

Early-Onset Alzheimer's Disease: Global Trends, Diagnostic Barriers, and Therapeutic Gaps

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ABSTRACT

Early-onset Alzheimer's disease (EOAD) is a severe neurodegenerative condition that particularly affects people under the age of 65. EOAD is often characterized by atypical symptoms, a rapid course and specific socioeconomic dysfunctions, but it remains poorly studied despite all of these factors. This review is intended to assess the current global situation of EOAD, especially the diagnostic challenges, worsening of EOAD burden at global level and significant therapeutic gaps. The paper integrates recent epidemiological data from the past decade, 121 clinical trial registries, and diagnostic frameworks to pinpoint systemic difficulties in handling EOAD globally. The analyses show that there are significant diagnostic delays for those with EOAD, due to clinician bias, lack of age-specific cognitive instruments and non-amnestic symptoms, including language problems and visuospatial difficulties. The increasing global burden of EOAD places substantial psychological and socioeconomic strain on patients, caregivers, and healthcare systems. Additionally, the available therapeutic options have not been tested in younger EOAD populations, as they are typically not included in the majority of disease-modifying therapies. EOAD represents a growing global health concern that is characterized by persistent diagnostic delays, limited therapeutic options, and inadequate representation in research. Overall, these findings underscore the critical need to understand and address the underdiagnosis, under-treatment and underrepresentation of EOAD in research and health care systems. Addressing this crisis and these gaps demands urgent implementation of age-specific diagnostic systems, international registries to accurately assess actual disease burden and age-specific clinical trials led.

Keywords: EOAD, epidemiological, neurodegenerative, psychological stress, caregiver

1. INTRODUCTION

The most common and widespread type of dementia globally is Alzheimer's Disease (AD), which primarily affects older adults. According to Zhang et al. (2025) reported that Early-onset Alzheimer's Disease is growing worldwide, especially among individuals between the ages of 40 and 64 years. Internationally, about 7.75 million people had EOAD in 2021, a hardship that is steadily increasing as we progress into 2026 (Lin et al., 2025). This is a significant increase from 1990, where 3.67 people had EOAD. Cases have risen up by 200%, a staggering figure that will continue to increase if diagnostic

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barriers continue globally (Zhang et al., 2025). Additionally, there are also sex differences in the occurrences of EOAD—women are much more likely to get diagnosed with EOAD than men (Peeters et al., 2020). EOAD impacts individuals during their productive years, affecting patients, families, and communities (Griffin et al., 2024). EOAD disrupts the body's normal functions, contributing to understanding the pathophysiology of the disease. Accelerated development and more tau/amyloid pathology in the parietal/neurocortex, rather than just the hippocampus, symbolize the pathophysiology of EOAD (Mendez, 2019). Genetic mutations such as APP, PSEN1, and PSEN2 connect to EOAD. These genetic mutations contribute to neuronal death, synapse negligence, and more decline than late-onset Alzheimer's disease.

The symptoms of EOAD are existent in subtle manners that are frequently ignored. These include executive dysfunction & cognitive decline, visual-spatial impairment, language difficulty (aphasia), and disorientation (Miller, 2023). In order to diagnose EOAD as quickly as possible, there are multiple procedures to go through. EOAD diagnosis involves observing biomarkers through PET scans, cerebrospinal fluid analysis, and government-approved blood tests for tau and amyloid proteins (Wells & Horton, 2022). EOAD is often associated with more accelerated progression and unconventional symptoms, complicating diagnosis procedures (Zhang et al., 2025). Especially in lower-resourced areas, this often leads to misdiagnoses and delays for patients, caused by a lack of awareness or caution. Although it is easier to get treatment in Western countries, there are many areas that are less fortunate. In Latin America and other low-income areas, there are not as many health professionals, and there is a lack of expenditure on biochemical research. Additionally, the number of cases of EOAD is increasing all around the world, with geographic disparities complicating its global management. Global trends indicate that East Asia and the Middle East are facing rising mortality rates while it is harder to get treatment in places such as Sub-Saharan Africa and Brazil (Fu et al., 2025). All together, the global burden of EOAD has increased due to diagnostic barriers and therapeutic gaps. EOAD is often misdiagnosed, and individuals with it are frequently left out from broader Alzheimer's research (Hammers et al., 2024). These diagnostic challenges contribute to delayed recognition of EOAD and reinforce its historical underrepresentation in Alzheimer's research and clinical trials.

It is critical to observe EOAD's global trends, diagnostic barriers, and therapeutic gaps, considering the universality of it. EOAD affects many regions and areas across the world and consequently has many repercussions. This review paper's objective is to understand the consequences of EOAD globally along with its diagnostic blockades and medicinal gaps.

