

Mitigating the Risks for Alzheimer's Disease

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ABSTRACT

Alzheimer's Disease (AD) is a neurodegenerative brain disorder that results in steady cognitive decline, primarily in older adults. Its impact is felt by millions of patients world-wide and their caregivers, families, and extended communities. Unfortunately, Alzheimer's is a growing concern due to population aging. Since there is currently no cure for AD, it is crucial that we understand the risk factors associated with the disease and take preventive measures to delay its onset. Surprisingly, there is a lack of adequate literature that provides a comprehensive summary of controllable risks and mitigation approaches for AD. This paper seeks to bridge this gap by examining modifiable risk factors and associated strategies for reducing the risk of developing AD. By promoting awareness and providing evidence-based insights, this paper aims to join the fight against this growing global health challenge.

Introduction

Alzheimer's Disease (AD) is a neurodegenerative brain disorder that is characterized by the progressive loss of cognitive function, including memory, thinking, and language skills (CDC, 2020). Typically seen in individuals 60 years and older, AD is one of the most common forms of dementia in the world. According to the World Health Organization, about 30-35 million people worldwide currently suffer from Alzheimer's (WHO, 2023).

Significantly, the impact of Alzheimer's extends far beyond those directly affected by the disease. AD also affects the emotional, social, and financial well-being of caregivers, families, and extended communities. In addition to the profound impact on individuals' quality of life, it is crucial to also recognize the staggering financial costs associated with Alzheimer's disease. The direct financial costs of Alzheimer's and other dementias in the US in 2023 due to medical care and support services are estimated at \$345 billion (Alzheimer's Association, 2023). This does not include the indirect expenses stemming from caregiving responsibilities, lost productivity, and the strain on families and communities. The magnitude of the economic impact of Alzheimer's underscores the urgent need for research into prevention and effective interventions to address this debilitating disease.

There are numerous medications available that may affect the progression of Alzheimer's disease in the brain, but currently, there are no known cures that can reverse the symptoms or underlying pathophysiology of the disease (Patnaik, 2015). Most individuals diagnosed with Alzheimer's are faced with the certainty of progressive neurodegeneration and rapid loss of quality of life, and potentially death. Therefore, it is crucial to research prevention, treatment, as well as opportunities for delaying the onset of Alzheimer's.

As with most diseases, there are two types of risk factors associated with Alzheimer's: those that are beyond our control, and those that can be modified through various interventions and lifestyle choices. Understanding and addressing the modifiable risk factors is crucial in preventing or delaying the onset of Alzheimer's disease. However, there isn't sufficient literature on the environmental and lifestyle factors that can mitigate the risks of Alzheimer's. This paper offers a meta-analysis, synthesizing available literature on the risk factors for AD, particularly focusing on those that can be modulated.

Additionally, neuroimaging evidence suggests that AD pathology begins 20 years or more before the appearance of clinical symptoms (Barthelemy, 2020; Coupé, 2019; Albert, 2015). In other words, evidence of AD onset might exist in patients as young as 40. As such, improved diagnosis of AD risk in younger patients can further incentivize research into these controllable factors.

Pathology and Treatment

The pathology of Alzheimer's has been extensively researched over the last few decades. AD is caused by the accumulation of amyloid plaques and neurofibrillary tau tangles. Amyloid plaques deteriorate the communication between neurons and lead to their gradual decay and death. Tau tangles disrupt the normal functioning of neurons from within. In the final stages of AD, brain atrophy can be severe, especially in areas related to memory and cognition.

Available medications only slow down the progression of AD. Cholinesterase inhibitors, for example, are prescribed for those with mild to moderate clinical symptoms. These medications prevent the breakdown of acetylcholine, a brain chemical that is important for memory and thinking. However, these medicines lose their effectiveness over time since the brain produces less acetylcholine as AD progresses. Another set of drugs targets the beta-amyloid protein build-up to help reduce the amyloid plaques in the brains of patients with mild to moderate symptoms. Drugs are also available for patients with moderate to severe AD but they are not guaranteed to work for all patients and often carry serious side-effects. Leqembi, a recent addition to the list of available medications, slows down AD progression by boosting patient's antibodies (Canady, 2023). Given the lack of definitive treatment options and the debilitating nature of this disease, it is important to understand how we can keep our brain young and healthy for as long as we can.

