

Understanding Alzheimer's Risk Factors Associated with the Prevalence of US Populations and Women

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ABSTRACT

Alzheimer's disease (AD), a fatal neurological disease, is the 6th leading cause of death in the United States ⁴³, affecting millions of people. This is a great concern as, by 2060, the number could grow to 13.8 million if no cure is discovered⁰. Despite sophisticated research and technology, finding a solution in the near future appears unattainable due to financing and the brain's complexity. Due to Alzheimer's disease affecting millions of people, the goal of this research is to inform and educate people about the risk factors, prevalence in individuals, and therapeutic treatments available early on for this disease so that one can minimize their risk of developing it. People are unaware of genetic, behavioral, and environmental vulnerabilities that raise their chances of acquiring the disease chronically, which is why this disease has affected millions and is one of the leading causes of mortality. People would avoid these risks if they were aware of them early on. Methods to reduce the chance of developing Alzheimer's disease are discovered through examining the risks and existing therapeutic treatments, as well as analyzing the prevalence of the disease in different ethnic groups and women in the United States through a variety of sources. The findings identified the major causes of Alzheimer's disease, why particular ethnic groups are more susceptible to the disease, and why women are disproportionately impacted by the disease (by millions) compared to males. Knowing all of this, plus the therapies, can help reduce the number of AD cases in the US.

Introduction

Alzheimer's disease (AD), a type of dementia, is one of the most severe public health crises, which currently affects over 6.2 million people in the US¹. Dementia is a general term for neurological diseases which lead to a long-term, persistent disturbance of mental processes resulting in brain disease and injury, memory problems, personality abnormalities, and impaired reasoning². Alzheimer's disease is the most frequent cause of dementia, accounting for 60-80% of all dementia cases³. It is characterized as an irreversible, progressive brain disorder that gradually damages memory and thinking capabilities, as well as the ability to do even the most basic tasks, for example, driving oneself to the store or even feeding oneself ⁴. Alzheimer's starts in the region of the brain that controls memory and chronically spreads to other regions, including areas that control speech and movement. This results in the symptoms developing gradually over time⁵. The occurrence of these symptoms varies from person to person and are often misdiagnosed as other illnesses commonly associated with old age.

Alzheimer's disease is classified by stages of progression. Early-stage symptoms include forgetting about recent conversations, misplacing items, forgetting the names of places or objects, having difficulty thinking of the correct word, and asking questions repeatedly. Middle-stage symptoms escalate to increasing confusion and disorientation, obsessive, repetitive, or impulsive behavior, and problems with speech or language. Late-stage symptoms typically feature difficulty with motor skills, weight loss, unintentional passing of urine, gradual loss of speech, and severe memory problems⁶. Though AD symptoms are well characterized now, this was not the case a century ago. In 1906, Dr. Alois Alzheimer, the namesake of the disease, was the first to observe abnormalities in the brain tissue of a

woman who died of an uncommon mental illness ⁷. The symptoms of this unusual mental illness included paranoia, progressive sleep, memory disturbance, aggression, and confusion, until her death 5 years later⁸. Since the discovery of Alzheimer's disease, millions of scientists and clinicians are researching to identify the risks and causes in order to aid in the development of a cure.

Although there is currently no cure for Alzheimer's disease, knowing the risks are essential to prevent the worsening of this disease. Presently, there are a range of risk factors associated with developing Alzheimer's, some of which are genetic, behavioral, and environmental in nature. Heredity risks include the gene APOE4, PS1, PS2, Trisomy 21, with additional genes being identified daily. Moreover, behavioral risks include day-to-day activities such as lack of sleep, poor diet, insufficient exercise. Furthermore, environmental risk factors include a lack of education, smoking, alcohol abuse and traumatic brain injury. Alzheimer's disease and the associated risk are thought to cause the abnormal functioning of two proteins in the brain, Amyloid-beta, and Tau, which cause the buildup of plaques and neurofibrillary tangles in and around the brain cells, known as neurons.

