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COMMENTARY

# What are the Risk Factors for Alzheimer's Disease?

**Brittney Benedetti[1,2], Shiv Singh[1,3], Darlene Vargas[1,2], Leith El-Zaim[1,4], Ashely Pruneda[1,2], Mia Padron[1,2], Nadia Ramirez[1,5]**

[1]2nd Annual Junior Clinical Research Internship, South Texas Academy for Education & Training in Research, DHR Health Institute for Research & Development
[2]PSJA Memorial High School, Alamo, TX
[3]Langley High School, Great Falls, VA
[4]South Texas ISH Science Academy, Mercedes, TX
[5]McAllen High School, McAllen, TX

All correspondence should be addressed to Program Director, 2nd Annual Junior Clinical Research Internship Program, DHR Health Institute for Research & Development, 5323 S McColl Road, Edinburg Texas, 78539

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## Introduction

Every 68 seconds a person in America is diagnosed with Alzheimer's disease. Today, 6 million Americans 65 years and older have been affected by Alzheimer's disease; this number is expected to double in the next 30 years (1). Alzheimer's disease is now the most common form of neurodegenerative dementia in the United States with a disproportionate disease burden in minority populations. Alzheimer's disease was first discovered by Alois Alzheimer's in 1901 when he was treating one of his patients (2). Alzheimer's disease is a type of dementia that refers to a particular onset and course of cognitive and functional decline associated with age together with a particular neuropathology. Alzheimer's disease is a disorder that causes degeneration of the cells in the brain, and it is the main cause of dementia, which is characterized by a decline in thinking and independence in personal daily activities. AD is considered a multifactorial disease (3). Alzheimer's disease care requires timely diagnosis and multidisciplinary management. Evaluation involves structured patient and caregiver history and symptom-function reviews, examination, and testing to delineate impairment level, determine the cognitive-behavioral syndrome, and diagnose cause. Additionally, several risk factors such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors play a role in the disease (4). Early reviews identified over 20 risk factors associated with Alzheimer's disease including age, familial inheritance, exposure to aluminum, traumatic brain injury and associated co-morbidities such as vascular disease and infection.

## Stages of Alzheimer's

Alzheimer's tends to set in during peoples mid-60's and proceeds to slowly worsen, affecting the memory, processing skills, and overall problem-solving skills of the subject. There isn't a set timeline for Alzheimer's and everyone's experience with the disease is different. Alzheimer's usually progresses in

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5 distinct stages. Stage one is preclinical Alzheimer's disease. Alzheimer's manifests itself long before any symptoms begin to show and during this stage it is practically impossible to know whether a subject has Alzheimer's or not (5).

Stage 2 would be mild cognitive impairment caused by Alzheimer's. This means that someone at this stage would suffer mild changes in memory and thinking ability. However, it should be noted that mild cognitive impairment (MCI) is a byproduct of Alzheimer's; not everyone who has Alzheimer's will experience it and not everyone who suffers from it has Alzheimer's (5).

The third stage of the disease is mild dementia. This is the stage where Alzheimer's is usually diagnosed, because at this stage it becomes fully apparent that the patient is suffering from the symptoms of Alzheimer's. Some symptoms that people may encounter are changes in personality, memory loss of recent events, difficulty with problem solving, and frequent loss of items of personal value (5).

The fourth stage is a progression of the previous stage, with amplified symptoms and a few new ones introduced. During this stage, people experience even more severe personality changes, increased memory loss, and in some cases, even lose the ability to perform everyday tasks without assistance (5).

The fifth and final stage of Alzheimer's is severe dementia. At this stage, the disease severely affects the mental function of the patient and harshly affects the physical abilities of the patient. Once it has progressed this far, the disease renders the patient incapable of doing anything without extensive assistance. The patient would require help with even the most menial of tasks. Bathing, clothing, eating, defecating, and in some extreme cases even walking would be beyond the patient's abilities. Additionally, the patient also becomes more vulnerable to infections, loses bowel control, bladder control and may even lose the ability to comprehend their surroundings (6).

