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

William Ma

ABSTRACT:

The mystery of Alzheimer's disease (AD) has continued to puzzle scientists studying the neurodegenerative disorder. While over 6 million Americans have currently been diagnosed with the disease, the underlying etiology of this condition has yet to be elucidated. One hallmark pathology of AD is the accumulation of extracellular proteins, one of which being amyloid beta, in the central nervous system. The precise mechanisms underlying the accumulation of these proteins have yet to be discovered, however studies show 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, laxative usage, and a history of viral disease. While there has been much focus on studying genetic factors that may contribute to the development of AD, the effects of environmental factors are often not considered. These environmental factors have been shown to play a key role in the onset of AD. Interestingly, the data reviewed in this article highlights the fact that many lifestyle factors have been linked to the progression of AD**.**

INTRODUCTION:

AD is a neurodegenerative disease that typically appears in patients over 60 years old. The disease is one of the most common causes of dementia with over 60-80% of dementia being a result of the disease.[1] 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.[2] 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 of increasing confusion, forgetfulness of important and meaningful events, and a tendency to wander. Finally, late stage AD often involves a severe case of dementia, with individuals losing the ability to complete activities of daily living (eating, using the restroom, etc.), have severely impaired cognitive function, eventually leading to death.

The disease progression could also be a burden on family members and healthcare workers, as patients with severe dementia can often forget those closest to them. Additionally, the cost of healthcare for those diagnosed with AD is often a burden on some, with the average cost of $20-30,000 per year.[3] The disease has become one of the leading causes of death in older individuals, and the mystery of its cause has continued to baffle scientists and researchers.

Most modern research conducted on AD points to the accumulation of the protein compound amyloid beta (Aβ) within the brain. The peptide is formed by a misfolding of a normally produced protein within the brain by the enzyme γ-secretase. The aggregation of the compounds have

[1] (*What Is Dementia?*, n.d.)

[2] (*Stages of Alzheimer's*, n.d.)

[3] (Rice et al., 2001)

been found in many patients diagnosed with AD, leading to the conclusion of correlation. While the amyloid beta hypothesis, as it is widely known as, has been the foremost theory to the causes of AD, there has been mention of other theories, such as the tau hypothesis, as having some credibility.

Many studies have shown that certain environmental and lifestyle factors lead to the accumulation of amyloid beta within the brain. Higher aluminum concentrations have been correlated with higher levels of Aβ. A study based on the Mediterranean based malmo diet has not been linked to rising Aβ levels[4], while another based on laxative usage has been linked to increasing levels of dementia.

CAUSES:

1. **Aluminum Exposure**

The true cause of Alzheimer's is still unknown, yet multiple studies conducted have shown that environmental factors play an important role in the etiology of the disease. One such factor explored was aluminum, which was found to be both non-essential to the brain and neurotoxic.[5] 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 sporadic AD. The research was done on brain samples of patients diagnosed with AD and analysis was performed on the varying aluminum levels within their brains. Both samples with familial AD and non-familial AD were used to ensure accurate data. The researchers found that higher levels of aluminum correspond to earlier onset and more aggressive etiology of AD.

The study used ethically approved samples of occipital, temporal, frontal, and parietal lobes of patients diagnosed with the disease, obtained with permission from the MRC London Neurodegenerative Diseases Brain Bank at Kings College in London.[6] Fluorescence microscopy was then used to identify the aluminum deposits from within prepared brain tissue from AD patients.

In all the samples viewed by the researchers, aluminum was present, leading to the conclusion that aluminum exposure is a potential cause of AD. Aluminum levels varied within the different lobes of the brain, with the highest mean concentration being found in the frontal lobe. Furthermore, aluminum levels within the samples corresponded with higher levels of amyloid beta. The researchers hypothesize that Aβ binds to aluminum in the brain, leading to further loss of cognitive function, especially in the frontal lobe where higher levels of aluminum have been observed. Since the frontal lobe is the main site that controls thinking, emotions, personality,and judgment,[7] the accumulation of aluminum likely led to loss of cognitive function as the metal would have impaired the frontal lobe's normal activity.

The final takeaway from this paper is that the correlation between aluminum levels in the brain and AD is positive; aluminum was found to be neurotoxic and likely contributed to both the onset and progression of AD in the individuals tested.