Interestingly, anyone is susceptible to many of the AD risk factors, however this neurodegenerative disease is more prevalent among specific populations in the United States due to heredity, lifestyle activities, and environmental factors. In figure 1, it displays the 2021 report by the United States Center for Disease Control (US CDC), among people ages 65 and older. African Americans have the highest prevalence of Alzheimer's disease and related dementias (13.8 percent), followed by Hispanics (12.2 percent), and non-Hispanic whites (10.3 percent), American Indian and Alaska Natives (9.1 percent), and Asian and Pacific Islanders (8.4 percent)¹⁰. Moreover, there is increasing evidence indicating that hormone levels, such as estrogen, contribute to the heightening risk of women developing Alzheimer's more often than men¹¹. To minimize the worsening in individuals at risk for AD, there are several therapeutic approaches being developed and tested. Therefore, understanding the genetic, behavioral, and environmental factors that contribute to the disease are essential for developing therapeutic treatments and addressing health disparities.

Prevalence of Alzheimer's in US Ethnic Groups According to CDC

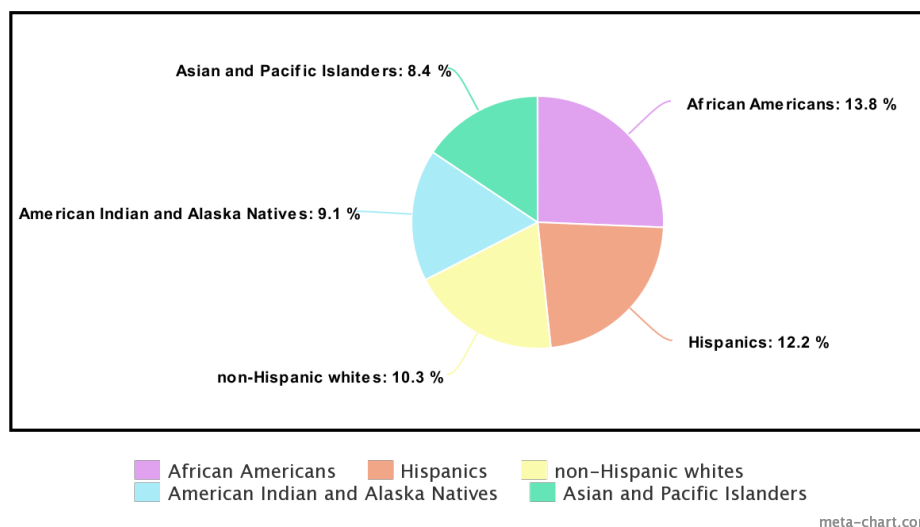


Figure 1. Prevalence of Alzheimer's Disease in US Ethnic Groups Ages 65 and Older

Genetic Risks of Alzheimer's Disease and its Prevalence

Scientists have conducted considerable research on whether Alzheimer's disease is genetic or not. The term, “genetic,” refers to a person's inherited DNA, often known as genes or heredity. This neurological disorder has several genes that play a crucial role in its progression. These genes are classified into two types: deterministic genes and risk genes. Deterministic genes are genes that directly cause a disease, thus guaranteeing an individual will inherit that disorder or disease. Deterministic genes for AD enhance the likelihood of Early Onset Alzheimer's disease, which occurs between the ages of 30 and 60. In contrast, risk genes increase the probability that an individual will develop the disease in their lifetime, however it does not guarantee disease¹². These risks lead to Late Onset AD, which occurs beyond the age of 65 and is the most common time for Alzheimer's to develop. The primary genetic risk factor that makes certain ethnicities and women susceptible to developing Alzheimer's is the APOE gene. This APOE gene is responsible for transfer of cholesterol and phospholipid in the brain¹³.

