The Role of APOE in Alzheimer's Disease: Genetic Variants, Mechanisms, and Therapeutic Implications

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Abstract

With the advances in diagnostics, medical technology, vaccinations, and treatments, the average global life expectancy has more than doubled over the last century. With this increased life expectancy comes an increase in age-related diseases. One disease that is expected to triple in the next few decades is Alzheimer's disease (AD). The APOE (Apolipoprotein E) gene is a critical genetic factor in AD, with its ε4 allele being the strongest known genetic risk factor for AD. APOE is involved in lipid metabolism and plays a crucial role in the clearance of β-amyloid (Aβ), a protein that forms plaques in the brains of AD patients. The presence of the ε4 allele is associated with an increased risk of amyloid accumulation, neuroinflammation, and tau pathology, which collectively contribute to neurodegeneration. Despite its central role in AD, the relationship between APOE and AD remains an active area of research as scientists strive to better understand the mechanisms involved and develop personalized strategies for prevention and treatment.

> O! let me not be mad, not mad, sweet heaven:
> keep me in temper; I would not be mad!
> (King Lear, Act 1, Scene 5)
>
> I fear I am not in my perfect mind.
> Methinks I should know you and know this man,
> Yet I am doubtful, for I am mainly ignorant
> What place this is, and all the skill I have
> Remembers not these garments; nor I know not
> Where I did lodge last night. Do not laugh at me,
> For, as I am a man, I think this lady
> To be my child Cordelia.
> (King Lear, Act 4 Scene 7)[1]

A Brief History of Alzheimer's Disease

Whether King Lear would have descended into "madness" without the betrayal of his daughters is unknown, but since the time Shakespeare penned the tragedy, scholars have noted that Lear exhibited many of symptoms of dementia: confusion, erratic behavior, and inability to recognize loved ones. People have known about age-related dementia since ancient times. Pythagoras noted that people aged 60 and over began to decay in mind and body, while those over 80 reverted to the physical and mental capacity of a child. He referred to these two age groups as having "senium"—old age.[2] Later, around the 2nd century CE, dementia was described by Aretheus, a Turkish physician. He grouped dementia, an irreversible disorder, with delirium, a reversible disorder.[3]

In 1906, Alois Alzheimer presented at the Meeting of the South-West German Psychiatrists in Tübingen. Here, he told the story of a 51-year-old woman, Auguste Deter, who exhibited memory loss and other cognitive symptoms including paranoia, and psychological changes. Upon her death, Alzheimer examined her brain and found what we now know as amyloid plaques and neurofibrillary tangles. In 1910, Alzheimer's mentor, German psychiatrist Emil Kraepelin, named the condition Alzheimer's disease (AD).

In the following decades, AD was recognized as a cause of dementia. Scientists and clinicians began to understand that the abnormal protein deposits in the brain were the cause of the neuronal damage and cognitive decline, but for more than a century, it wasn't possible to determine whether amyloid plaques or tau tangles were present in a patient's brain until a post-mortem examination of the brain was performed; AD could not be definitively diagnosed in a living patient.

Since then, there have been tremendous efforts to determine disease progression and staging, understand which genes are involved in early- and late-onset disease, and investigate

methods to prevent the disease, diagnose it earlier and less invasively, and treat it.

Alzheimer's Disease Diagnosis

Recent advancements have furthered our understanding of how AD can be diagnosed. Diagnosis of AD usually begins when patients present with mild cognitive impairment. The clinician works through the patient's medical history, performs a physical and neurological exam, and does a cognitive assessment, including assessing memory, attention, language, and problem solving. If cognitive impairment is suspected, the clinician may order blood tests to rule out conditions that may cause cognitive decline (e.g., certain vitamin deficiencies, hormonal imbalance). After other causes of the cognitive decline have been ruled out, the clinician may send the patient for imaging studies using biomarkers.

The advent of AD biomarkers has allowed identification of AD pathology when the patient is alive, which has enhanced clinicians' ability to accurately diagnose and stage disease and provided opportunities to intervene with disease modifying treatments (DMTs) for early-stage disease. Both cerebrospinal fluid (CSF) and blood are used to measure levels of certain proteins associated with AD—such as β-amyloid (Aβ) and phosphorylated-Tau (p-Tau). As AD is a progressive condition, diagnosis may involve monitoring the patient's symptoms and cognitive function over time. Early risk detection and diagnosis are important for managing the disease and improving the patient's and caregiver's quality of life. Various technologies including positron emission tomography (PET) imaging, fluid biomarkers, and genetic risk profiling can aid in early risk detection, diagnosis, and treatment allocation of AD.