Methodology

A literature review was conducted through the use of online databases such as PubMed, Lancet and Google Scholar, to find relevant studies on genetic factors in AD and their role in treatment. Search terms included "early-onset Alzheimer's disease," "young-onset Alzheimer's disease," "global prevalence," "epidemiology," "diagnostic barriers," "early diagnosis," "therapeutic gaps," "treatment challenges," "disease management," and "healthcare disparities." Relevant publications were chosen, and additional

sources were identified through reference tracking of the chosen articles. Both human clinical studies and experimental model-based research were included.

2. GENETIC AND MOLECULAR MECHANISMS

2.1 Autosomal Dominant EOAD

2.1.1 APP:

APP, or the Amyloid Precursor Protein gene, is a rare and dominant genetic mutation of Early-onset Alzheimer's disease. It only accounts for less than 1% of all Alzheimer's disease cases but includes an abundant portion of EOAD (before 65 years of age) cases (Kalampokini et al., 2021). These mutations increase the chances of amyloid-beta production, leading to hastened amyloid plaque deposition and rapid cognitive decline (Ryan & Rosser, 2014).

The generality of autosomal dominant mutations in the APP gene is not common; it is important for a small portion of all Alzheimer's cases. It is known to appear only in families with a history of early-onset Alzheimer's disease (TCW & Goate, 2017). The APP genetic mutation is usually responsible for leading to Early-onset Alzheimer's disease and ranges between 40-64 years old. The symptoms of APP include progressive memory loss, executive dysfunction, and early-onset psychiatric symptoms (Liu et al., 2022).

The APP gene mutation usually occurs in or in close proximity to the amyloid-beta area, often causing progression of the protein fragment (Lee et al., 2021). When the mutations in the APP gene switch its processing toward the amyloidogenic pathway, the enzymes split the protein to construct amyloid-beta peptides (Hampel et al., 2021). There are specific effects of the molecular mechanisms in the APP gene. These effects include an increase in neuroinflammation and plaque accumulation as well as aggregation and decreased clearance (Siddapaji & Gopal, 2021).

Mutations in the APP gene are frequently associated with EOAD (Orobets & Karamyshev, 2023). Through a comprehensive genetic screen analysis, Lanoiselee et al. (2017) identified novel pathogenic mutations in 53 families affected by early-onset Alzheimer's disease. It was determined that there were 20 APP mutations in 18/129 cases (Lanoiselee, 2017). The disease generally progresses over years and starts much earlier than we can discover the first symptoms (Orobets & Karamyshev, 2023). The stages of APP gene-related disease progression are the preclinical phase, vascular and early pathological changes, mild cognitive impairment, dementia, and terminal stage.

2.1.2 PSEN1 & PSEN2

Mutations in PSEN1 (presenilin-1) and PSEN2 (presenilin-2) are the main causes of autosomal dominant Early-onset Alzheimer's disease (Lanoiselee, 2017). It typically causes symptoms before the age of 65. More than 300 pathogenic mutations have been observed in PSEN1 is a more frequent cause of familial EOAD, while PSEN2 has fewer identified mutations (Bagaria, 2022).

The PSEN1 and PSEN2 genetic mutations code for proteins that make up the catalytic subunit of γ -secretase, an enzyme associated with the APP genetic mutation (Lanoiselee, 2017). PSEN1 mutations generally result in symptom onset during the fourth and fifth decades of life. Zapata-Restrepo et al. (2025) found that PSEN1-associated EOAD is usually characterized by a more aggressive disease trajectory than other genetic forms, with much earlier symptom manifestation and accelerated cognitive decline. PSEN2 mutations have a wider range of onset, ranging from 39 to 83 years (Leochico, 2025).

The inheritance pattern for both PSEN1 and PSEN2 mutations is half and half—a child of a carrier has a 50% chance of inheriting the gene and obtaining the disease (Ambriz, 2025). If the gene mutations are inherited, the individual will most likely develop EOAD. Although these mutations are a cause of the majority of all familial EOAD cases, they only make up 1% of Alzheimer's cases overall (Lanoiselee, 2017).

Research indexed by PLOS Medicine indicated that diagnosis and screening for both PSEN1 and PSEN2 mutations are crucial to be done for families with a history of EOAD (Lanoiselee, 2017). According to the study, identifying these mutations is essential for accurate diagnosis and genetic counseling of affected families. The study detected numerous mutations, with PSEN1 being the most prevalent. The mutations account for the majority of autosomal dominant cases. The study further establishes the need for testing in both familial and irregular EOAD cases. Early identification of the 50% inheritance risk for relatives is made possible by genetic testing (Cruchaga, 2012).