The brain, like every other organ in our body, requires energy to function. This energy is broken down from the foods we eat and delivered to the brain's key cells, neurons, through the vast network of vasculature throughout the brain¹⁴. The APOE gene is involved in the production of Apolipoprotein E, a protein that aids in the transport of cholesterol, a type of fat found in the bloodstream. There are three variants of the APOE gene: APOE2, APOE3, and APOE4. A person's APOE genetic makeup, otherwise known as genotype, is determined by the combination of two copies, or alleles, of the gene. An individual inherits one allele from each parent; thus, one can have the following combinations depending on the parental genes: E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, or E4/E4¹⁵. APOE3 is the most generic form of the gene, whereas APOE4 is associated with an increased risk and lower age of onset of Alzheimer's disease, and APOE2 is rarer and seems to be protective against Alzheimer's. While all APOE protein isoforms consist of 299 amino acids, these three variants differ from each other by a single amino acid¹⁶. In other words, one sequence change can increase or decrease a person's chance of developing the disease. The two amino acids involved in this change are cysteine and arginine. APOE3 contains cysteine at position 112 and arginine at position 158 (Cys112, Arg 158)¹. In contrast, APOE2 contains cysteine at position 158 instead of arginine (Cys 112, Cys 158), and APOE4 consists of arginine at position 112 instead of cysteine (Arg 112, Arg 158)¹⁷. The reason APOE affects the frequency of developing Alzheimer's is due to how it affects the A β aggregation and clearance and therefore directly influences the development of amyloid plaques, cognitive amyloid angiopathy, and tau-related pathology¹⁸. Deposition of the amyloid β -protein (A β) is one of the two primary hallmarks of Alzheimer's disease. The other main hallmark is associated with neurofibrillary tangles due to tau protein build-up. A β is known to be a large membrane protein that is responsible for neuronal growth and repair¹⁹. Plaques around neurons cause them to die, possibly by inducing an immunological response in the surrounding area. As a result, an abnormal amount of amyloid-beta plaques can cause neurons to die quickly, signaling the onset of Alzheimer's disease. In APOE4 carriers, A β deposition in the form of senile plaques is more common than in non-carriers²⁰. Having one or two APOE4 alleles increases the risk of developing Alzheimer's. Alternatively, APOE2 has a much lower binding affinity for low-density lipoprotein which means less amyloid-beta plaques around neurons²¹. This explains why individuals with APOE4 have a higher risk of developing Alzheimer's compared to APOE2 and APOE3. As APOE is a genetic component, the variant of the gene varies in frequency among populations, putting some people at a higher risk and others at a reduced risk.

APOE Prevalence in US Populations

There is a definite relationship between having an APOE variant and having the risk of acquiring Alzheimer's disease in different ethnic groups. African Americans have the highest prevalence of the APOE4 allele in the United States. When compared to other populations, African Americans with AD or dementias have the APOE4 allele at a rate of

22%. Additionally, from table 1, a report from Alzheimer Association concluded how the e4 allele is more seen in African American populations compared to European Americans/Caucasians²². This provides a compelling explanation for why African Americans may have the highest rate of Alzheimer's disease in the United States. APOE3 is the most common and "neutral" in all human populations, and it is not increased or decreased in any specific group. Asian Americans have the fewest cases of Alzheimer's disease, which may be explained by the prevalence of the APOE2 allele in the population. APOE2 levels were found to be higher in Asian countries such as China, the Middle East, India, and others. Furthermore, when compared to other ethnicities, Asian Americans have the lowest APOE4 allele frequency²³. The lower reported incidence rates of AD in Asian Americans relative to others may be correlated by greater levels of APOE2 alleles. As the APOE variants differ in frequency among ethnic groups, it also differs in frequency among gender.