Alzheimer's Disease Prevalence, Statistics, and Economics

AD and dementia are significant global health concerns, affecting millions of individuals and their families. Every year, more than 10 million new cases of dementia are diagnosed, translating to a new diagnosis every 3.2 seconds.[4] Driven by projected increases in population and population aging, the number of people living with dementia is expected to increase from 57.4 million people globally to 152.8 million people globally by 2050—almost tripling.[5] Of those with dementia, over 60% live in low- and middle-income countries,[6] and by 2050, this proportion is expected to rise to over 70%.[4] As AD is the most prevalent form of dementia, making up 60-80% of all dementias, making it a public health priority.[7]

Dementia is the 7th leading cause of death and a major cause of disability and caregiver dependency in the global elderly population.[6] As AD dementia progresses, there's an increased need for healthcare, caregiver support, and professional nursing care; 75% of people with AD will need long-term care compared with just 4% of the general population.[8]

In addition to the emotional toll that dementia takes on families and caregivers, dementia has a severe economic impact at societal and individual levels.[9] If dementia were a country, its GDP would be the 14th largest in the world[4]—including direct and indirect costs, the total cost of dementia was estimated to cost global economies ~1.3 trillion dollars in 2019.[6] In the U.S. alone, the 2024 cost of institutional long-term care and hospice for those with AD and other dementias was estimated at ~$360 billion USD. The 2022 estimate of informal, unpaid care was valued at $339 billion USD[11]; family members and close friends (disproportionately women) provide on average 5 hours of care and supervision each day.[9] Further, families of patients who are Medicare beneficiaries pay more than $10,000 annually "for health care and long-term care services not covered by other sources."[10]

And while women are more likely to have and die from dementia (women are 1.17 times more likely to have dementia than men, and in 2019 1.5 million women died from dementia as compared with 0.8 million men),[12] they also bear a higher proportion of the economic burden of dementia as women provide ~70% of the care hours for those living with dementia.[9,11]

Genetic Risk Profiling and Fluid Biomarkers of Alzheimer's Disease

There are several genetic variants associated with an increased risk of AD. Disease development is influenced by genetic variants in combination with race,[13] certain health conditions,[14] and lifestyle and environmental factors.[15,16] Four of the major genes associated with developing AD are apolipoproteins, amyloid precursor protein, presenilins, and tau proteins.

Apolipoproteins

One of the most significant genetic contributors to AD development is the apolipoprotein E (APOE) gene, particularly the apolipoprotein E-ε4 (APOEε4) allele.

Normally, apolipoproteins are involved in the transport of lipids and the regulation of lipid metabolism. APOE is involved in the

uptake of cholesterol from the bloodstream. There are three main alleles of the APOE gene based on the amino acids found at positions 112 and 158: APOE ε2, APOE ε3, and APOE ε4. APOE ε2 has cysteine at both positions. APOE ε3 has cysteine at position 112 and arginine at position 158, and APOE ε4 has arginine at both positions. Each person inherits one allele from their mother and one from their father, which leads to six possible combinations of APOE alleles: APOE 2/2, 2/3, 2/4, 3/3, 3/4, 4/4. [17]

APOE ε2 is considered to have a protective effect against AD. While it does not entirely prevent the disease, individuals with this allele tend to develop AD later in life compared with those with the APOE ε4 allele. Only about 5% to 10% of people carry this allele.[17] The precise mechanism isn't fully understood, but it's thought that APOE ε2 may promote better clearance of amyloid plaques, a hallmark of AD.[17,18] APOE ε3 is the most common allele, present in about 70% of the population. It is considered "neutral" because it neither increases nor decreases the risk of AD. It's often referred to as the "normal" allele in terms of its association with disease risk.[17,19]

APOE ε4 is a significant risk factor for both early- and late-onset AD. Early onset familial AD (EOFAD) typically manifests before age 65, accounts for less than 5% of all AD cases, and is often inherited in an autosomal dominant manner. This means that a single copy of the mutated APOE ε4 gene from either parent can increase the risk of the disease. In contrast, late-onset AD, which occurs after the age of 65, is more common and involves a complex interplay of genetic, environmental, and lifestyle factors.[20]

The genetic underpinnings of late-onset AD are less understood and likely involve multiple genes and their interactions with non-genetic factors.[21] While there are variations among individuals of different races, approximately 25% of people are heterozygous (one copy of the neutral APOE ε3 or one copy of the protective APOE ε2) for the APOE ε4 allele, while just 2-3% are homozygous (APOE ε4/ε4 genotype).[10,21]