2.2 Pathophysiological Pathways

2.2.1 Amyloid-beta aggregation

Mutations in APP, PSEN1, and PSEN2 lead to amyloid-beta aggregation. EOAD is linked to genetic mutations in APP, PSEN1, and PSEN2—these genetic mutations heighten the efficiency of production of highly pathogenic amyloid-beta 42 (TCW & Goate, 2017). Early axonal injury and cognitive decline are primarily caused by these mutations accelerating the protein aggregation and self-fabrication of amyloid-beta 42 (Varte et al., 2025).

Amyloid-beta aggregation in EOAD consists of these genetic drivers: APP, PSEN1, and PSEN2. As opposed to late-onset Alzheimer's, EOAD is often motivated by familial mutations that upgrade an immoderate collection of amyloid-beta peptides, which are much more vulnerable to accumulation (Valdez-Gaziola et al., 2024). Within the context of EOAD, mutations instantly elevate the amyloidogenic route (Kim & Hecht, 2009).

Early amyloid PET positivity (pre-symptomatic stage) has been shown to identify amyloid pathology years before the onset of dementia in many individuals at risk for EOAD, although its predictive value changes depending on clinical and genetic context (Chapleau et al., 2022). Amyloid PET findings influence diagnostic and management decisions (>30% of cases), even before severe impairment (Windon et al., 2025). Amyloid PET provides a direct measure of amyloid burden and provides high confidence in diagnosing EOAD as a cause of cognitive issues (Altomare et al., 2023).

The strongest validation of the amyloid cascade hypothesis seen in EOAD is the evidence that amyloid-beta deposition is the initial pathological event that triggers tau accumulation and cognitive issues (Levin et al., 2022). These findings provide strong support for the amyloid cascade hypothesis; however, the hypothesis remains the subject of ongoing investigation, and many other mechanisms are also believed to contribute to disease progressions. Autosomal dominant mutations in APP, PSEN1, and PSEN2 lead to EOAD, providing the support that amyloid is the facilitator (Levin et al., 2022).

2.2.2 Tau hyperphosphorylation

Tau hyperphosphorylation in EOAD is a pathology that is excessively aggressive, featuring high tau accumulation in brain hubs and faster spreading (Rawat et al., 2022). Most of the time, genetic mutations in APP, PSEN1, and PSEN2 are responsible for familial EOAD cases. The tau hyperphosphorylation pathway is instantly advanced by these genetic variations.

Microtubules in axons are stabilized by normal tau, yet hyperphosphorylation causes it to detach, which destabilizes the microtubule network and creates harmful neurofibrillary tangles (Summer, 2026). Axonal dysfunction brought on by these pathogenic variations impairs transports and causes neural deterioration (Summer, 2026).

A reliable biomarker for predicting cognitive decline in EOAD is tau PET imaging. There is a significant correlation between increased tau protein levels in the brain and a quicker rate of memory loss and functional decline. Unlike amyloid PET, tau PET shows a dynamic relationship with worsening symptoms (Tanner & Rabinovici, 2021). Ioannou et al. (2024) evaluated the ability of tau PET imaging to predict disease progression using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The study included 396 cognitively impaired individuals, allowing researchers to assess the relationship between tau burden and subsequent cognitive decline.

The evidence was solidified further when the findings suggested that high tau PET intake resulted in rapid progression with cognitive decline in the individuals (Ioannou et al., 2024).

2.2.3 Neuroinflammation

An important aspect of EOAD is neuroinflammation, which is characterized by chronic microglia and astrocyte mobilization (Fakorede et al., 2025). Neuroinflammation represents a pathological response associated with amyloid plaque accumulation and tau pathology. Chronic neuroinflammation is believed to contribute to synaptic dysfunction, neuronal loss, and cognitive decline, although the extent of its casual role remains an area of active investigation (Faokerede et al., 2025).

Elevated cerebrospinal fluid (CSF) and plasma cytokines suggest neuroinflammation. In neuroinflammatory disorders, significant elevations are disclosed for Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-a), IL-10, Interferon-alpha (IFN-a), and chemokines like CXCL13 and CXCL10 (Lepenietier et al., 2019). More concentrations in the CSF are noticed in the Central Nervous System (CNS), and it is usually higher than in the blood plasma (Margetis & Baker). 2025). Hints of

central illness suggest that plasma levels manifest a strong association with CSF, and this happens incredibly often (Bettcher et al., 2018).

A sign of neuroinflammation is when the microglia in the brain are triggered (especially in people with EOAD), and PET imaging is a tool that helps to detect it. When the microglia are activated, it usually means they are switching to a diseased state where they are not able to work as properly as before, and this can point toward chronic damage (Lavissee et al., 2020). Additionally, PET imaging does not exactly identify what causes the disease, but it can help to recognize the disease's severity, serving its purpose as a disease amplifier.

