Understanding the Environmental Factors that Can Contribute to Alzheimer's to Aid in the Design of Treatments
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Abstract

Alzheimer's Disease (AD) is a neurodegenerative disease that is estimated to affect over 6.7 million Americans age 65 and over as of 2023 ("About Alzheimer's Disease"). There is abundant evidence that AD is caused by the misfolding of proteins and the accumulation of these non-functional aggregates in the brain. Some genes have been indicated in AD, but these genes do not account for all cases, suggesting that environmental factors substantially affect the onset of the disease. Environmental factors related to Alzheimer's include education, other pre-existing diseases such as diabetes, and lifestyle. This review aims to summarize the findings of the correlation between AD with these three categories. A greater understanding of these factors could allow for better preventative approaches to treating the disease.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the misfolding and aggregation of two specific proteins, amyloid beta and tau, in the brain. The disease targets older individuals and causes them to lose neurons, leading to memory loss (Chin-Chan et al.). The disease is characterized by six Braak stages which track the severity of the disease. Stages one and two are asymptomatic, three and four show mild symptoms, including agitation and depression, and five and six demonstrate severe dementia or loss of cognitive function (Moreno-Jiménez et al., Ehrenberg et al., "What is Dementia?"). In some cases, AD is caused by genetic factors through mutations in the APP, PS1, and PS2 genes (Chin-Chan et al.). For AD cases that present without mutations in these genes, it is likely that environmental factors play a large role. These environmental factors can be split into three categories (Figure 1). The disease is affected by factors relating to education (such as learning languages), pre-existing diseases (such as diabetes and hearing loss), and lifestyle (such as sleep and eating habits) (Zhang et al.). The primary focus of this review is to explain the importance of the correlation between these environmental factors and the disease. AD affects about fifty million people around the globe. The treatment and care can be quite expensive, with a worldwide cost of over one trillion USD ("Alzheimer's Disease"). A deeper understanding of the causes of the disease and how to prevent it could greatly benefit a significant number of people by teaching them the precautionary measures they can take to avoid the disease. This knowledge could also benefit people who are already diagnosed with the disease, as taking care of their lifestyle can reduce the severity of AD symptoms.

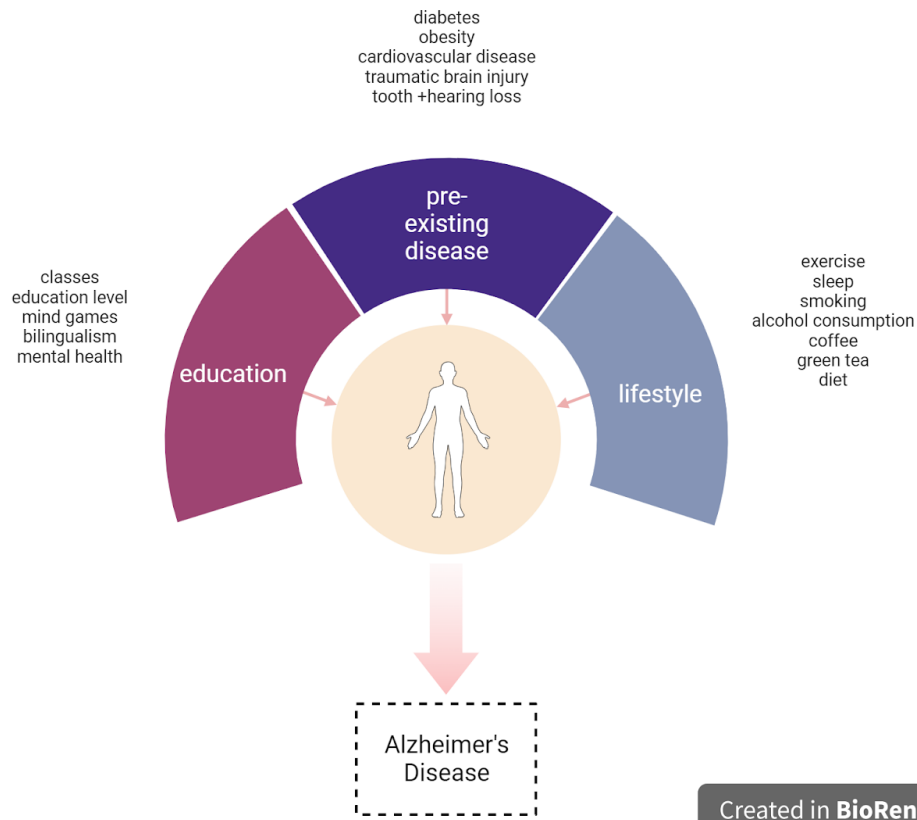**Figure 1: Environmental Factors correlating with Alzheimer's Disease**

Figure 1. This figure depicts the three primary categories of environmental factors correlating with AD and examples within them.