## Genetics

There are genetic risk factors that contribute to why Alzheimer's Disease affects many individuals worldwide. According to researchers, approximately 70% of the risk of developing AD can be attributed to genetics (7). As one of the most severe neurodegenerative diseases, Alzheimer's disease (AD) is a terrible condition (8).

The strongest genetic risk factor for sporadic Alzheimer's disease is still the APOE 4 allele. However, there are currently no APOE-specific treatments available (9). The most important genetic risk factor for late-onset AD is the APOE 4 allele, but its specific function in the condition is yet unknown. Apolipoprotein E (ApoE) is abundantly expressed in the brain and is produced by the APOE gene. There are three different isoforms; the two that affect AD risk are apoE2, which increases risk and apoE3, which is the most common allele in the population. It is strongly contested how ApoE affects the development and progression of disease because it has a variety of roles that affect both neuronal and non-neuronal cells (10). Presenilin 1 (PSEN1) was discovered to be an EOAD gene with unidentified functions using genetic mapping, gene cloning, and mutation screening of candidate genes.

A second presenilin protein, known as presenilin 2, was found in the area connected to AD in a group of families known as Volga-German descendants. It was discovered based on protein homology (PSEN2) (11). As per the Alzheimer's and Dementia textbook issue 12 volume 6, researchers have found that Early Onset Alzheimer Disease (EOAD) has a heritability of between 92 and 100 percent and is nearly entirely genetically based. Between 35 and 60 percent of EOAD patients have at least one first-degree family who is afflicted, and in 10 to 15 percent of these familial EOAD patients, autosomal dominant transmission is the mode of heredity (11).

The three EOAD genes, which code for the presenilin 1 and 2 (PSEN1 and PSEN2) and the amyloid precursor protein (APP), were shown to have high-penetrant mutations by genetic analysis of unusually large and informative monogenic pedigrees (11).

Adults with Down syndrome develop the neuropathological hallmarks of Alzheimer's disease and are at very high risk of developing early-onset dementia, which is now the leading cause of death in this population (12). Diagnosing dementia in patients who have Down syndrome is a lot harder than others who do not have the genetic disorder. Fluid and imaging biomarkers in those who have Down syndrome have shown great diagnostic performances and a strikingly similar being of changes with respect to sporadic and autosomal dominant Alzheimer's disease (13).

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## External and Environmental Factors

It is commonly established and proven that exposure to pollution, intentionally and unintentionally, can cause harmful effects to various parts of the human body. However, some of these negative effects go beyond just lung damage and heart diseases. According to a study in England, 39% of a large number of adults aged 50 to 79 were diagnosed with dementia, 29% with Alzheimer's disease, and 32% with vascular dementia (14). All affected patients were living in an area that contained the highest annual concentration of pollution (14). Compared to the other study participants who lived in an area of lower concentration, they were 1.4 times more likely to be diagnosed with those 3 cognitive diseases (14).

A prevalent (and intentional) source of bodily harm from toxic pollutants is smoking, which causes a risk of Alzheimer's disease and other forms of dementia. A blog from Alzheimer's Research UK explains and establishes how the excessive inhalation of tobacco smoke can possibly cause oxidative stress, an imbalance of antioxidants which the body uses to remove toxic molecules. This imbalance damages cells in the brain, resulting in an increased risk of cognitive diseases (15).

Our dietary lifestyle has major effects on our overall physical and even mental health. A lack of regulation and moderation of the intake of certain foods can cause long-term damaging effects on various parts of the body. According to a USC News article, a diet consisting of foods that are high in fat, sugars, and cholesterol may affect people who carry the ApoE4 gene by causing a greater risk of Alzheimer's disease. To prove this statement, researchers from the USC Davis School of Gerontology presented the results of their experiment involving an unhealthy diet, genes, and their effect on mice. According to the researchers, the mice that carried the Alzheimer's related gene were fed an unhealthy diet and were later found to have more signs of brain inflammation, however those with a variant of the gene showed no such signs. This concludes that genetics carry heavy influence over outcome, however, a consistent healthy diet can potentially lower the risk factor for such brain diseases in the future (16).