2.2.4 Mitochondrial dysfunction

The path to neuronal damage is marked by mitochondrial dysfunction, which is an initial event in EOAD that occurs before amyloid plaque and tau tangle accumulation (D'Alessandro et al., 2025). These deficiencies form a brutal cycle with amyloid-beta toxicity, making it harder for the cells to get the energy they need, and it accelerates neurodegeneration, therefore leading to EOAD (Wang et al., 2025).

People born with mutations in the PSEN1 and PSEN2 genes are more likely to acquire familial EOAD. Familial EOAD mutations in PSEN1 and PSEN2 cause mitochondrial dysfunction, which leads to a buildup of amyloid-beta and an increase in reactive oxygen species (ROS) (Sarasija et al., 2018). Mutations in presenilins decrease the coherence of mitophagy—removal of damaged mitochondria—allowing dysfunctional mitochondria to pile up and resulting in damage (Martin-Maestro et al., 2017).

Fluorodeoxyglucose (FDG) and PET are tests that see if the brain cells are getting the energy that they need (Bouter, 2019). Neuronal loss and memory deficits usually appear years before clinical symptoms of Alzheimer's, which showcases its connection to EOAD. The mitochondrial cascade hypothesis states that genetic, environmental, or lifestyle factors cause mitochondrial efficiency to decline over time (Swerdlow et al., 2014). Within the EOAD context, the hypothesis helps to explain that mitochondrial deficiency is one potential contributor rather than being an outcome.

2.2.5 Synaptic failure

An event that is closely connected to cognitive decline is synaptic failure, which is widely considered to be an important feature of EOAD pathology (Arendt, 2009). As a result of amyloid-beta oligomers and tau pathology, the connections between brain cells are ruined and disrupted—this happens a lot in the hippocampus (Crimins et al., 2013). Before the brain cells start dying, synaptic failure usually takes place right before (Henstridge et al., 2016).

A sign of synaptic damage is when the fluid that surrounds the brain—cerebrospinal fluid (CSF)—starts to increase rapidly (Nilsson et al., 2024). In a study executed by Luisa Agnello, 136 individuals were evaluated (33 patients had Alzheimer's and 70 patients had non-neurodegenerative neurological diseases), and CSF neurogranin levels were measured (Agnello et al., 2021). The results were that Alzheimer's patients showed levels of neurogranin as a cause of increased CSF (Agnello et al., 2021).

fMRI studies in EOAD consistently show a significant decrease in connectivity with the Default Mode Network (DMN), specifically in the posterior cingulate cortex and precuneus. EED studies demonstrate a “slowing” of electrical activity, marked by decreased connectivity in the alpha and beta frequency bands of posterior regions. Disruptions or problems in these networks relate directly to the sternness of cognitive impairment and amyloid load.

2.3 Differences Between Early-Onset and Late-Onset AD

Comparative Analysis of Early-Onset vs. Late-Onset Alzheimer's disease (graph)

Feature	EOAD	LOAD
Age	Under 65 years old	65 years and older
Initial Presentation	Highly atypical; nonamnesic deficits (language, executive, visuospatial)	Typical; primary amnesic deficits (short-term memory loss)
Genetic driver	Stronger genetic link; rare mutations (<i>APP</i> , <i>PSEN1</i> , <i>PSEN2</i>)	Driven primarily by age and <i>APOE4</i> allele expression
Neuropathology	High density of amyloid plaques and neurofibrillary tangles across wider neocortical areas	Plaques/tangles heavily focused within the hippocampus and medial temporal lobes
Diagnostic Lag	Critically prolonged; symptoms are often initially attributed to stress or burnout	Shorter; clinical pathways are well-optimized for elderly cohorts
Social & Economic Impact	Disrupts peak earning years, careers, and young dependent care setups	Occurs primarily during retirement; impacts elder care support networks

2.3.1 Faster progression

There are many differences that exist between Early-onset Alzheimer's Disease (EOAD) and Late-onset Alzheimer's Disease (LOAD). EOAD affects individuals under 65 years of age, and the symptoms include visuospatial deficiencies, language difficulties, and cognitive dysfunction (Valdez-Gaxiola et al., 2024). LOAD typically occurs after EOAD, generally progresses faster, and starts with subtle memory

loss as well as gradual cognitive decline (Valdez-Gaxiola et al., 2024). EOAD is characterized by a faster rate of cognitive decline compared to LOAD.