Table 1. Percentage of African Americans and European Americans with Specified APOE Pairs

APOE Pair	African Americans*:	European Americans*:
e3/e3	45.2	63.4
e3/e4	28.6	21.4
e3/e2	15.1	10.2
e2/e4	5.7	2.4
e4/e4	4.5	2.4
e2/e2	0.7	0.2

***Percentages do not add up to 100 due to rounding**

APOE Prevalence in Women

Women are disproportionately affected by AD more than men. Out of the 5 million people living with Alzheimer's in the U.S., 3.2 million are women⁴² APOE4 is a gene that can appear in both men and women; however, the severity and long-term effect greatly varies between genders. Women with APOE4 are more likely than men to have worse memory performance, greater brain atrophy, and lower brain metabolism²⁴. APOE4 increases the risk of developing the disease but does not guarantee it. However, women are more likely to develop mild cognitive impairment or Alzheimer's disease than men with the allele. A report from 1997 concluded that females with the APOE4 variant were four times more likely to have Alzheimer's compared with people with the more common, neutral form of the gene²⁵. This APOE4 gender bias may be explained by hormones and tau protein. Spinal fluid measures of the protein tau seemed more indicative of Alzheimer's in APOE4 women than APOE4 men. Additionally, the APOE gene includes stretches of DNA that is known to bind estrogen. Hormones are known to regulate APOE expression in a tissue-specific manner²⁵. Estrogen is a primary hormone needed to regulate women's health. Women being more susceptible to developing AD due can be explained by APOE binding to estrogen in greater quantities, and tau levels in the spinal fluid are higher in women than in men. While genetics serves as a major risk for developing Alzheimer's disease, the prevalence of Alzheimer's disease might be influenced by one's behaviors, such as lifestyle choices or day-to-day activities. Sleep is a major behavioral risk factor associated with Alzheimer's disease.

Behavioral Risks of Alzheimer's Disease and its Prevalence

Sleep is necessary for normal cognitive functioning. Even when an individual is asleep, the brain and body are quite

active. When one is awake, different brain chemicals, including those associated with neurological disorders, naturally accumulate in your brain. These substances must be removed to avoid any harm to the brain or the development of a neurological disorder. Therefore, sleep routine is critical to human health. The brain uses cerebral spinal fluid to wash out some of these chemicals or toxins while one is asleep. Amyloid is one of the substances that accumulate in the brain when awake and is one of the hallmarks of the development of Alzheimer's disease²⁶. Sleep is critical to prevent amyloid from accumulating around neurons and causing them to die. As a result, chronic sleep deprivation, or insomnia, can raise beta-amyloid levels in the brain, increasing the risk of Alzheimer's disease (citation).

Stress Prevalence and Cortisol in US Populations correlated to AD

One of the primary causes of lack of sleep or insomnia is stress. Cortisol, the hormone that regulates stress and the flight or fight response, is the reason stress greatly affects sleeping patterns. Sleep and stress response are both associated with a complex regulatory pathway in the brain called the hypothalamic-pituitary-adrenal axis (HPA Axis)²⁷. Therefore, when stress disrupts the HPA axis, it can disrupt one's sleep as well. Normally, cortisol levels are at the lowest when sleeping. High cortisol levels, or high stress-stress levels, during bedtime, can result in improper sleep. High cortisol levels in individuals have been associated with an increased risk for dementia and Alzheimer's disease. One reason that AD is more prevalent in the African American and Hispanic populations may be the result of the amount of cortisol levels at bedtime due to stress. According to the CDC's 2020 report on the prevalence of stress, Hispanic American and Black Americans on average have the highest amount of stress compared to White Americans and Other American populations (Native American/Alaska Native, Asian, multiracial, etc.) due to factors like depression, suicidal thoughts, and substance use²⁸. This report is shown in table 2. This can cause cortisol levels as well as other important sleep hormones, such as epinephrine and norephedrine, to rise. One study concluded that Hispanic Americans and Black Americans on average are more stressed than White Americans due to higher average cortisol, epinephrine, and norephedrine levels²⁹. Insomnia or other sleeping disorders causing lack of sleep caused by stress in Hispanic Americans and African Americans may result in higher AD prevalence in those populations. Stress is not the only factor that has a significant impact on sleep. Other chemicals and physiological factors are important in sleep, and it differs substantially between men and women.