APOE ε4 heterozygotes make up 7% of global dementia cases.[13] Although inheriting APOE ε4 significantly increases the risk of developing AD and is associated with an earlier age of onset,[13] even inheriting two copies does not guarantee AD development. For individuals with a single copy, there is an ~3-fold increased risk; for those with two copies, the risk rises to ~15 fold over those with no copies of the APOE ε4 allele.[21] But the risk varies by both race and sex, with Blacks and Hispanics developing cognitive decline at a younger age and dying sooner than their White counterparts regardless of APOE ε4 status.[13]

Amyloid Related Imaging Abnormalities (ARIA)

Testing for APOE ε4 zygosity is done both to determine risk for developing AD and to understand risk for developing Amyloid-Related Imaging Abnormalities (ARIA), a significant side effect associated with anti-amyloid therapies used in treating AD. Both APOE ε4 heterozygous and homozygous individuals are at an increased risk for developing ARIA,[22] although the mechanism is poorly understood. Signs and symptoms related to ARIA were first described in 2009[23] and again in 2010[24] in studies involving the investigational drug, bapineuzumab. The term ARIA was coined in 2010[25] to describe a variety of MRI findings seen in patients who were taking investigational anti-Aβ medications. Later, it was included as a warning on monoclonal antibody medications for treating AD.[26]

Neuroinflammation is a critical process in AD, and APOE ε4 has been linked to an increased inflammatory response in the brain. APOE ε4 carriers may have an altered immune system response, with higher levels of pro-inflammatory cytokines and exaggerated activation of microglia (the brain's resident immune cells). This heightened neuroinflammatory response can exacerbate vascular injury and contribute to the breakdown of the blood-brain barrier, making the brain more vulnerable to damage from amyloid-targeting therapies. The neuroinflammation associated with APOE ε4 may also impair the brain's ability to clear amyloid plaques, further contributing to the development of ARIA and possibly influencing how individuals respond to amyloid-based treatments.[27]

APOE ε4 is thought to impair the integrity of blood vessels in the brain, making them more susceptible to damage during amyloid-targeting treatments. This reduction in cerebrovascular integrity can increase the risk of blood-brain barrier disruption and microvascular damage, which in turn may lead to the development of ARIA.

Two types of ARIA are recognized based on their MRI appearance. ARIA-E is characterized by brain swelling and fluid accumulation showing edema and effusion on MRI. ARIA-H is characterized by the presence of microhemorrhages and hemosiderin deposits. AD imaging features cortical and parietal atrophy—likely due to loss of dendrites and neurons—and protein deposits.[22] Imaging from those with ARIA is similar in atrophy, but also includes areas of small dark spots (microhemorrhages) or signal intensity (edema).[25] ARIA abnormalities are believed to result from the breakdown of the

blood-brain barrier due to the mobilization of amyloid plaques in the brain.[25] Although many cases of ARIA are asymptomatic and detected incidentally during imaging, symptoms may include headaches, confusion, and gait disturbances.[25]

The management of ARIA typically involves monitoring and, if necessary, withholding further treatment with the amyloid-lowering agent. In some cases, steroids may be administered to reduce cerebral edema. The occurrence of ARIA underscores the importance of careful monitoring in patients undergoing anti-amyloid therapy.

Amyloid precursor protein (APP)

Normally, amyloid precursor protein (APP) plays a role in brain development, neuronal signaling, and other cellular functions. However, it is best known for its connection to the development of AD. Understanding the role of APP in AD can help in developing targeted therapies and prevention strategies for those at higher genetic risk.

The exact mechanisms by which APP influences AD pathology are still under investigation, but it is believed that mutations in APP affect the proteolytic process of γ-secretase, leading to formation of Aβ, a peptide that plays a central role in AD.[28] Aβ impacts clearance, aggregation, and degradation of the Aβ protein, leading to the neurodegenerative changes associated with AD.[29] APP mutations are a primary genetic factor associated with EOFAD.[28] Similarly, excessive accumulation of even normal Aβ is a common characteristic of AD.

