, Feskens EJM, de Groot CPGM, Grodstein F, van de Rest O. Association of long-term adherence to the MIND Diet with cognitive function and cognitive decline in American women. *J Nutr Health Aging*. 2018;22(2):222-229. doi:10.1007/s12603-017-0909-0

21. Andrews SJ, Goate A, Anstey KJ. Association between alcohol consumption and Alzheimer's disease: A Mendelian randomization study. *Alzheimers Dement*. 2020;16(2):345-353. doi: 10.1016/j.jalz.2019.09.086

22. Venkataraman A, Kalk N, Sewell G, Ritchie CW, Lingford-Hughes A. Alcohol and alzheimer's disease-does alcohol dependence contribute to beta-amyloid deposition, neuro inflammation and neurodegeneration in Alzheimer's disease? *Alcohol*. 2017;52(2):151-158. doi:10.1093/alcalc/agw092

23. Topiwala A, Allan CL, Valkanova V, et al. Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study. *BMJ*. 2017;357:j2353. Published 2017 Jun 6. doi:10.1136/bmj.j2353

24. Zhang R, Shen L, Miles T, et al. Association of low to moderate alcohol drinking with cognitive functions from middle to older age among US adults. *JAMA Netw Open*. 2020;3(6):e207922. Published 2020 Jun 1. doi:10.1001/jamanetworkopen.2020.7922

25. Burke SL, Hu T, Spadola CE, Burgess A, Li T, Cadet T. Treatment of sleep disturbance may reduce the risk of future probable Alzheimer's Disease. *J Aging Health*. 2019;31(2):322-342. doi:10.1177/0898264318795567

26. Sabia S, Fayosse A, Dumurgier J, et al. Association of sleep duration in middle and old age with incidence of dementia. *Nat Commun*. 2021;12(1):2289. Published 2021 Apr 20. doi:10.1038/s41467-021-22354-2

27. Westwood AJ, Beiser A, Jain N, et al. Prolonged sleep duration as a marker of early neurodegeneration predicting incident dementia. *Neurology*. 2017;88(12):1172-1179. doi:10.1212/WNL.0000000000003732

28. Brzecka A, Leszek J, Ashraf GM, et al. Sleep disorders associated with Alzheimer's disease: a perspective. *Front Neurosci*. 2018;12:330. doi:10.3389/fnins.2018.00330

29. Fonte C, Smania N, Pedrinolla A, et al. Comparison between physical and cognitive treatment in patients with MCI and Alzheimer's disease. *Aging*. 2019;11(10):3138-3155. doi:10.18632/aging.101970

30. Cox KL, Cyarto EV, Ellis KA, et al. A randomized controlled trial of adherence to a 24-month home-based physical activity program and the health benefits for older adults at risk of Alzheimer's disease: the AIBL active-study. *J Alzheimers Dis*. 2019;70(s1):S187-S205. doi:10.3233/JAD-180521

31. Cunningham C, O' Sullivan R, Caserotti P, Tully MA. Consequences of physical inactivity in older adults: a systematic review of reviews and meta-analyses. *Scand J Med Sci Sports*. 2020;30(5):816-827. doi:10.1111/sms.13616

32. Jia RX, Liang JH, Xu Y, Wang YQ. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: a meta-analysis. *BMC Geriatr*. 2019;19(1):181. Published 2019 Jul 2. doi:10.1186/s12877-019-1175-2

33. Lennon MJ, Makkar SR, Crawford JD, Sachdev PS. Midlife hypertension and alzheimer's disease: A systematic review and meta-analysis. *J Alzheimers Dis*. 2019;71(1):307-316. doi:10.3233/JAD-190474

34. Hughes D, Judge C, Murphy R, et al. Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. *JAMA*. 2020;323(19):1934-1944. doi:10.1001/jama.2020.4249

35. Hersi M, Irvine B, Gupta P, Gomes J, Birkett N, Krewski D. Risk factors associated with the onset and progression of Alzheimer's disease: a systematic review of the evidence. *Neurotoxicology*. 2017;61:143-187. doi:10.1016/j.neuro.2017.03.006

