Investigating the Environmental Causes of Alzheimer's Disease: a narrative review

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ABSTRACT:

The mystery of Alzheimer's disease (AD) has continued to puzzle scientists studying this neurodegenerative disorder. While over 6 million Americans have been diagnosed with the disease,[1] the underlying etiology of AD is still unknown. One hallmark pathology of AD is the accumulation of extracellular proteins, including amyloid beta, in the central nervous system. The precise mechanisms underlying the accumulation of these proteins have yet to be discovered, however studies have shown that certain environmental factors may play a key role in the development of the disorder. The following article reviews recent scientific literature demonstrating that various environmental agents may be linked to the onset of AD. The environmental agents reviewed here include aluminum exposure, alcohol, viral infection, and sleep. While there has been much focus on genetic factors that may contribute to the development of AD, the effects of environmental factors have long been ignored. Interestingly, the data reviewed in this article highlights the fact that many lifestyle factors have been linked to the onset and progression of AD.

INTRODUCTION:

AD is a neurodegenerative disease that typically appears in patients over 60 years old. Over 60-80% of all dementia cases are a result of AD.[2] It is a slow, painful process for both the patient and their families, with the gradual loss of memory often leading to cognitive decline and death. AD is a progressive disease with several stages.[3] Early stage AD often consists of mild symptoms including memory lapses and short-term memory loss. The middle stage of the disease can often be the longest, with symptoms such as increased confusion, forgetfulness of important and meaningful events, and a tendency to wander. Finally, late stage AD often involves severe dementia, where individuals have severe cognitive dysfunction, eventually losing the ability to complete daily activities required to live independently, such as eating and using the restroom.

Disease progression can be a burden on family members and healthcare workers, as patients with severe dementia often forget those closest to them. Additionally, the cost of healthcare for those diagnosed with AD is often a burden, with the average cost of care being $20,000-$30,000 per year.[4] AD has become the sixth leading cause of death in older individuals[5], and the mystery of its underlying cause has continued to baffle scientists and researchers.

The aggregation of the protein amyloid beta (Aβ) within the brain is diagnostic of AD. Aβ is a misfolded protein that is produced within the brain by the enzyme γ-secretase. Many studies

[1] ("2022 Alzheimer's Disease Facts and Figures," 2022)
[2] (*What Is Dementia?*, n.d.)
[3] (*Stages of Alzheimer's*, n.d.)
[4] (Rice et al., 2001)
[5] ("2022 Alzheimer's Disease Facts and Figures," 2022)

have shown that certain environmental and lifestyle factors lead to the accumulation of Aβ within the brain. Higher aluminum concentrations have been correlated with higher levels of Aβ. Additionally, alcohol consumption, certain viruses, and lack of sleep have all been associated with AD.

CAUSES:

1. **Aluminum Exposure**

The underlying cause of AD remains unknown, yet multiple studies have shown that environmental factors play an important role in the etiology of the disease. One such environmental factor is aluminum, which is both non-endogenous and neurotoxic to the human brain.[6] In 2016, a group from Keele University in London wanted to test the hypothesis that higher levels of aluminum might be responsible for the onset of AD. Aluminum levels were assessed from fixed brain samples of patients diagnosed with AD. Researchers found that higher levels of aluminum corresponded to both an earlier onset and a more aggressive form of AD.

The study used fluorescence microscopy to identify aluminum deposits within 12 brain samples of deceased patients that were diagnosed with AD from the MRC London Brain Bank.[7] In all the samples assessed by the researchers, aluminum was detected. In these samples, the aluminum content of the brain was significantly higher when compared to a previous study that quantified the levels of various metals in the brains of patients with no known history of AD. Additionally, aluminum levels within the diseased samples corresponded with higher levels of Aβ. The researchers hypothesized that Aβ binds to aluminum in the brain, leading to loss of cognitive function. Further, aluminum levels varied within the different lobes of the brain, with the highest mean concentration found in the frontal lobe. Since the frontal lobe is involved in controlling thinking, emotions, personality, and judgment,[8] the authors hypothesized that accumulation of aluminum may lead to loss of cognitive function.

2. **Alcohol Consumption**

Alcohol consumption has been linked to many diseases such as strokes, heart disease, and breast cancer.[9] Previous studies conducted on adults have also shown a positive correlation between alcohol consumption and dementia.[10] A 2023 study performed by Dr. Keun Hye Jeon and colleagues further investigates the relationship between alcohol and AD. The researchers

[6] (Exley et al., 2014)
[7] (Mirza et al., 2016)
[8] (*Frontal Lobe*, n.d.)
[9] (*Drinking Too Much Alcohol Can Harm Your Health. Learn the Facts | CDC*, 2023)
[10] (Liu et al., 2019)

investigated the association between habits in alcohol consumption and the risk of developing AD. They hypothesized that heavier alcohol consumption would lead to greater risk of AD.

A South Korean database of patients who self-reported their levels of alcohol consumption was used for the study.[11] The authors approximated a standard drink of alcohol (12 fl oz of beer, 5 fl oz of wine, or 1.5 fl oz of liquor)[12] to contain 8 grams of alcohol. The patients were classified into one of 4 groups of drinkers: none (0 g per day), mild (<15 g per day), moderate (15-29.9 g per day), or heavy (30 g per day). Patients with similar ages and medical history were used to ensure unbiased comparisons. Despite this, the study's location could potentially lead to bias, as the population of South Korea is generally homogenous and could possibly limit the generalizability of the study.