Table 2. Weighted prevalence estimates of current depression, suicidal thoughts/ideation, and substance use increase or initiation among adults aged ≥18 years, by race/ethnicity

Stress Prevalence by Category in US Ethnic Groups

Race/Ethnicity	Unweighted no. of persons	Current Depression	Suicidal thoughts/Ideation	Substance use increase or initiation
Total	1004	28.6 (25.6–31.5)	8.4 (6.6-10.2)	18.2 (15.7–20.7)
White, NH*	657	25.3 (21.9–28.7)	5.3 (3.6-6.9)	14.3 (11.6–17.0)
Black, NH*	100	27.7 (18.7–36.7)	5.2 (0.7-9.7)	15.6 (8.4–22.7)
Hispanic/Latino	118	40.3 (31.3–49.3)	22.9 (15.2-30.6)	36.9 (28.1–45.7)
Other, NH*	129	31.4 (22.8–40.0)	8.9 (3.6-14.1)	15.1 (8.4–21.7)

Hormones Associated with Lack of Sleep in Women

In general, sleep quality women report their sleep quality is worse than the sleep quality men report (citation). This may be due to variations in their daily activities. According to research, women are 40 percent more likely than males to experience sleep deprivation. In addition, women are twice as likely as men to suffer from worry and depression,

both of which are strongly associated with sleeplessness³⁰. All this may be influenced by hormones. Hormones influence sleep patterns. Every month and throughout their lifetimes, women experience hormonal changes that disrupt their circadian rhythms and generate a greater need for sleep³¹. This can be related to menopause, which is significant to understand because it normally occurs when a woman is in her 50s, which is a primary age for Alzheimer's disease symptoms to develop. Hot flashes affect up to 85 percent of women during menopause. When this happens at night, women awaken in a cold sweat, which in turn, disrupting their sleep³⁰. Additionally, women are more likely to develop sleep apnea at menopause. Even if an individual does not wake up, this sleep condition causes breathing pauses, which may impair the quality of one's sleep. This leads to women with sleep apnea waking up feeling less refreshed, as well as fatigue and excessive sleepiness during the day³¹. As a result, women have more sleep issues, especially during menopause. This sleep disturbance being more widespread in women due to their hormones and may be associated with why they are more likely to develop Alzheimer's disease than men³⁰. Behavioral and genetic risk factors are not the only risks that account for AD, another significant risk factor implicated in AD are environmental factors.

Environmental Risks of Alzheimer's Disease and its Prevalence

In general, environmental (non-genetic) or external factors play a significant role in the development of diseases. As a result, even if there is no genetic mutation or disruption in behavioral characteristics, external stimuli can alter one's body in a variety of ways. For example, environmental toxins raise the risk of cancer, heart disease, asthma, and a variety of other disorders³¹. However, environmental factors are not only the ones present in the atmosphere. External factors may include unsafe housing conditions, poverty, lack of education, and dangerous labor conditions. A significant environmental factor associated with Alzheimer's is poor education.

Education is critical for improving cognitive functions such as concentration, attention to detail, memory recall, problem solving, and lowering the risk of developing dementia³². This is because education promotes neuroplasticity. Simply put, the more one learns, the more connections between neurons are formed and strengthened, therefore, increasing mental stimulation in the brain. Going to school, working in a mentally stimulating career, and participating in other mentally stimulating activities all contribute to neuroplasticity. As neurons are damaged and die across the brain in Alzheimer's disease, connections between networks of neurons break down and many brain regions begin to shrink. This can be defined as neurodegeneration. As a result, the lack of engaging in activities that strengthen these neuronal networks can exacerbate the symptoms associated with AD.