The APP gene is located on chromosome 21 (21q21.2-3),[30] making individuals with Down syndrome (trisomy 21) at particularly high risk for developing AD. Excess APP leads to an increase in Aβ plaques in the brain, and by age 40, nearly all of those with Down syndrome have significant levels of both amyloid plaques and tau tangles, hallmarks of AD—but only 50% of individuals with Down syndrome will develop AD dementia over age 40.[14] While having Down syndrome certainly increases the chances of developing AD, it is not currently understood why some with Down syndrome develop dementia and others don't. Research into the genetic and biological mechanisms linking Down syndrome and AD is ongoing, with the hope of finding effective treatments for both those with and without the extra copy of chromosome 21.

Presenilins

As the catalytic subunit of the transmembrane protein γ-secretase, presenilins (presenilin-1 (PS1) and presenilin-2 (PS2)) are involved in protein processing, signal pathway regulation, and calcium homeostasis. Among other things, γ-secretase regulates cleavage of APP, leading to the formation of Aβ peptides. Excessive or abnormal cleavage of APP is known to be involved in the development of AD.[31]

Mutations PS1 and PS2 have also been shown to be causative factors for EOFAD. As stated above, APP mutations lead to mis-cleavage of the protein and the formation of Aβ. Similarly, mutations in PS1 and PS2 can lead to mis-cleavage of APP.

As with mutations in APP, mutations in presenilin genes and mis-cleavage of APP contribute to the formation of amyloid plaques, a hallmark of AD. PS1 and PS2 gene mutations can cause partial loss of function in γ-secretase and are the primary genetic cause of EOFAD.

Despite that just 1% of the population carries APP mutations, 6% carry PS1 mutations, and >1% carries PS2 mutations,[32] most individuals with APP and presenilin mutations will develop AD.[33]

Phosphorylated Tau (p-Tau)

Tau proteins normally stabilize microtubules in neurons and are essential for maintaining cell structure and facilitating intracellular transport. However, in AD tau proteins become abnormally phosphorylated (phosphorylated Tau (p-Tau)). This hyperphosphorylation causes tau to detach from the microtubules, resulting in destabilization and collapse of microtubules, abnormal axonal transport, dysfunction of the post-synaptic region, and interference in cell signaling.[16,34] The dissociated p-Tau proteins then aggregate into the neurofibrillary tangles seen in AD. The tangles disrupt neural communication and contribute to cell death, resulting in impairment of cognitive functions.[34] Interestingly, tau mutations are also linked with frontotemporal dementia, parkinsonism, and other tauopathies.[16]

Increases in p-Tau and neurofibrillary tangles are strongly correlated with the severity of disease symptoms.[16] Currently, increases in p-Tau aggregates can be seen using tau-PET scans and measuring p-Tau in the CSF and plasma.

Other factors

AD is a complex, heterogenous disease, which can be seen in its genetic association, clinical presentation, and progression. While blood-based biomarkers are emerging as a promising, less-invasive and more cost-effective alternative for early detection and monitoring, cognitive symptoms, rates of progression, and age of onset can differ based on, among

others, genetic, environmental, and socioeconomic factors. It's long been known that homozygosity for the APOE ε4 allele increases the risk of developing AD, but more recently, diversity in race has also been shown to play a role.[13] Despite the disproportionate prevalence of AD in underrepresented groups, most testing levels for AD biomarkers are based on white volunteers.[35] A 2022 study showed that models of amyloidosis in cohorts of predominantly Non-Hispanic White (NHW) individuals could lead to misdiagnosis of Black individuals, furthering health inequities.[36]. Despite Black Americans having more dementia risk factors and an increased likelihood of developing dementia,[37] they are 35% less likely to be diagnosed with dementia at the initial visit as compared with White individuals.[38] Similarly, Hispanic people are ~1.5 times more likely to develop AD than NHW[39] but are certainly not 1.5 times more likely to be diagnosed.

Using samples from a variety of races and ethnicities may help facilitate development of universally applicable blood-based tests for AD that align with the current gold standards for neurodegenerative testing—PET and CSF. Aligning standards between existing and new diagnostic tests is a fundamental step that underpins the credibility, acceptance, and success of new diagnostics. Given the complex, multifaceted etiology of AD, incorporating biomarker-based panels in complement with PET imaging may aid in AD diagnosis, prognosis, characterization, and monitoring,[40] and would make blood-based biomarkers useful for large-scale screening or monitoring disease progression in individuals with mild cognitive concerns.

Treatments for Alzheimer's Disease

Currently, there is no cure for AD. Treatments for AD focus on managing symptoms and slowing the progression of the disease. Recent advancements in AD research have led to the development of new treatments targeting the underlying causes of the disease, helping to reduce and control some of the cognitive and behavioral changes associated with the disease.