In a 3-year longitudinal and observational study conducted by Carina Wattmo and Asa K. Wallin, patients with EOAD showed faster cognitive deterioration than patients with LOAD (Wattmo & Wallin, 2017). At the 12, 18, and 30 month marks, EOAD patients revealed a more rapid decline in the Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-Cog) compared to the LOAD group (Wattmo & Wallin, 2017). This study as a whole suggests a more rapid progression of cognitive impairment in younger-onset patients. Although researchers have found a more aggressive disease path for individuals with EOAD, they also have a longer overall survival time after diagnosis.

2.3.2 Greater cortical involvement

Early-Onset Alzheimer's Disease (EOAD) is known to exhibit greater and a more vast assortment of neocortical involvement compared to Late-Onset Alzheimer's Disease (LOAD) (Valdez-Gaxiola, 2024). EOAD displays increased tau burden and lessened gray matter in parietal and frontal regions as well as faster progression (Mendez, 2018). These frequently lead to a heightened and more widespread activation of the cerebral cortex, or greater cortical involvement (Mendez, 2018).

Individuals with EOAD often experience faster rates of brain atrophy and cognitive decline when compared to those with LOAD. EOAD demonstrates higher neocortical tau burden in proportion to amyloid, while LOAD shows a greater strain of neurofibrillary tangles in the hippocampus (Mendez, 2018). This is apparent with a study conducted by Hanna Cho, where the aim was to describe amyloid-beta and tau emission from the Longitudinal Early-onset Alzheimer's Disease Study (Cho et al., 2024). In the study, 75% of participants were assigned to a cohort based on amyloid-PET (Cho et al., 2024). From these participants, 95% were tau-PET positive, and the signal was heightened in cortical regions (Cho et al., 2024). While these findings strengthen evidence for extensive cortical tau involvement in EOAD, further longitudinal studies involving larger and more diverse populations are needed to determine whether these patterns are consistent across all EOAD subtypes and genetic backgrounds.

2.3.3 Atypical presentations (posterior cortical atrophy, language variants)

Atypical EOAD is presented before age 65, essentially involving posterior cortical atrophy and language deficits (Jones et al., 2025). These variants show heightened visuospatial, language, or executive dysfunction, sometimes leading to initial misdiagnosis due to intact memory (Jones et al., 2025). While sharing amyloid-beta and tau pathology, atypical variants demonstrate distinct and more localized atrophy norms (Whitwell, 2024).

Posterior cortical atrophy (PCA) primarily affects the posterior regions of the brain, leading to progressive visuospatial impairments that interfere with activities such as reading, writing, and spatial navigation (Crutch et al., 2017). In the UCSF International Multicenter study led by Dr. Marianne Chapleau, 1000 patients from over 16 countries were involved (Chapleau, 2024). The study confirmed that PCA is a

predictor of EOAD. Logopenic variant primary progressive aphasia (lvPPA) is characterized by impaired repetition of phrases, slowed and hesitant speech, and word-finding difficulties, while the abilities to produce speech and grammar remain intact (Gorno-Tempini et al., 2011). The NACC Multicenter Analysis, a large-scale study of over 5000 patients, found that individuals with EOAD had worse verbal fluency at the time of diagnosis than those with LOAD (Galilee et al., 2025). Collectively, these findings support the hypothesis that EOAD is characterized by widespread cortical tau deposition, which likely contributes to its greater neocortical involvement, atypical clinical presentation, and more rapid cognitive decline compared with LOAD.

3. DIAGNOSTIC CHALLENGES AND BARRIERS

3.1 Clinical Misdiagnosis

As a result of its habit to present with behavioral, emotional, or language changes rather than memory loss, EOAD is misdiagnosed as stress-related disorders, burnout, or even depression (Raphael, 2025). This sudden confusion leads to significant delays in referring patients to specialists (Giebel et al., 2024). The misdiagnosis challenges in EOAD are enhanced specifically by initial treatment efforts.

Problems with focusing or work or navigation issues are frequently mistaken for professional burnout, even though these are actually early symptoms of EOAD. Specialists and clinicians also have a lack of suspicion since Alzheimer's is considered a disease for the elderly, and therefore they do not consider it a threat for patients in their 40s and 50s. This results in diagnostic gaps where symptoms are dismissed due to common delusions (Kvello-Alme et al., 2021).

3.2 Biomarker Limitations

Something that creates barriers to effective management are biomarker limitations in EOAD (Perez-Martinez, 2025). The limitations in EOAD biomarker testing include the lack of standardized cutoffs for CSF assays, limited access to PET imaging centers, and high costs that often restrict insurance coverage to research specific diagnostic scenarios (VandeVrede & Schindler, 2024). These tools meet logistical hurdles that block their routine clinical adoption for early detection despite being reliable for identifying amyloid or tau pathology (VandeVrede & Schindler, 2024). These events usually happen before the symptoms appear.