Lack of Education Prevalence correlating to AD in US Populations

More education is associated with a lower risk of Alzheimer's disease, which can be attributed to neuroplasticity. Education trends among distinct ethnic groups in the United States can help explain how they link to the prevalence of Alzheimer's disease in these groups. In the Journal of Gerontology Series B, a study on Racial and Educational Disparities in Dementia and Dementia-Free Life Expectancy compared the educational levels of White Americans and Black Americans and their Alzheimer rates. The sample sizes of the study consisted of 16,113 White respondents and 2,822 Black respondents aged 65 and up³³. The distributions of the level of education for blacks and whites varied significantly. 51.2 percent of blacks lacked a high school diploma, compared to 28.5 percent of whites. In contrast, 24.7 percent of Blacks and 33 percent of Whites had graduated from high school. Additionally, 24.1 percent of blacks and 38.5 percent of whites had attended some college or more. Whites, on average, have higher levels of schooling. Nursing facility residencies were approximately equal between the two groups, with whites accounting for 3.2 percent and blacks accounting for 3.4 percent. When compared to whites, blacks had a substantially greater prevalence of dementia (17.5 percent) (7.5 percent)³³. The report concluded in the journal is shown in table 3. Another study from the Racial and Ethnic Disparities in Alzheimer's Disease: A Literature Review presented that 89 percent of Hispanics

and 75 percent of African Americans over the age of 55 with cognitive impairment have less than 12 years of schooling, compared to 47 percent of Whites who have less than 12 years of education³⁴. The findings from this review are shown in figure 2. Cognitive decline is a common aspect of Alzheimer's disease, and it is characterized by issues with memory, language, thinking, and judgment³⁵. One reason African Americans and Hispanics in the US have a higher prevalence of Alzheimer's disease may be related by their education level throughout life. In terms of gender, education levels can also relate to why women are more susceptible to AD.

Education Level and Dementia Results from Black Americans and White Americans

Table 3. Descriptive Information for Analytic Sample of Black and White Health and Retirement Study Respondents (2000–2014)

Demographic Variable	White Americans, % (N= 16113)	Black Americans, % (N= 2822)
Without High School (HS) Diploma	28.55	51.24
HS Diploma	32.95	24.70
College or more	38.50	24.06
Percent living in nursing home	3.15	3.40
Percent with dementia over total study period	7.53	17.57