---

[4] *(Glans et al., 2023)*

[5] *(Exley et al., 2023)*

[6] *(Mirza et al.)*

[7] *(Frontal Lobe, n.d.)*

2. Alcohol Consumption

Alcohol is increasingly being linked to causing strokes, heart disease, and even breast cancer.[8] What has not been previously considered, however, is how frequent consumption of alcohol contributes to the etiology of AD and dementia. Previous studies conducted, such as one conducted by Dr. Yangyang Liu et al., in 2019 on Japanese adults have been shown to have a positive correlation between alcohol consumption and dementia.[9] A 2023 study performed by Dr. Keun Hye Jeon et al. further investigates this relationship with AD, with the study being based on South Korean adults.

The researchers investigated the question of what the association between changes in alcohol consumption was on developing AD or dementia. They hypothesized that heavier alcohol consumption would lead to greater risk of AD. Due to little previous research on the subject, the researchers decided to dig further into the topic.

Data from a South Korean database of patients with varying levels of alcohol consumption was used,[10] with the study being done entirely within South Korea alone. Patients with similar ages and medical history were used to ensure more accurate data. Despite this, the study's location could potentially lead to bias, as the population of South Korea is generally homogenous and could possibly not reflect the rest of the world. Additionally, since the patient data came from a questionnaire, there is a slight chance of error due to misreporting.

The researchers concluded that regular alcohol consumption is 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, quitters, patients who were previously alcohol drinkers, were found to have a higher risk of developing AD than those who never consumed alcohol. This leads to the conclusion that greater consumption of alcohol is an environmental factor in the etiology of AD.

3. Exposure to the Viruses

Viruses are increasingly being linked to causing lasting chronic conditions, in addition to their normal viral infections. Oncoviruses, for instance, are viruses that are linked to causing some forms of cancer. Studies on the Epstein-Barr virus, a member of the hepatitis virus family that has been linked to causing multiple sclerosis, another deadly neurodegenerative disease, have caused growing interest in the long-term effects of viral infections. A study by Kjetil Bjornevik et al. determined that the virus is responsible for increasing the risk of developing the condition.[11] Due to the COVID-19 pandemic that started in 2019, more research has been conducted on this subject of viral infection, especially in causing neurodegeneration; Dr. Kristin S. Levine and her team conducted a study in 2022 investigating the effects of different viruses in the etiology of AD and causing neurodegeneration.[12] Data was collected from the UK Biobank and the FinnGen project. The study contained over 300,000 individuals and studied the effects of 22 replicated viruses. Individuals without a history of

[8] (*Drinking Too Much Alcohol Can Harm Your Health. Learn the Facts | CDC*, 2023)

[9] Liu et al.

[10] (Jeon et al., 2023)

[11] (*Longitudinal Analysis Reveals High Prevalence of Epstein-Barr Virus Associated with Multiple Sclerosis | Science*, n.d.)

[12] (Levine et al., 2023)

neurodegenerative disorders were chosen as a control group. All individuals in the study were individuals living in the UK. This could potentially lead to less accurate results, as the UK has a generally homogenous population. Despite this, the study also made sure to separate individuals not of European ancestry into a different group of study.

The results of this study showed a positive correlation between exposure to different viruses and AD. In data from both biobanks, patients exposed to viruses such as the influenza virus were more likely to be diagnosed with AD. Additionally, infections from influenza and pneumonia were shown to have the most significant association with neurodegeneration. The study concluded that many of the viruses studied were able to surpass the blood-brain barrier, leading the brain to be susceptible to viral infection. As a result, these viruses were deemed to be neurotrophic. The researchers hypothesize this allows the neurotropic viruses to lower the cognitive reserve, allowing for increased neurodegeneration. The risk of neurodegeneration does not go away after the infection leaves, however, as the study also concludes that an AD diagnosis can still occur 5-15 years after infection.

Further studies could be conducted in determining 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, as it stops some infections from occurring. As the study states that vaccination rates for influenza is less than 50% in the United States[13], increasing the rate of vaccination could lead to less cases of AD. The more research conducted in this subject, though, will surely lead to more accurate and responsive treatments.

4. Sleep

Sleep is very important to the human body; it gives the body a chance to recover and go through processes not possible during the day. Previous studies have shown a correlation between worse sleep quality and AD onset. A study conducted by Dr. P.N. Prinz et al. concluded that sleep habits and mental function worsen with the later stages of dementia.[14] Another study conducted by Dr. Prinz et al. 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 lead 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.[15]

The study consisted of participants in a neuroimaging study in Baltimore. Patients chosen had to be free of any previous neurological disorders, metastatic cancer, or cardiac conditions. A sample size of 70 people was chosen, which is relatively small for a major study. This could lead to potential sources of error or skewed data, as a larger sample size would produce more accurate results. Most patients surveyed were elderly with an almost even split between sexes. Furthermore, the study mostly consisted of white or Caucasian Americans, with only a few African-Americans being involved.