CSF amyloid and tau assays are highly sensitive for EOAD yet face restrictions such as lack of global cutoff standardization and increased assay variability between platforms (Omar & Preddy, 2020). Additionally, there are many diagnostic delays due to the invasiveness of lumbar punctures, leading to a 50% misdiagnosis rate (Omar & Preddy, 2020). PET imaging centers are frequently confined to specialized academic medical centers, reducing access to patients that reside in rural or smaller settings (Barbosu & Trollip, 2026). Moreover, amyloid PET scans show high accuracy; however, they do not measure neuronal damage frankly, and many cognitively healthy individuals show positive amyloid scans

(Pontecorvo & Minton, 2011). In addition, biomarker combinations show inconsistent classification, which largely depends on the disease stage (Illan-Gala et al., 2018). As a result, EOAD represents numerous biomarker-related limitations.

3.3 Genetic Testing Constraints

Genetic testing for EOAD faces constraints due to the lack of disease-modifying treatments, which often lead to ethical concerns regarding psychological distress (Kim et al., 2015). Significant challenges include the need for rigorous counseling for pre-symptomatic testing, risks of stigma, potential discrimination in long-term health insurance, and informed consent limitations due to cognitive decline (Roberts et al., 2021).

Testing for PSEN1, PSEN2, or APP mutations is widely controversial because no treatment alters the disease course, making results predictive with significant psychological burden (Tsao, 2013). While diagnostic testing for symptomatic individuals is more accepted, presymptomatic testing is for at-risk individuals (Pierron et al., 2025). As EOAD causes early cognitive impairment, determining whether a patient can consent to testing is complex (Howe, 2012). There are also significant concerns regarding discrimination in long-term care insurance, disability insurance, and life insurance (Howe, 2012). Although there are laws such as the Genetic Information Nondiscrimination Act (GINA) that protect against health insurance discrimination, they often do not cover these other areas (Tenenbaum & Goodman, 2017).

3.4 Barriers in Low- and Middle-Income Countries

In low-and middle-income countries, diagnosing and managing EOAD is severely hindered by systemic shortages and cultural barriers (Sideman et al., 2022). There is a significant shortage of a dementia-capable workforce, including neurologists and geriatricians (Raphael, 2022). Since specialists are rare, primary care physicians are usually the first and only point of contact, yet many lack the specific training to recognize early cognitive signs in younger patients (Raphael, 2022).

Essential tools such as PET scans, CSF assays, and advanced MRI are often restricted to high-income settings and are largely unaffordable to low-and middle-income countries (Aguirre et al., 2019). Additionally, in many regions there is stigma surrounding neurological and cognitive disorders (Elliot et al., 2018). Families start to hide affected individuals from the public as a cause of fearing social isolation, leading to them not being able to seek early interventions or community support (Dehbozorgi et al., 2022). In a study conducted by David A Perez-Martinez, it was found that 90% of cases in low and middle income countries went undiagnosed since they lacked adequate health financing (Perez-Martinez et al., 2025). For EOAD, these systemic barriers are especially concerning because younger patients are already at increased risk of delayed recognition due to atypical symptoms and the misconception that Alzheimer's primarily affects older adults.

4. CURRENT THERAPEUTIC LANDSCAPE

4.1 Symptomatic Pharmacotherapy

Symptomatic pharmacotherapy is the use of medications to relieve the physical and psychological signs of an illness, instead of treating its underlying cause. In EOAD, symptomatic pharmacotherapy mostly relies on two primary classes of FDA-approved drugs: cholinesterase inhibitors and NMDA receptor antagonists (Miculas et al., 2022). The goal of these medications is to alleviate cognitive and functional symptoms rather than stopping the underlying neurodegenerative process (Wu & Fuh, 2025).

Cholinesterase inhibitors are drugs that are typically the first-line treatment for mild to moderate EOAD cases (Birks, 2006). These drugs work by preventing the breakdown of acetylcholine, which is an important transmitter that is accountable for memory and learning. NMDA receptor antagonists are medications that are usually prescribed for moderate to severe stages, and they work in combination with cholinesterase inhibitors (Singh & Patel, 2026). By overseeing glutamate, a neurotransmitter that leads to cell damage frequently, their pursuit is placed. Cholinesterase inhibitors and NMDA receptor antagonists usually are used when targeting the symptoms of EOAD (Parsons et al., 2013).