Education

One category of environmental factors correlated with AD is education. One study followed subjects 45 years and older across a long-term study to observe the impact of continued education. The study showed that attending university classes increases and maintains cognitive reserve, a measure of brain agility, proven by better language processing and testing assessment scores. This study found that there is a positive association between participating in cognitively stimulating activities and reduced incidence of dementia (Matyas et al.). Intelligence, measured through the level of educational attainment, has proven a correlational relationship with decreasing the risk of AD (Andrews et al.). Mind games, such as sudoku and crosswords, are key to sustaining memory and maintaining cognitive speed in old age (Suo et al.). Learning additional languages is one specific form of cognitive stimulation connected to decreased AD risk. Compared to monolinguals, bilinguals have heightened neural activity in brain regions that play a key role in higher-order processing (Grady et al.). Bilinguals were also shown to be more educated and had a superior professional position on average compared to monolinguals. A cognitive study on the Cantonese/Mandarin population concludes that monolinguals manifest AD before bilingual subjects (Zheng et al.). In contrast to the benefits of education, issues with mental health, specifically work and school-related depression, have been shown to have a negative correlational relationship with AD (Diniz et al.).

Pre-existing Diseases

Another category of environmental factors that has an association with dementia is pre-existing diseases. Diabetes, a disease characterized by high blood glucose levels due to low insulin levels or inefficient use of insulin, has been implicated in the development of AD ("What is Diabetes?"). Insulin has been proven to be connected to brain metabolism, and a defective insulin pathway, a key trait of diabetes, is associated with issues in memory ("Obesity"). Obesity, which is characterized by a body mass index of 30 or more due to extreme fat accumulation, is highly comorbid with diabetes and has been implicated in AD as well (Ebrahimpour et al.). Insulin resistance, a significant characteristic of diabetes and obesity, is shown to be correlated with tau hyperphosphorylation and amyloid beta aggregation (De Felice et al.). Diseases that impact cardiovascular function have also been implicated in the onset of AD. One such disease, Atrial fibrillation (AF), characterized by fast and irregular heartbeats, was found to be highly predictive of the future development of dementia when assessing and comparing AF and AF-free populations over the course of a long-term study ("What Is AFIB?", Kim et al.). A prospective treatment option, oral anticoagulants–used to prevent blood clots and strokes–has been proven to decrease the incidence of dementia, further supporting the potential correlational relationship between cardiovascular function and AD ("What Are Direct-Acting Oral Anticoagulants?"). Injury of brain cells beyond repair by traumatic brain injury (TBI) caused by a significant hit to the brain is also correlated with AD ("Traumatic Brain Injury"). TBI has been associated with dementia, although this risk decreases time-dependent from when the injury occurred. Multiple TBIs are shown to have a cumulative effect and have a higher association with dementia (Nordström & Nordström). Although direct connections have not been established, relationships also exist between hearing and tooth loss to AD risk. An inverse correlation between number of teeth and AD risk has been observed (Takeuchi et al.). However, it is possible that this correlation exists in part because both tooth loss and dementia risk increase with age. A correlation between hearing loss and Alzheimer's disease has also been observed. Possible treatment for hearing loss includes hearing aids and cochlear implants (Hung et al.).

Lifestyle

A long-term study of an elderly Japanese population had two groups, one that performed exercise once a week and a control group with no physical activity. The study concluded that the exercise group showed a lower incidence of dementia and suggested physical activity has an inverse correlation with AD (Kishimoto et al.). In another long-term study on obstructive sleep apnea (OSA), a type of breathing loss where muscles in the throat prevent oxygen intake due to airway blockage, and length of sleep, researchers concluded that extreme cases of OSA and sleep duration of less than seven hours correlated with dementia (Figure 2) ("Central Sleep Apnea", Lutsey et al.). In a study on smoking, researchers found that for every additional 20 cigarettes a day, there is a 34% growth in the risk of dementia. The study concluded current smokers, compared to never smokers and former smokers, have the highest risk of dementia (Zhong et al.). Frequent alcohol consumption, five or more times a day, also correlates with an increased risk of dementia (Langballe et al.). In terms of beverages, the incidence of AD is decreased with the consumption of 1-2 cups of coffee daily (Wu et al.). Green tea has also been shown to benefit cognition and overall brain function, suggesting a possible correlation with a decreased risk of AD (Mancini et al.). Three diets, DASH (dietary approaches to stop

hypertension), Mediterranean, and MIND (a hybrid of Mediterranean and DASH), were correlated with a lower risk for AD (Figure 3) (Morris et al.). A 15-year-long study in Sweden tested the association between air pollution and the risk of dementia. The results show that the group with the highest exposure to traffic-related pollution was most likely to be diagnosed with dementia, suggesting a correlation between pollution and AD (Oudin et al.).