[13] *(Levine et al., 2023)*

[14] *(Prinz et al.)*

[15] *(Spira et al., 2013)*

This could potentially produce a homogenous sample. People with varying sleep schedules were chosen to increase variability.

The study took 5 years to complete with patients first being asked about their sleep habits and then receiving an MRI after the 5 year period ended. Sleep habits were self-reported; patients were asked a set of questions relating to their sleep habits throughout the course of the study. Patients were asked about the average amount of sleep they received. The main method of 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.

Most of the patients reported getting 6-7 hours of sleep, with the next closest group being patients who received more than 7 hours of sleep. Four participants were actually diagnosed with dementia during the study and were removed from the data. The researchers concluded that fewer hours of sleep or worse sleep quality is directly associated with greater deposition of Aβ. This could potentially mean that sleep quality is associated with causing AD, as Aβ deposition is often thought of as a direct cause of AD. Disturbed sleep, however, was not associated with greater Aβ burden, implying that only the time spent sleeping could lead to greater Aβ deposition. The investigation of such factors will be a good subject for further research into the etiology of AD; further investigations into the causes of Aβ accumulation could be necessary to show the true correlation between AD and sleep.

CONCLUSION:

Summary

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 should reduce the overall number of reported AD cases. Less frequent drinking and exposure to aluminum or other neurotoxic materials should be incorporated into healthy lifestyle guides, as well as government encouragement or other incentives for increasing vaccination. Schools could also change their hours to better incorporate high school students' sleep schedules, starting school at a later time to ensure students have the necessary hours of sleep.

***BIBLIOGRAPHY*:**

Drinking too much alcohol can harm your health. Learn the facts | CDC. (2023, March 23).

https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm

Frontal Lobe: What It Is, Function, Location & Damage. (n.d.). Cleveland Clinic. Retrieved

August 8, 2023, from https://my.clevelandclinic.org/health/body/24501-frontal-lobe

Glans, I., Sonestedt, E., Nägga, K., Gustavsson, A.-M., González-Padilla, E., Borne, Y., Stomrud, E., Melander, O., Nilsson, P. M., Palmqvist, S., & Hansson, O. (2023). Association Between Dietary Habits in Midlife With Dementia Incidence Over a 20-Year Period. *Neurology*, *100*(1), e28–e37. https://doi.org/10.1212/WNL.0000000000201336

Jeon, K. H., Han, K., Jeong, S.-M., Park, J., Yoo, J. E., Yoo, J., Lee, J., Kim, S., & Shin, D. W. (2023). Changes in Alcohol Consumption and Risk of Dementia in a Nationwide Cohort in South Korea. *JAMA Network Open*, *6*(2), e2254771. https://doi.org/10.1001/jamanetworkopen.2022.54771

Levine, K. S., Leonard, H. L., Blauwendraat, C., Iwaki, H., Johnson, N., Bandres-Ciga, S., Ferrucci, L., Faghri, F., Singleton, A. B., & Nalls, M. A. (2023). Virus exposure and neurodegenerative disease risk across national biobanks. *Neuron*, *111*(7), 1086-1093.e2. https://doi.org/10.1016/j.neuron.2022.12.029

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis | *Science*. (n.d.). Retrieved August 8, 2023, from https://www.science.org/doi/10.1126/science.abj8222

Rice, D. P., Fillit, H. M., Max, W., Knopman, D. S., Lloyd, J. R., & Duttagupta, S. (2001). Prevalence, costs, and treatment of Alzheimer's disease and related dementia: A managed care perspective. *The American Journal of Managed Care*, *7*(8), 809–818.

Spira, A. P., Gamaldo, A. A., An, Y., Wu, M. N., Simonsick, E. M., Bilgel, M., Zhou, Y., Wong, D. F., Ferrucci, L., & Resnick, S. M. (2013). Self-reported Sleep and β-Amyloid Deposition in

Community-Dwelling Older Adults. *JAMA Neurology*, *70*(12), 1537–1543. https://doi.org/10.1001/jamaneurol.2013.4258

Stages of Alzheimer's. (n.d.). Alzheimer's Disease and Dementia. Retrieved August 8, 2023, from https://alz.org/alzheimers-dementia/stages

What Is Dementia? (n.d.). Alzheimer's Disease and Dementia. Retrieved August 8, 2023, from https://alz.org/alzheimers-dementia/what-is-dementia