4.2 Disease-Modifying Therapies

Disease-modifying therapies for EOAD primarily consist of anti-amyloid monoclonal antibodies and have transitioned from trials to clinical practice (Filippi et al., 2026). Other therapies include FDA-approved treatments such as Lecanemab and Donanemab, both of which slow disease progression (Goswami et al., 2026). However, evidence regarding their efficacy and safety specifically in EOAD remains limited because younger patients have been underrepresented in major clinical trials (Yang et al., 2025).

Anti-amyloid monoclonal antibodies are disease-modifying therapies designed to treat EOAD. They are designed to target beta-amyloid pathology, although the decree of clinical benefit remains modest and continues to be evaluated (Alkhalifa, 2025). EOAD accounts for a smaller cohort of Alzheimer's cases in contrast to late-onset but presents highly unique, social, and biological features (Gaxiola, 2024). In the past, clinical trial representation has faced several barriers. Trials have struggled with a lack of racial, ethnic, and socioeconomic diversity as well as underrepresentation of younger patients (Wise-Brown et al., 2024). Targeted platform trials and more inclusive recruitment strategies are emphasized by the Alzheimer's research community in order to actually address these representation deficiencies. Evidence specific to EOAD is still limited, and the applicability of those results to younger patients remain uncertain.

4.3 Non-Pharmacological Interventions

Non-pharmacological interventions are evidence-based, medication-free strategies that protect cognitive function, manage symptoms, and improve quality of life (Berg-Werger & Stewart, 2017).

Non-Pharmacological interventions are needed in order to manage EOAD and focus on promoting brain health through daily habits instead of consuming or taking medications. Such interventions may promote patient independence while improving adaptation to disease-related challenges (Li et al., 2022).

Cognitive interventions use targeted training and personalized adaptations to operate memory and problem-solving challenges in daily life (Wu et al., 2025). Structured lifestyle changes fight against the biological and vascular risk factors associated with EOAD progression (Arora, 2023). These lifestyle changes include physical exercise, dietary approaches, and sleep support. Support systems help EOAD patients process their diagnosis and reduce anxiety about the disease burden that is placed upon them (Kang et al., 2022). Activities such as music and art therapy as well as expressive writing awaken positive memories, helping patients process the realities of their diagnosis (Benett & Vasiiu, 2024).

5. THERAPEUTIC GAPS SPECIFIC TO EOAD

5.1 Underrepresentation in Clinical Trials

Clinical trials have historically failed to capture the distinct genetic, pathological, and psychological characteristics of individuals with EOAD, resulting in significant therapeutic gaps. Current research and trial designs frequently exclude or fail to capture the distinct genetic, pathological, and psychological realities of patients experiencing cognitive decline before the age of 65 (Szigeti & Doody, 2011). Underrepresentation in EOAD clinical trials limits medical advancements. Narrow trial demographics exclude diverse populations that are disproportionately affected by EOAD. This lack of diversity creates blind spots regarding the safety and efficacy of emerging treatments (Lin et al., 2026).

The drivers of underrepresentation in clinical trials include amyloid thresholds, restrictive eligibility criteria, biomarker limitations, and systemic barriers (Langbaum et al., 2024). In a study conducted by Breton M. Asken, Hispanic individuals had a greater amyloid burden than non-Hispanic participants (Asken et al., 2025). Marginalized populations, like Hispanic and Black individuals, often show reports with lower levels of the amyloid protein in the early stages of the disease (Asken et al., 2025). Another operator is that many trials require participants to have English fluency, therefore excluding non-English speakers (Egleston et al., 2016). In addition, lack of access to specialized neurologists and burdensome trial protocols prevent many eligible minority patients from joining in (Hamel et al., 2016).

5.2 Lack of Age-Specific Guidelines

A key criteria for EOAD is experiencing symptom onset prior to the age of 65 (Mendez, 2017). Since it affects younger individuals in their most active years, the condition presents unique challenges. As of now, there is a distinct lack of age-specific guidelines and dedicated treatment protocols for this demographic (Griffin et al., 2024).

Alzheimer's disease guidelines are heavily designed for LOAD, as the vast majority of cases occur in older adults (Jack et al., 2024). Moreover, EOAD frequently presents with non-memory symptoms such as aphasia, executive dysfunction, or visuospatial issues (Mendez et al., 2012). Standard neuropsychological tests are often not appropriately validated for younger populations. Since standalone EOAD protocols are absent, neurologists adapt standard Alzheimer's care to fit the unique psychosocial and medical needs of younger patients (Mendez, 2018). These include disease-modifying therapies, symptomatic medications, and multimodal lifestyle interventions (Wu & Fuh, 2025)

5.3 Employment and Legal Protection Gaps

EOAD as a whole affects a person's ability to work, but it is still protected under disability laws like the American Disabilities Act (ADA) (Harris et al., 2019). Despite being shielded by the ADA, structural gaps are still present since the disease's rapid cognitive decline prompts individuals to leave their jobs (Jost & Kujach, 2025). Managing EOAD in the workplace demands balancing between legal protections, securing accommodations, and grasping the limitations as well as the restrictions of present policies (Harris et al., 2019).