36. Hayden MR. Type 2 Diabetes Mellitus increases the risk of Late-Onset Alzheimer's Disease: ultrastructural remodeling of the neurovascular unit and diabetic gliopathy. *Brain Sci*. 2019;9(10):262. Published 2019 Sep 29. doi:10.3390/brainsci9100262

37. Zhang J, Zhang Y, Zou J, Cao F. A meta-analysis of cohort studies: traumatic brain injury and risk of Alzheimer's Disease. *PLoS One*. 2021;16(6):e0253206. Published 2021 Jun 22. doi:10.1371/journal.pone.0253206

38. LoBue C, Wadsworth H, Wilmoth K, et al. Traumatic brain injury history is associated with earlier age of onset of Alzheimer disease. *Clin Neuropsychol*. 2017;31(1):85-98. doi:10.1080/13854046.2016.1257069

39. Tolppanen AM, Taipale H, Hartikainen S. Head or brain injuries and Alzheimer's disease: a nested case-control register study. *Alzheimers Dement*. 2017;13(12):1371-1379. doi:10.1016/j.jalz.2017.04.010

40. Zhou Z, Wang P, Fang Y. Social engagement and its change are associated with dementia risk among Chinese older adults: a longitudinal study. *Sci Rep*. 2018;8(1):1551. Published 2018 Jan 24. doi:10.1038/s41598-017-17879-w

41. Biddle KD, d'Oleire Uquillas F, Jacobs HIL, et al. Social engagement and amyloid-β-related cognitive decline in cognitively normal older adults. *Am J Geriatr Psychiatry*. 2019;27(11):1247-1256. doi:10.1016/j.jagp.2019.05.005

42. Penninkilampi R, Casey AN, Singh MF, Brodaty H. The association between social engagement, loneliness, and risk of dementia: a systematic review and meta-analysis. *J Alzheimers Dis*. 2018;66(4):1619-1633. doi:10.3233/JAD-180439

43. Sundström A, Adolfsson AN, Nordin M, Adolfsson R. Loneliness Increases the risk of all-cause dementia and Alzheimer's disease. *J Gerontol B Psychol Sci Soc Sci*. 2020;75(5):919-926. doi:10.1093/geronb/gbz139

44. Van Loenhoud AC, van der Flier WM, Wink AM, et al. Cognitive reserve and clinical progression in Alzheimer disease: a paradoxical relationship. *Neurology*. 2019;93(4): e334-e346. doi:10.1212/WNL.0000000000007821

45. Soldan A, Pettigrew C, Cai Q, et al. Cognitive reserve and long-term change in cognition in aging and preclinical Alzheimer's disease. *Neurobiol Aging*. 2017; 60:164-172. doi:10.1016/j.neurobiolaging.2017.09.002

46. Eijansantos E, Allen I, Deleon J, et al. History of psychiatric disease inversely correlates with age of onset in alzheimer's disease. *Neurology*. 2021 96 (15 Supplement) 2474.

47. Santabárbara J, Lipnicki DM, Olaya B, et al. Does anxiety increase the risk of all-cause dementia? An updated meta-analysis of prospective cohort studies. *J Clin Med*. 2020;9(6):1791. Published 2020 Jun 9. doi:10.3390/jcm9061791

48. Cantón-Habas V, Rich-Ruiz M, Romero-Saldaña M, Carrera-González MDP. Depression as a risk factor for dementia and Alzheimer's disease. *Biomedicines*. 2020;8(11):457. Published 2020 Oct 28. doi:10.3390/biomedicines8110457

49. Almeida OP, Hankey GJ, Yeap BB, Golledge J, Flicker L. Depression as a modifiable factor to decrease the risk of dementia. *Transl Psychiatry*. 2017;7(5):e1117. Published 2017 May 2. doi:10.1038/tp.2017.90

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