Figure 2: Sleep Loss Positive Feedback Loop
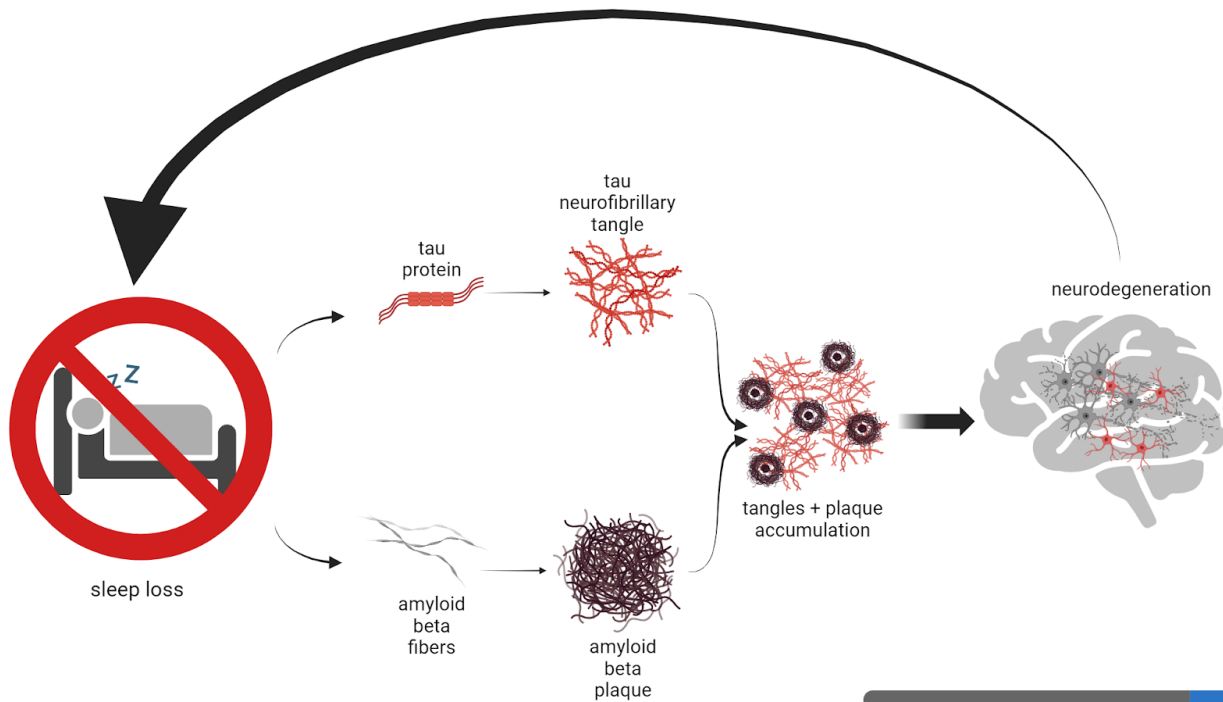
Figure 2. This figure depicts the accumulation of the amyloid and tau proteins due to a lack of sleep which leads to neurodegeneration which can then cause further sleep loss. Adapted from [Lutsey, P. L., Misialek, J. R., Mosley, T. H., Gottesman, R. F., Punjabi, N. M., Shahar, E., MacLehose, R. F., Ogilvie, R. P., Knopman, D. S., & Alonso, A. (2017b). Sleep characteristics and risk of dementia and Alzheimer's disease: The Atherosclerosis Risk in Communities Study. Alzheimers & Dementia, 14(2), 157–166. https://doi.org/10.1016/j.jalz.2017.06.2269].
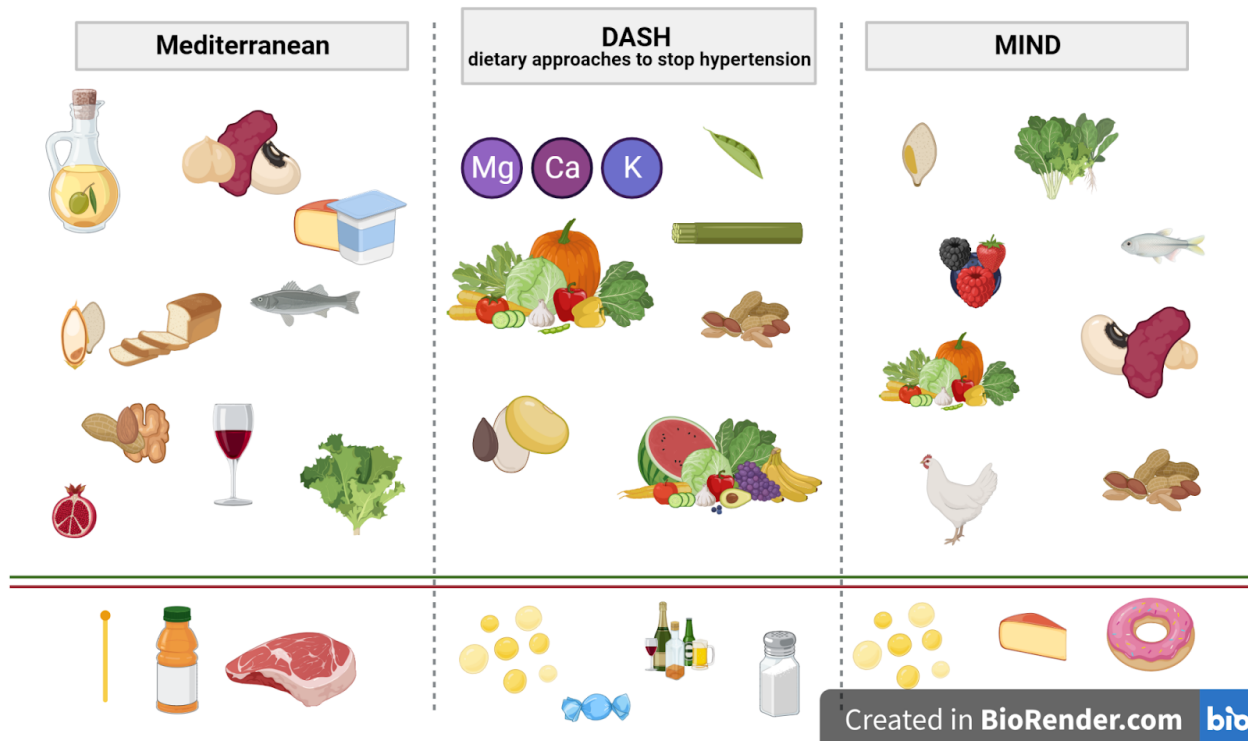
Figure 3: Diets