Cholinesterase Inhibitors

Medications such as cholinesterase inhibitors (e.g., donepezil, galantamine, and rivastigmine) work by preventing the breakdown of acetylcholine, a neurotransmitter important for memory and learning. They are commonly prescribed to treat memory, language, and judgement challenges by supporting communication between nerve cells. Donepezil has been approved to treat all stages of AD.[41] Rivastigmine[42] and galantamine[43] are both approved to treat mild-to-moderate AD. Cholinesterase inhibitors have been shown to alleviate symptoms and improve cognition and behavior in those with AD.[41–43] Unfortunately, as the disease progresses, the brain's production of acetylcholine decreases, and the medications lose their effectiveness.

Glutamate modulators

Memantine, a glutamate modulator, slows neurotoxicity associated with moderate to severe AD. It helps regulate glutamate, another neurotransmitter involved in learning and memory. It is also used to treat Lewy body dementia and mixed dementias.[44] Similarly, riluzole, a glutamate modulator approved for treatment of amyotrophic lateral sclerosis (ALS) but not yet approved for treatment of AD, has shown promise in early clinical trials to reduce cognitive decline.[45]

Disease-modifying immunotherapy drugs

For decades, there were no approved disease modifying treatments (DMTs) that could slow or halt the underlying disease process of AD dementia—and as with most diseases, the drug discovery process is slow.[46] In 2011, the National Institute on Aging and Alzheimer's Association introduced a research framework for AD diagnosis based on biomarkers of neurodegeneration, which has enabled more accurate disease detection.[46,47]

Where cholinesterase inhibitors and glutamate modulators work by interfering with neural cellular pathways, immunotherapy drugs target removal of Aβ proteins at different stages of plaque formation and helping to clear them from the brain. These DMTs have been shown to slow the rate of cognitive decline, offering the potential to extend the time that patients with early-stage AD can live independently.[48–50]

Regulatory-approved Disease Modifying Therapies

Lecanemab (Lequembi®), a humanized IgG1 monoclonal antibody (mAb) directed against aggregated soluble and insoluble forms of Aβ, has shown promise in slowing progression of early AD. It reduces brain amyloid levels by binding to Aβ protofibrils, which are toxic to neurons, leading to a moderately smaller decline in cognition and function.[51]

Donanemab (Kisula™), also a humanized IgG1 mAb, is directed against the insoluble N-terminal truncated for of the β-amyloid protein (N3pG), which is localized to brain amyloid plaques in patients with AD. In the TRAILBLAZER-ALZ phase 3 trial, which assessed the efficacy of donanemab and potential adverse events in a group with low to medium tau pathology and a separate group with high tau pathology, scientists

showed that donanemab was able to slow the progression of AD.[50]

Lecanemab[51,52] and donanemab[50,53] treatments have been associated with ARIA development. Recent studies exploring modified dosing regimens to mitigate this risk have shown promising results in reducing the incidence of ARIA-E while maintaining therapeutic efficacy.[52,53] Both therapies highlight the need for vigilant monitoring and individualized treatment plans to manage the potential side effects associated with ARIA in AD patients.

In addition to medications used to treat AD itself, there are medications approved to treat some of the side effects of AD such as agitation and psychosis. Similarly, non-pharmacological interventions play a crucial role in managing AD. Cognitive therapies, such as memory training and cognitive stimulation, can help maintain cognitive function and delay the progression of symptoms.

Immunotherapy drugs like lecanemab and donanemab aim to reduce amyloid plaques in the brain, a hallmark of AD. These drugs have shown promise in slowing cognitive decline in early-stage AD patients. Ongoing research continues to explore other potential treatments, including those targeting tau protein tangles and inflammation in the brain.

While there is currently no cure for AD, these advancements offer hope for more effective treatments in the future. These medications don't work for everyone, but they have shown promise in slowing progression of disease symptoms. Studies have shown that DMTs reduced the levels of amyloid in the brain and slowed the rate of cognitive decline among some study participants over the course of 18 months. Further, slowing disease progress with these DMTs may translate into healthcare cost savings.[8] In the United States, the average annual cost of adult day care is 26,000 USD and memory care is approximately 65,000 USD.[8,54] Delaying the need for care may also lead to significant cost savings for families and a lower impact on the already overburdened healthcare system.