The researchers concluded that regular alcohol consumption is positively correlated with the onset of AD and dementia. In fact, the highest percentage of those found with AD came from the heaviest drinkers. In addition, patients who quit drinking alcohol were found to have a higher risk of developing AD than those who had never consumed alcohol. In summary, the authors concluded that greater alcohol consumption may play a role in the development of AD.

3. Exposure to the Viruses

Viruses are increasingly being linked to chronic conditions, in addition to the acute symptoms observed upon initial infection. Oncoviruses, for instance, are viruses that are linked to causing some forms of cancer. In addition, the Epstein-Barr virus, a member of the hepatitis virus family, has been linked to multiple sclerosis, which is another deadly neurodegenerative disease. These findings have caused growing interest in the long-term effects of viral infections.[13] Due to the COVID-19 pandemic, more research has been conducted on the subject of viral infection, especially in the setting of neurodegeneration. For example, Dr. Kristin S. Levine and her team conducted a study in 2022 investigating the effects of different viruses in the etiology of AD and neurodegeneration.[14]

Data was collected from biobanks in the United Kingdom and Finland, called the UK Biobank and FinnGen, respectively. The study contained over 300,000 individuals and studied the effects of 22 viruses. Individuals without a history of neurodegenerative disorders were chosen as a control group. All individuals in the study were individuals living in the UK.

The results of this study revealed a positive correlation between exposure to different viruses and development of AD. In data from both biobanks, patients with a history of viral infection were more likely to be diagnosed with AD. Interestingly, infection from the influenza virus was shown to have the strongest association with neurodegeneration. The study concluded that many of the viruses studied were able to penetrate the blood-brain barrier,

[11] (Jeon et al., 2023)
[12] (*What Is A Standard Drink? | National Institute on Alcohol Abuse and Alcoholism (NIAAA)*, n.d.)
[13] (*Longitudinal Analysis Reveals High Prevalence of Epstein-Barr Virus Associated with Multiple Sclerosis | Science*, n.d.)
[14] (Levine et al., 2023)

resulting in susceptibility of viral infection in the brain. In other words, these viruses were deemed to be neurotrophic. The researchers hypothesize this allows the neurotrophic viruses to lower the cognitive reserve, which the authors define as resistance to neurodegeneration, leading to further cognitive decline. The study also concludes that an AD diagnosis can still occur 5-15 years after infection, demonstrating the risk of neurodegeneration is not abrogated after the infection is cleared.

Additional studies could be conducted to determine possible links between specific viruses and AD. This could allow for the creation of new treatments and preventative measures for AD. The researchers further hypothesize that vaccines can be used as a preventative measure for AD, by preventing viral infections. As the study states that vaccination rates for influenza is less than 50% in the United States[15], increasing the rate of vaccination against the influenza virus could lead to fewer cases of AD. More research conducted in this subject, though, will lead to more accurate and responsive treatments for neurodegenerative disorders.

4. Sleep

Sleep is very important to the human body; it gives the body a chance to complete restorative processes not possible during waking hours. Previous studies have shown a correlation between worse sleep quality and AD onset. A study conducted by Dr. P.N. Prinz and colleagues concluded that sleep habits and mental function worsen with the later stages of dementia.[16] Another study conducted by Dr. Prinz and colleagues further tested this theory, concluding that, from the small sample of patients with varying sleep habits, less REM sleep is correlated with a higher risk of AD onset. In 2013, a team led by Dr. Adam Spira decided to investigate whether or not sleep habits affect the deposition of Aβ in the brain, causing or contributing to the onset of AD.[17]

The study consisted of participants in a neuroimaging study in Baltimore. Patients with any previous neurological disorders, metastatic cancer, or cardiac conditions were excluded from the study. Most patients who were surveyed were elderly. Furthermore, the study mostly consisted of white Americans, with only a few minority patients being included, limiting the generalizability of the study to the world's population. They selected people with a variety of sleep schedules to increase the diversity of sleep habits studied.

The study took 5 years to complete with patients first being asked about their sleep habits and then undergoing a Magnetic Resonance Imaging (MRI) session at the end of the study. Sleep habits were self-reported; patients were asked a set of questions relating to their sleep habits throughout the course of the study. The main method of neural data collection was through MRIs and image processing to identify plaques of Aβ within the brain. Images from all lobes of the brain were analyzed and categorized by region.

[15] (Levine et al., 2023)
[16] (Prinz et al.)
[17] (Spira et al., 2013)

Most patients reported getting 6-7 hours of sleep, although a subset received more than 7 hours of sleep. Four participants were diagnosed with dementia during the study and were removed from the patient cohort. The researchers concluded that fewer hours of sleep or worse sleep quality is associated with greater deposition of Aβ. This could potentially mean that sleep quality is associated with AD, as Aβ deposition is diagnostic of AD. Disturbed sleep, however, was not associated with greater Aβ burden, implying that only a sleep deficit could lead to greater Aβ deposition. The investigation of such factors will be an important subject for future research into the etiology of AD. Further investigations into the causes of Aβ accumulation could be helpful in demystifying the true correlation between AD and sleep.

CONCLUSION:

The reported findings above show that environmental factors play a significant role in the etiology of AD. Adjustments to ordinary lifestyle habits, therefore, could be utilized to reduce the risk of AD onset. While there are a variety of environmental causes that have been linked to AD, including some of the factors discussed in this paper, changes to healthier lifestyles may reduce the overall number of reported AD cases. Less frequent drinking and decreased exposure to aluminum or other neurotoxic materials should be incorporated into healthy lifestyle guides. It may also help to have additional government encouragement or other incentives for increasing vaccination to prevent viral infection. Schools could also change their hours to better incorporate high school students' sleep schedules by starting school at a later time to ensure that students have the necessary hours of sleep to maintain good health.

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