Although negative emotions such as stress, anger, and anxiety are often considered to be mere states of mind, they can potentially influence the risk of dementia and related diseases. It has been found that people with Alzheimer's commonly have raised levels of the stress level cortisol, which potentially plays a role in neurodegeneration. Patients with Alzheimer's that have consistently high levels of stress are found to have less success when it comes to coping with the pathological changes that are brought on by Alzheimer's disease. It can be established that the best way to reduce this risk factor is to find healthy ways to reduce stress in everyday life. An environment that constantly induces negative emotions can inflict long term negative issues on the brain. A healthy and calm kept mind seems to be the best way to prevent any potential risks or influences of dementia or particularly Alzheimer's disease (17).

## Family History

Many people affected by dementia are concerned that they may inherit or pass on dementia. People with first-degree family history of Alzheimer's disease are at an increased risk of developing dementia by 30% (18). Subjective memory impairment among individuals with no measurable cognitive deficits may also indicate elevated dementia risk. The researchers say that it remains unclear whether nondemented people with a positive family history of Alzheimer's disease are more likely to experience cognitive deficits and whether such an association reflects underlying neuropathology. They investigated subjective memory impairment in 40 healthy adults and 35 patients with amnestic. (18). This suggests that subjective memory impairment could reflect preclinical stage neurodegeneration among individuals with the family history risk factors (18). The majority of dementia is not inherited by children and grandchildren. In rarer types of dementia, there may be a strong genetic link, but these are only a tiny proportion of overall cases of dementia. According to researchers, a child whose biological mother or father carries a genetic mutation for one of these three genes has a 50/50 chance of inheriting that mutation (19). They say if the mutation is in fact inherited, the child has a very strong probability of developing early-onset Alzheimer's disease (19). The researchers suggest that if Alzheimer's runs in the family, patients should keep the brain sharp and engage in new learning throughout their lifetime. Other ways to prevent getting Alzheimer's is eating a brain-healthy diet, preventing head injury, and getting screenings.

The researchers say the Self-Administered Gerocognitive Exam, known as SAGE, is a brief pen and paper cognitive assessment tool designed to detect the early signs of cognitive, memory or thinking impairment. The test evaluates your thinking abilities.

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This can help your doctor understand how well your brain is functioning (20).

## Obesity & Diabetes

According to researchers, factors such as cerebrovascular diseases (loss of blood flow to the part of the brain, which causes damage to the brain tissue), diabetes (a class of conditions where there is an excess of blood sugar; high blood glucose), & obesity (Complex interactions between genetic, socioeconomic, and cultural factors lead to obesity.) increase the risk of Alzheimer's disease development. Diabetes and obesity are among the modifiable risk factors for Alzheimer's disease. It's interesting to note that new epidemiological studies show that diabetes considerably raises the likelihood of getting Alzheimer's Disease, indicating that diabetes may be a causal factor in the pathogenesis of Alzheimer's Disease. (21). A study observed that Obesity is a chronic, multifaceted disorder that affects many different organs and tissues abnormally and has a severe impact on human health. Amyloid plaques and neurofibrillary tangles in the brain are connected with Alzheimer's disease, a neurodegenerative condition that progresses and cannot be reversed. Although there is a link between obesity and Alzheimer's disease, the chemicals and molecular mechanisms behind this connection have not yet been fully understood. (22). Oxidative stress, mitochondrial dysfunction, and inflammation have all been found to contribute to the neurodegenerative processes seen in these illnesses. Researchers discovered critical links between diabetes and Alzheimer's disease that are provided by the advanced glycation end products produced by chronic hyperglycemia (posing risk to a variety of cell types and are strongly correlated with the myriad of DM-Related complications, causing long-term complications if untreated). Despite being an immune-privileged organ, the brain has been shown to interact with peripheral and central inflammation. Aging-related damage to the blood brain barrier can cause immune cells to infiltrate the brain, aggravating the central inflammatory response. A key contributing factor to cognitive impairment, neuroinflammation may be the main mechanism behind illnesses linked to aging (23). Further research could help evaluate whether early interventions and lifestyle modifications could lower dementia risk, for obesity and diabetes continue to be serious public health problems in the U.S today.