Blood-based biomarkers

There is growing interest in using blood-based biomarkers to enable earlier and more accurate diagnosis, monitor disease progression, and evaluate treatment effectiveness.[55] With amyloid-altering treatment availability, identifying relevant AD-associated biomarkers in the blood may help detect AD pathology years before clinical symptoms appear, allowing for early intervention and potentially slowing disease progression. Blood tests are more accessible, less invasive, and less costly than lumbar puncture for CSF analysis and amyloid or tau PET scans, which are often only prescribed if disease is suspected and the clinician expects that treatment would positively affect patient management.[56]

Blood biomarkers may also be used to track progression of AD and effectiveness of treatment by measuring changes in specific protein levels that reflect the underlying pathology. This allows clinicians to tailor treatment plans to individual patients' needs and disease stages. In clinical trials,[56,57] these biomarkers can streamline recruitment, assess drug efficacy, and monitor treatment safety. Specific biomarkers like p-Tau, Aβ, and NfL are particularly promising for detecting neurodegeneration associated with AD pathology.

The availability of blood-based biomarkers and disease-modifying therapies is anticipated to lead to a significant increase in patients seeking to determine their eligibility for these treatments.[55]

Conclusion

AD presents a complex and multifaceted challenge and impacts millions globally. Although the understanding of AD has advanced significantly, the prevalence of AD is projected to rise dramatically, posing substantial economic and social burdens on caregivers, families, and healthcare systems. Genetic factors, including both risk and deterministic genes will play a crucial role in early detection and intervention. Continued research efforts in genetics, early diagnostics through biomarkers, and innovative therapeutic approaches hold promise for mitigating the impact of AD.

The comprehensive exploration of dementia, particularly AD, underscores the significant strides made in understanding its history, biomarkers, genetics, and treatment options. The identification of proteins such as p-Taus, Aβ, and NfL as AD biomarkers is revolutionizing early diagnosis and monitoring of disease progression.

The genetic underpinnings, especially the role of the APOE ε4 allele, have provided critical insights into the hereditary risk factors associated with AD. APOE ε4 remains the most potent genetic risk factor, influencing Aβ deposition and tau pathology, thereby accelerating disease onset and progression. Current medications offer some relief and highlight the urgent need for more effective treatments. As research continues to evolve, the integration of genetic information, biomarker discovery, and therapeutic

advancements holds promise for more personalized and effective management of AD.

While Dr. Alzheimer's initial presentation received a lukewarm reception,[3] ultimately his work set the wheels in motion to help manage the healthcare crisis on the horizon.