Cognitive Decline (in %) of US Ethnic Groups below 12 years of Education

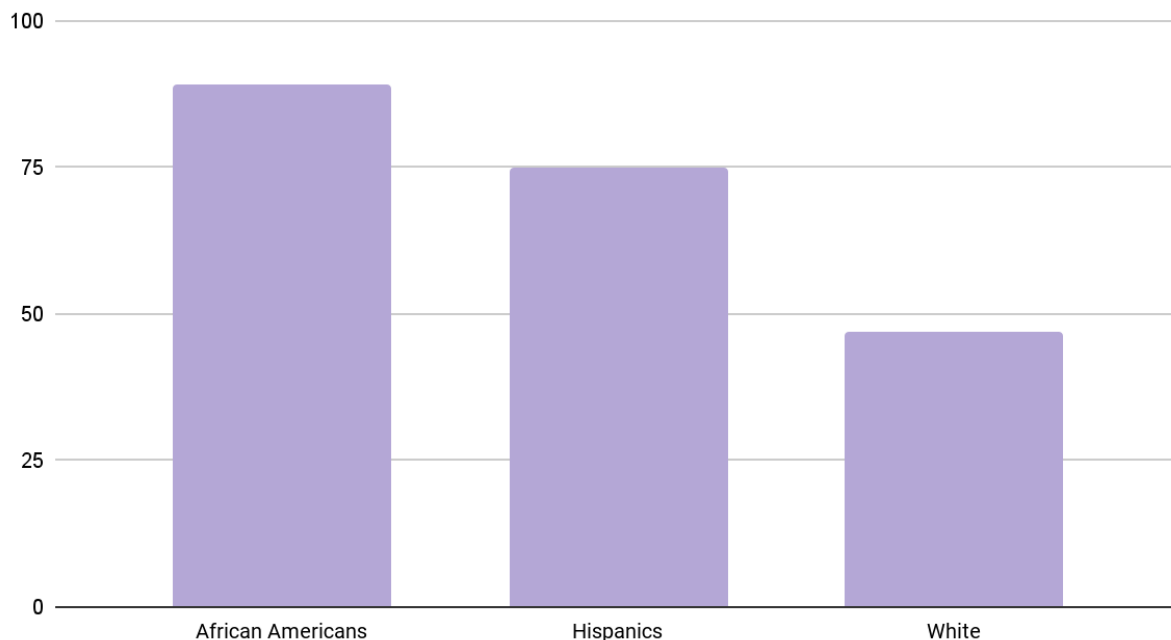


Figure 2. Cognitive Decline in % of US Ethnic Groups below 12 years of education

Lack of Education Prevalence correlated to AD in Women

During the last century, women, compared to men, have had fewer options for higher education in the United States, hence the risk of AD caused by a lack of education is higher among women. According to research, lower education may have a more detrimental influence on AD in women. In a study researching how education impacts dementia in both genders, 190 incident cases of dementia, including 140 cases of Alzheimer's disease were identified. The incidence rates of Alzheimer's disease were 0.8/100 person-years in men and 1.4/100 person-years in women.³⁶ Women's educational prospects have vastly improved in recent decades, which may explain why the rate of Alzheimer's in women is dropping³⁷. As a result, the level of education is correlated with neuroplasticity, which has been shown to slow the progression of Alzheimer's disease in women.

Conclusion: Therapeutic Treatments Associated with each AD Risk

Knowing the prevalence of these genetic, behavioral, and environmental risks factors among certain populations will be critical to developing therapeutic treatments to lessen severity and minimize high mortality rates of AD and ultimately a cure. It is well known that Alzheimer's disease worsens over time. Thus, by the time a person is diagnosed with Alzheimer's, the plaques and neurofibrillary tangles have been accumulating for the preceding 30 years. As a result, understanding the risks and targeting therapeutic treatments to early indicators of the disease can only aid in preventing or lessening the severity as one ages.

As science and technology evolve, new therapeutic solutions for a wide range of diseases are being developed. For the primary genetic risk, APOE4, gene editing by Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and anti-apoE4 immunotherapy are two treatments targeted to reduce or prevent amyloid plaques and neurofibrillary tangles in the brain³⁸. Conversion of the APOE4 gene to either APOE3 or APOE2 and elimination of the concentration difference would result in the optimal treatment, answering the crux of the apoE4 dilemma³⁸. In addition, in apoE4 immunotherapy, antibodies against these molecules are introduced or generated in the periphery and, after penetration into the brain, can neutralize their target (this approach assumes a toxic effect of apoE4)³⁸. Though these treatments are excellent if you have a genetic susceptibility to Alzheimer's disease, they may raise several ethical concerns.

Another promising therapeutic treatment is Trazodone and light treatment. These two treatments are effective in treating sleep abnormalities and disruptions, which are a common behavioral risk factor for amyloid plaques accumulating in the brain. Trazodone is commonly used for stress and depression problems during sleep as it works to balance chemicals in the brain. Studies conclude that trazodone has a positive effect on dementia-associated AD by slowing the rate of cognitive decline³⁹. Bright light therapy, on the other hand, has been shown to be effective in treating disturbed circadian rhythms and may be a beneficial adjuvant therapy in the treatment of sleep problems in dementia⁴⁰.

Finally, cognitive stimulation therapy and cognitive rehabilitation are treatments to increase neuroplasticity because of a lack of education and learning, which is a major environmental risk factor for Alzheimer's disease. Cognitive stimulation therapy entails participating in group activities and exercises aimed at improving memory and problem-solving abilities⁴¹. Cognitive rehabilitation works by encouraging one to use the portions of one's brain that are fully functioning to assist the areas that are not fully operational⁴¹. More than 6 million people in the United States have Alzheimer's disease, and the number is growing every day. To improve one's quality of life, it is necessary to understand the disease characteristics, risks, prevalence, and therapies. Alzheimer's disease and the fatalities it causes can be reduced by educating oneself and one's community with the goal of curing Alzheimer's Disease.

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