Age and Genetics

Before we look at modifiable risks, it is useful to quickly preview the known fixed risks for AD.

Age is one of the most well-known factors in the category of uncontrollable risks. The probability of protein misfolding and abnormal protein generation go up with age. While AD commonly affects individuals over the age of 60, its risk increases significantly with increasing age, doubling every five years after the age of 65 (Mount, 2006). Due to increasing life expectancy, aging-related neurodegeneration is a growing global health threat (CDC, 2020).

Aside from age, certain risk factors for AD are also genetically inherited. One common hereditary risk for AD is a variant of the APOE gene. The presence of the APOE $\epsilon 4$ allele is one of the most well-known mutations of the APOE gene that increases risk for late-onset AD, but other genetic variants exist (Yamazaki 2019). 67% of people with AD had at least one copy of the APOE $\epsilon 4$ allele, while it is present in only 12% of the overall population (Ward, 2012; Poirer, 1993).

Additionally, family history of AD has also been shown to increase risk for AD. However, a family history of AD is not required for the onset of AD. Incidentally, studies have shown that the risk for AD is higher if a parent or a sibling has Alzheimer's. In fact, the risk also increases if more than one immediate blood relative has AD (Lautenschlager, 1996).

Environmental Risks

The good news is that research shows it is possible to lower one's risk of developing AD. This can also be inferred from the fact that the correlation to genetic factors is strong but nowhere close to 100%. Environment, lifestyle, and mental outlook that result from childhood, personality, education, exercise, and stress tolerance have been shown to also significantly modulate one's risk of developing AD (Lesuis, 2018; Segerstrom, 2020; Gupta 2021). A curated summary of these modifiable risk factors and information on how to mitigate these risks can be useful for the wider population, especially for those not very familiar with AD literature.

These non-genetic risk factors typically either promote brain health or suppress conditions that can harm or injure parts of our brain.

Cognitive Reserve

Cognitive reserve can be defined as a kind of brain resilience. Intellectual rigor, higher education, stimulating experiences, prosocial behavior, and other beneficial lifestyle and personality factors are believed to help grow it. Individuals with a higher cognitive reserve are thought to have a greater capacity to cope better with age related neurodegeneration and cognitive decline.

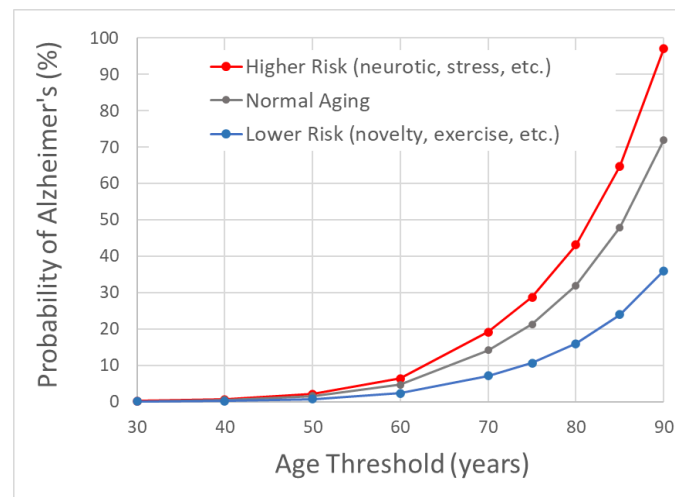


Figure 1. Qualitative illustration of modulation of Alzheimer's risk with age and cognitive reserve

Fig. 1 is only a qualitative illustration of how AD risk can be modulated by lifestyle factors such as exercise, stress, openness, exposure to novelty, education, etc. Alzheimer's is known to affect 10% of the population aged 65 and older and about 50% of the population aged 85 and older (Mount, 2006). While it is difficult to quantitatively determine the impact of lifestyle factors on Alzheimer's risk, there is sufficient evidence to show that the impact can be significant. For example, there is twice the risk to those who are prone to psychological distress than those who are not (Wilson, 2003).