References

1. Shakespeare W. Act 4, Scene 7. In: *King Lear*. ; 1608. Accessed February 18, 2025. https://www.folger.edu/explore/shakespeares-works/king-lear/read/
2. Temple University LKS of M. Alzheimer's Disease | Lewis Katz School of Medicine . 2025. Accessed February 18, 2025. https://medicine.temple.edu/departments-centers/research-centers/alzheimers-center-temple-act/stay-informed/alzheimers-disease
3. Yang HD, Kim DH, Lee SB, Young LD. History of Alzheimer's disease. *Dement Neurocognitive Disord*. 2016;15(4):115-121. doi:10.12779/dnd.2016.15.4.115
4. Alzheimer's Disease International (ADI). Dementia statistics. Accessed February 26, 2025. https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/
5. GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7(2):e105-e125. doi:10.1016/S2468-2667(21)00249-8
6. World Health Organization. Dementia. WHO Fact Sheet. March 15, 2023. Accessed February 19, 2025. https://www.who.int/news-room/fact-sheets/detail/dementia
7. WHO. *A Public Health Priority*. World Health Organization; 2012.
8. Skaria AP. The economic and societal burden of Alzheimer disease: managed care considerations. *Am J Manag Care*. 2022;28(10 Suppl):S188-S196. doi:10.37765/ajmc.2022.89236
9. World Health Organization. *Global Action Plan on the Public Health Response to Dementia 2017 - 2025*. World Health Organization; 2017.
10. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2024;20(5):3708-3821. doi:10.1002/alz.13809
11. Alzheimer's Association. 2023 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2023;19(4):1598-1695. doi:10.1002/alz.13016
12. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet*. 2020;395(10219):200-211. doi:10.1016/S0140-6736(19)32989-7
13. Powell DS, Kuo P-L, Qureshi R, et al. The relationship of APOE ε4, race, and sex on the age of onset and risk of dementia. *Front Neurol*. 2021;12:735036. doi:10.3389/fneur.2021.735036
14. NIH National Institute on Aging. Alzheimer's Disease in People With Down Syndrome. November 30, 2020. Accessed March 2, 2025. https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/alzheimers-disease-people-down-syndrome
15. Semmens EO, Leary CS, Fitzpatrick AL, et al. Air pollution and dementia in older adults in the Ginkgo Evaluation of Memory Study. *Alzheimers Dement*. 2023;19(2):549-559. doi:10.1002/alz.12654
16. Rawat P, Sehar U, Bisht J, Selman A, Culberson J, Reddy PH. Phosphorylated tau in Alzheimer's disease and other tauopathies. *Int J Mol Sci*. 2022;23(21). doi:10.3390/ijms232112841
17. National Institute on Aging. Alzheimer's Disease Genetics Fact Sheet. National Institute on Aging. March 1, 2023. Accessed March 17, 2025. https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/alzheimers-disease-genetics-fact-sheet
18. Li Z, Shue F, Zhao N, Shinohara M, Bu G. APOE2: protective mechanism and therapeutic implications for Alzheimer's disease. *Mol Neurodegener*. 2020;15(1):63. doi:10.1186/s13024-020-00413-4
19. Zhong L, Xie Y-Z, Cao T-T, et al. A rapid and cost-effective method for genotyping apolipoprotein E gene polymorphism. *Mol Neurodegener*. 2016;11:2. doi:10.1186/s13024-016-0069-4
20. National Institute on Aging. What Causes Alzheimer's Disease? NIH. July 2, 2024. Accessed March 12, 2025. https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/what-causes-alzheimers-disease
21. Gharbi-Meliani A, Dugravot A, Sabia S, et al. The association of APOE ε4 with cognitive function over the adult life course and incidence of dementia: 20 years follow-up of the Whitehall II study. *Alzheimers Res Ther*. 2021;13(1):5. doi:10.1186/s13195-020-00740-0
22. Johnson KA, Fox NC, Sperling RA, Klunk WE. Brain imaging in Alzheimer disease. *Cold Spring Harb Perspect Med*. 2012;2(4):a006213. doi:10.1101/cshperspect.a006213
23. Salloway S, Sperling R, Gilman S, et al. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. *Neurology*. 2009;73(24):2061-2070. doi:10.1212/WNL.0b013e3181c67808
24. Black RS, Sperling RA, Safirstein B, et al. A single ascending dose study of bapineuzumab in patients with Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2010;24(2):198-203. doi:10.1097/WAD.0b013e3181c53b00
25. Sperling RA, Jack CR, Black SE, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimers Dement*. 2011;7(4):367-385. doi:10.1016/j.jalz.2011.05.2351
26. FDA. FDA Grants Accelerated Approval for Alzheimer's Drug . FDA News Release. June 7, 2021. Accessed March 5, 2025. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug
27. Foley KE, Wilcock DM. Three major effects of APOEε4 on Aβ immunotherapy induced ARIA. *Front Aging Neurosci*. 2024;16:1412006. doi:10.3389/fnagi.2024.1412006
28. Murrell JR, Hake AM, Quaid KA, Farlow MR, Ghetti B. Early-onset Alzheimer disease caused by a new mutation (V717L) in the amyloid precursor protein gene. *Arch Neurol*. 2000;57(6):885-887. doi:10.1001/archneur.57.6.885
29. Raulin A-C, Doss SV, Trottier ZA, Ikezu TC, Bu G, Liu C-C. ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies. *Mol Neurodegener*. 2022;17(1):72. doi:10.1186/s13024-022-00574-4
30. TCW J, Goate AM. Genetics of β-Amyloid Precursor Protein in Alzheimer's Disease. *Cold Spring Harb Perspect Med*. 2017;7(6). doi:10.1101/cshperspect.a024539
31. Nadendla S, Mohiuddin SS. Biochemistry, Presenilin. In: *StatPearls*. StatPearls Publishing; 2025.
32. Bagaria J, Bagyinszky E, An SSA. Genetics, Functions, and Clinical Impact of Presenilin-1 (PSEN1) Gene. *Int J Mol Sci*. 2022;23(18). doi:10.3390/ijms231810970
33. Xiao X, Liu H, Liu X, Zhang W, Zhang S, Jiao B. APP, PSEN1, and PSEN2 Variants in Alzheimer's Disease: Systematic Re-evaluation According to ACMG Guidelines. *Front Aging Neurosci*. 2021;13:695808. doi:10.3389/fnagi.2021.695808
34. Mietelska-Porowska A, Wasik U, Goras M, Filipek A, Niewiadomska G. Tau protein modifications and interactions: their role in function and dysfunction. *Int J Mol Sci*. 2014;15(3):4671-4713. doi:10.3390/ijms15034671
35. Ashford MT, Raman R, Miller G, et al. Screening and enrollment of underrepresented ethnocultural and educational populations in the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimers Dement*. February 25, 2022. doi:10.1002/alz.12640
36. Schindler SE, Karikari TK, Ashton NJ, et al. Effect of race on prediction of brain amyloidosis by plasma aβ42/aβ40, phosphorylated tau, and neurofilament light. *Neurology*. 2022;99(3):e245-e257. doi:10.1212/WNL.0000000000200358