## How TBI'S can affect with Alzheimer's Disease

As reported in the Alzheimer's Association traumatic brain injury and Alzheimer's disease are both disastrous neurological disorders, whose complex is not yet understood. Cerebrovascular pathology, a key element in both conditions, could represent a mechanistic link between AB/tau deposition after TBI and the development of Alzheimer's disease. (24)

More research is needed to fully understand the relationship between traumatic brain injury and Alzheimer's and to understand why moderate, severe and repeated mild traumatic brain injuries are at an increased risk. Current research on how traumatic brain injuries changes brain chemistry indicates a relationship between traumatic brain injury hallmark protein abnormalities linked to Alzheimer's. Within hours after injury, severe traumatic brain injury is seen to increase levels of beta amyloid, one hallmark protein (25).

Traumatic brain injuries affect over 1.7 million people every year and are often followed by changes in brain structure and function and by cognitive problems such as memory deficits, impaired social function, and difficulty with decision making. Although mild TBI's are known as concussion, it is also a risk for Alzheimer's disease. Using MRI'S is a way to tell the similarities between Alzheimer and TBI'S in how the brain's gray and white matter degrade after injury. In multiple brain areas of both TBI and Alzheimer's participants, the researchers found reduced cortical thickness when compared to the healthy controls. Cortical thickness is roughly correlated with brain age and its thinning is often associated with reductions in attention, memory and verbal fluency, as well as with decreased ability to make decisions, integrate new information and adapt one's behavior to new situations, among other deficits. (26)

## Treatment

As of 2022, the number of people living with Alzheimer's in Texas is about 400,000. With no cure or true method of treatment, by the year of 2050, Americans 65 and up with this disease are predicted to be as many as 12.7 million people (27). While there is no known cure at this time, there are several ways to manage the disease with more currently in the research phase.

The current treatment that we have today is not a cure but options to manage the disease slow its progression. Over the years, there has been a lot of progression in the understanding of pathophysiology, methods to diagnose the disease, and treatments. There are two categories of pharmacological therapy that are available to patients. They include the cholinesterase inhibitors, a group of medicines that block the normal breakdown of acetylcholine. Donepezil, rivastigmine, and galantamine are the recommended therapies for people with mild, moderate, or severe Alzheimer's Disease Dementia (28). These methods are able to show beneficial effects on awareness, activities of daily living, behavior, and overall clinical rating (28). In the past ten years, the omega-3 fatty acid supplements including fish oil have gained a lot of attention owing to their cardiovascular benefits (28). "Two recent randomized, controlled, double-blinded studies showed improvement in thinking and memory in patients with MCI who took fish oil supplements, though these studies were limited by small sample size." (28) There are also many other hands-on activities that patients can take part of to improve neuropsychiatric symptoms and their quality of life. Several case studies show that art therapy has improved one's attention, provides pleasure, social behavior skills, and self-esteem (29).

Our future holds a lot of opportunities for new ways to help these patients who are developing Alzheimer's or have already been diagnosed with AD. The research into further treatments of Alzheimer's disease will include targeting of the neurofibrillary tangles and senile plaques. (28) All around there are debates on which anomaly mark to slow down neurologic decline and how soon the treatment should be initiated. Spreading the information of clinical trials and including family members will bring in patients at the opportune time. By doing that, we will be able to slow these early stages of Alzheimer's. The Clinical Trials in AD Committee in 2016 studied many of these trials to strive to identify the most effectful measures of patient recruitment and retention, infrastructure development, and patient evaluation including biomarkers and objective testing for the clinical end result. (2) When having to push through with trying to find the correct solution you will run into different encounters in learning which medicines will help, and which will not. With a collaborative attempt between researchers, exclusive and public funding, and screening of at-risk populations, a better predictor of successful clinical trials can be created. (28)

## Conclusion

Alzheimer's is one of the world's most common diseases that we are facing today. The risk factors that come along with this disease are influencing our communities, families, and friends. Our healthcare communities are coming together, researching, and learning new information every day that will eventually slow down the rise of cases. Someday in the future Alzheimer's may be eradicated and no one will ever have to deal with the fear of this disease.

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