Personality, Education, and Experiences

Some of the personality traits from the Big 5 (McCrae, 1999), for example, have been shown to be correlated to AD risk. The five-factor model of personality (FFM) describes five personality traits: openness, extraversion, agreeableness, neuroticism, and conscientiousness. Changes in age are also generally accompanied by fluctuations in these traits.

Greater openness to new experiences has been shown to lower the risk of developing AD (Duberstein, 2011). People who display more prosocial or extraverted behavior have also been shown to have a lower risk of developing AD (Segerstrom, 2020; Malinchoc, 1997). Also, people with greater agreeableness also have a lower risk of developing AD (Segerstrom 2020; Terracciano, 2014). Similarly, the risk of developing AD is also lower for individuals who are less neurotic and more conscientious (Terracciano, 2014; Wilson, 2007). An interesting study looked at older adults (ages around 85) that had the brain pathology (i.e. amyloid plaques and tau tangles) that could cause AD. A set of individuals within this group were identified as less neurotic and more conscientious and the remaining were assessed as more neurotic and less conscientious. The group with more conscientious and less neurotic behavior were found to be cognitively healthy and disease free compared to those who were more neurotic or less conscientious despite the presence of similar brain pathology in both sets (Terracciano, 2013).

It therefore helps to pay close attention to diversity of experiences and our disposition to lower the risk of Alzheimer's. For example, educational attainment and frequent exposure to novel experiences have been correlated to greater openness (Tang, 2017). Additionally, loving-kindness meditation has been shown to increase extraversion (Hutcherson, 2008). In loving-kindness meditation, practitioners typically reflect deeply on

generating unconditional feelings of love, understanding and connectedness towards all beings, even those towards those people that they find difficult or challenging. Increasing empathy by understanding different perspectives and talking to people with different viewpoints can increase agreeableness (Yang, 2021). Similarly, mindfulness meditation has been shown to decrease neuroticism (Innes, 2018).

Brain Chaos

Chaos in the brain refers to the complex and dynamic fluctuations in the neural network signals of the brain (Jørgensen, 2008). It is believed that chaos promotes creativity, resilience, and neural plasticity by allowing us to switch more easily and flexibly between different tasks, thoughts, and mental states. These spontaneous fluctuations - within reasonable limits - are therefore essential for memory, learning, and overall brain health. People with greater chaos in their brain have also been shown to have greater openness (DeYoung, 2018). As a result, those with more chaos in their brain signal data will carry more cognitive reserve and protection against AD (Jeong, 1997). It would therefore be useful to study how chaos levels can be boosted in the brains of those with suboptimal levels.

Stress

Stress can be defined as a psychological and physiological response to a perceived threat. It is typically triggered by challenges in relationships or other work commitments or financial difficulties. While a moderate amount of stress can even be beneficial, chronic stress, on the other hand, can be very harmful.

When the brain is under stress, whether it is physical or emotional, the body releases a plethora of hormones, the primary one being cortisol. Cortisol, often referred to as the “stress hormone” is released by the adrenal glands into the bloodstream to regulate our physiological responses to a stressful event. Cortisol is received by two receptors: the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). The MR is activated at low to moderate stress levels and its activation is not harmful even if it is frequent. However, repeated and frequent experiences of high stress levels activates the GR (Caruso, 2018). High levels of GR activation has been known to result in mood disorders, increased inflammation, cognitive impairments, suppression of the immune system, and more. More specifically, frequent GR activation has been correlated with neuronal damage in the hippocampus. Additionally, those with a genetic mutation that inhibits GR from working effectively have a much lower risk of developing AD (Caruso, 2018). Frequently, AD patients have been found to have high stress levels, as supported by the high cortisol levels found in the bodily fluids of AD patients (Zheng, 2020; Caruso, 2018).