37. Alzheimer's Association. 2020 Race and Ethnicity Fact Sheet. March 2020.

38. Lennon JC, Aita SL, Bene VAD, et al. Black and White individuals differ in dementia prevalence, risk factors, and symptomatic presentation. *Alzheimers Dement*. 2022;18(8):1461-1471. doi:10.1002/alz.12509

39. Alzheimer's Association. Hispanic Americans More Likely to Develop Dementia. Why? July 22, 2022. Accessed January 29, 2025. https://www.alz.org/news/2022/hispanic-americans-more-likely-to-develop-dementia-why

40. Hardy-Sosa A, León-Arcia K, Llibre-Guerra JJ, et al. Diagnostic Accuracy of Blood-Based Biomarker Panels: A Systematic Review. *Front Aging Neurosci*. 2022;14:683689. doi:10.3389/fnagi.2022.683689

41. Kumar A, Gupta V, Sharma S. Donepezil. In: *StatPearls*. StatPearls Publishing; 2025.

42. ALZ Forum. Rivastigmine. ALZ Forum Therapeutics. November 2, 2022. Accessed March 3, 2025. https://www.alzforum.org/therapeutics/rivastigmine

43. ALZ Forum. Galantamine. ALZ Forum Therapeutics. March 6, 2014. Accessed March 3, 2025. https://www.alzforum.org/therapeutics/galantamine

44. Kuns B, Rosani A, Patel P, Varghese D. Memantine. In: *StatPearls*. StatPearls Publishing; 2025.

45. Matthews DC, Mao X, Dowd K, et al. Riluzole, a glutamate modulator, slows cerebral glucose metabolism decline in patients with Alzheimer's disease. *Brain*. 2021;144(12):3742-3755. doi:10.1093/brain/awab222

46. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2019. *Alzheimers Dement (N Y)*. 2019;5:272-293. doi:10.1016/j.trci.2019.05.008

47. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018

48. Hartz SM, Schindler SE, Streitz ML, et al. Assessing the clinical meaningfulness of slowing CDR-SB progression with disease-modifying therapies for Alzheimer's disease. *Alzheimers Dement (N Y)*. 2025;11(1):e70033. doi:10.1002/trc2.70033

49. van Dyck CH. Anti-Amyloid-β Monoclonal Antibodies for Alzheimer's Disease: Pitfalls and Promise. *Biol Psychiatry*. 2018;83(4):311-319. doi:10.1016/j.biopsych.2017.08.010

50. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. 2023;330(6):512-527. doi:10.1001/jama.2023.13239

51. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948

52. Honig LS, Barakos J, Dhadda S, et al. ARIA in patients treated with lecanemab (BAN2401) in a phase 2 study in early Alzheimer's disease. *Alzheimers Dement (N Y)*. 2023;9(1):e12377. doi:10.1002/trc2.12377

53. Rashad A, Rasool A, Shaheryar M, et al. Donanemab for Alzheimer's disease: A systematic review of clinical trials. *Healthcare (Basel)*. 2022;11(1). doi:10.3390/healthcare11010032

54. Gentworth. Cost Care Survey. CareScout. 2024. Accessed March 4, 2025. https://www.carescout.com/cost-of-care

55. Mielke MM, Anderson M, Ashford JW, et al. Recommendations for clinical implementation of blood-based biomarkers for Alzheimer's disease. *Alzheimers Dement*. 2024;20(11):8216-8224. doi:10.1002/alz.14184

56. Hampel H, Hu Y, Cummings J, et al. Blood-based biomarkers for Alzheimer's disease: Current state and future use in a transformed global healthcare landscape. *Neuron*. 2023;111(18):2781-2799. doi:10.1016/j.neuron.2023.05.017

57. Hampel H, O'Bryant SE, Molinuevo JL, et al. Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic. *Nat Rev Neurol*. 2018;14(11):639-652. doi:10.1038/s41582-018-0079-7

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