Figure 3. This figure depicts the three diets correlated with lowering the risk of AD: Mediterrenean, DASH, and MIND. The foods above the green line indicate items that should be eaten with the diet, while those below the red line indicate items that should be avoided. Adapted from [https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/dash-diet/art-20048456, https://my.clevelandclinic.org/health/articles/16037-mediterranean-diet, https://www.hsph.harvard.edu/nutritionsource/healthy-weight/diet-reviews/mind-diet/]

Summary/Conclusions

If AD is not treated, it can lead to severe cognitive decline with severe effects of sleep loss, depression, anxiety, and agitation. Some pharmaceutical treatments for AD have an anti-amyloid approach, which aims to minimize disease progression. But this treatment can have drastic side effects, including allergic reactions, swelling, bleeding, headaches, nausea, change in vision, and falling. Popular drugs of this type include Aducanumab and Lacanemab. Cholinesterase inhibitors, another type of drug, minimize cognitive symptoms related to AD, such as memory loss. Donepezil, Rivastigmine, and Galantamine are commonly prescribed ("Medications for Memory, Cognition and Dementia-Related Behaviors"). While these drugs can treat the disease, they can cost up to $60,000 annually (Sinha & Barocas). We could benefit from a more holistic approach encompassing environmental factors as they are much less expensive and have no side effects. Continuation of education has shown a strong correlation with maintaining cognitive vigor, and a healthy lifestyle nurtures the body, suggesting a decrease in the risk of AD. Regarding pre-existing diseases, many correlate not only to AD but also to each other, suggesting that poor self-care can have an additive effect. So by maintaining beneficial day-to-day habits, individuals can decrease their risk of AD and other diseases.

Extensive research has shown that approximately one-third of all AD cases can be credited to environmental factors alone (Killin et al.). This suggests that maintaining a healthy lifestyle can often prevent the disease. Studies also propose that preexisting AD can be less severe if environmental risk factors are addressed ("Alzheimer's Disease Fact Sheet"). This is extremely important as Alzheimer's care can be quite expensive, ranging from 20 - 40 thousand dollars a year or more, depending on the severity, suggesting that just by modifying one's lifestyle, costs can reduce (Leon et al.). Further research on treatment for the disease is still needed, but as the research summarized in this review suggests, taking adequate care of oneself daily likely results in a greatly reduced risk of AD diagnosis and severity.

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