In order to reduce the risk of developing AD, it is important to reduce levels of chronic stress. While approaches to accomplish this may vary on an individual basis, evidence has shown that, if necessary, cortisol levels can be reduced by regulating the activity of glucocorticoid receptors in the body. Engaging in creative outlets and other hobbies has been shown to have a de-stressing effect on people. The role of music as protection against memory loss is significant. While music has been shown to be an effective therapy for AD patients (Moreira, 2018; Pongan, 2017), it has been shown to also offer protection against AD. For example, musicians have a lower risk of memory loss or other abnormal or unhealthy aging compared to non-musicians (Hanna-Pladdy, 2011). Additionally, aerobic exercise has been shown to lower stress (Chen, 2016) and also reduce Alzheimer’s symptoms (Panza, 2018). Regular meditation practice has also been shown to decrease stress levels, therefore lowering the risk of developing AD (Innes, 2018).

Boosting Brain Health

There are also activities that increase our cognitive reserve by modifying the biology of the brain. These modifications include changes to neuronal connections or to brain structure or volume. For example, in addition to reducing stress levels, aerobic exercise also promotes neurogenesis. Exercise releases hormones, such as brain-derived neurotrophic factor (BDNF), that strengthen synaptic connections between neurons. It also stimulates other hormones that release growth factors that result in better cognitive function and mood (Bathina, 2015). In

addition, the sustained practice of loving-kindness meditation has also been shown to modulate the structure and volume of the amygdala (Desbordes, 2012). Interestingly, areas that support positive thinking have been found to grow and those that promote negative thinking have been found to shrink.

Conclusion

Treatment options for Alzheimer's can only slow down its progress, there is unfortunately no known permanent cure. AD already affects 30-35 million people worldwide. With rising life expectancy and population aging, we can only expect a global health crisis since Alzheimer's is a burden to the patients as well as their families, caregivers, and their extended community.

There is, however, some good news. While there are hereditary risks of developing AD, it is possible to reduce the impact of these risks through lifestyle changes. Aerobic exercises, sustained practice of loving-kindness and mindful meditations, embracing novel experiences often, taking up activities that can help us de-stress, and staying alert to decrease neuroticism and increase openness, extraversion, agreeableness, and conscientiousness can all help reduce the risk of developing Alzheimer's.

Research Questions for Further Investigation

While we understand most of the biology of how exercise, meditation, and stress help lower the risk of Alzheimer's, it is not entirely clear how novelty, education, music, openness, extraversion, conscientiousness, or neuroticism affect AD risk. There are several key questions that need to be further investigated and better understood.

One hypothesis is that novel experiences and cognitive stimulation promote brain plasticity through creation of new neural connections and pathways, which can help to potentially mitigate the effects of Alzheimer's pathology. Alternatively, they can also promote chaos in the brain and thus promote overall brain health or cognitive reserve. Finally, they can strengthen the salience network and ward off some of the AD risk. Since musical experiences are emotional in nature, perhaps their salience helps explain the protection they receive?

Separately, larger amygdalae have been indirectly linked to a lower risk of developing AD. People with larger amygdalae tend to have more emotional memories. These emotional memories are often better protected even during AD. The absence of APOE $\epsilon 4$ allele also reduces the risk of developing AD and, incidentally, those without the APOE $\epsilon 4$ allele tend to have larger amygdalae. Additionally, those with a more prosocial behavior also are known to have larger amygdalae. Larger amygdalae have also been linked to enhanced autobiographical memory (Ally, 2013). The amygdala size doesn't have a causative relationship with AD risk that is known yet. But it is worth investigating if there is a more direct link between amygdala structure and Alzheimer's risk.

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