Under the American Disabilities Act, qualified individuals with EOAD are legally protected from workplace discrimination and termination that is solely based on their diagnosis (Harris et al., 2019). However, employment gaps persist as a pervasive reality (Park et al., 2025). Studies show that a significant portion of affected individuals experience declining work performance and leave their jobs within one year of diagnosis, often leading to forced early retirement (Sakata & Okumara, 2017). In a study conducted by Nobuo Sakata and Yasuyuki Okumara, 143 employees that had EOAD were analyzed, and after 600 days after their diagnoses, most of them left their jobs (Sakata & Okumara, 2017). These findings illustrate the occupational consequences of EOAD, demonstrating how rapid cognitive decline can reduce workforce participation despite existing legal protections.

5.4 Caregiver Support Deficits

Caring for EOAD patients introduces unique deficits in support, typically compounded by career interruption and intensive care needs (Vu et al., 2022). Caregivers often face a dual crisis: unexpected out-of-pocket costs and the severe emotional strain of juggling active, younger households with caregiving (Caldera, 2025). In EOAD, financial vulnerability often develops years before clinicians formally diagnose clinical symptoms (Gresenz et al., 2024). It manifests primarily through impaired financial decision-making, missed bill payments, declining credit scores, and heightened susceptibility to financial exploitation and scams (Gresenz et al., 2024).

Younger caregivers of individuals with EOAD face severe support deficits because medical and community services typically target older populations (Gibson et al., 2014). Since this condition impacts individuals under the age of 65, younger caregivers frequently juggle demanding careers and mounting financial pressure (Honda et al., 2025). Many standard eldercare and dementia programs exclude those under 65, leaving younger caregivers without access to age-appropriate day programs, respite care, or

legal/financial planning assistance (Sobers et al., 2025). Caregivers of individuals with early-onset Alzheimer's ideas frequently report that coordinating care comes with a major source of stress since they must balance caregiving responsibilities with work and family obligations (van Vliet et al., 2011).

6. CONCLUSION

Early-onset Alzheimer's Disease (EOAD) represents a distinct clinical and socioeconomic crisis that demands an immediate shift from passive management to systemic action. By striking individuals during their peak productive years, EOAD exposes critical vulnerabilities across global healthcare systems. To reduce the profound diagnostic delays, misdiagnoses, and lack of specialized tools that currently characterize the disease, the medical community must address three critical pillars. First, the healthcare system needs to bridge critical knowledge gaps by resolving the diagnostic uncertainties between atypical EOAD presentations and psychiatric conditions such as burnout or depression. Simultaneously, researchers ought to prioritize the development of age-specific biomarkers, digital cognitive screening tools, and disease-modifying therapies tailored specifically for younger cohorts. Finally, healthcare systems and clinicians must implement practical changes by establishing updated diagnostic protocols as well as constructing patient-centric support networks. Ultimately, integrating advanced early-detection techniques with socioeconomic support may transform care from a framework of temporary relief into a permanent model that will indefinitely lift the burden on patients, families, and society as a whole.

REFERENCES

1. Agnello, L., Lo Sasso, B., Bivona, G., Gambino, C. M., Giglio, R. V., Iacolino, G., ... & Ciaccio, M. (2021). Neurogranin as a reliable biomarker for synaptic dysfunction in Alzheimer's disease. *Diagnostics*, 11(12), 2339. <https://doi.org/10.3390/diagnostics11122339>
2. Alkhalifa, A., et al. (2025). Anti-amyloid monoclonal antibodies for Alzheimer's disease: Evidence, ARIA risk, and precision patient selection. *Frontiers in Aging Neuroscience*, 17. <https://doi.org/10.3389/fnagi.2025.12470750>
3. Altomare, D., et al. (2023). Clinical effect of early versus late amyloid positron emission tomography in memory clinic patients. *JAMA Network Open*, 6(5), e2314378. <https://doi.org/10.1001/jamanetworkopen.2023.14378>
4. Arora, S., et al. (2023). Diet and lifestyle impact the development and progression of Alzheimer's dementia. *Nutrients*, 15(12), 2698. <https://doi.org/10.3390/nu15122698>
5. Arendt, T. (2009). Synaptic degeneration in Alzheimer's disease. *Acta Neuropathologica*, 118(1), 167–179. <https://doi.org/10.1007/s00401-009-0536-x>
6. Asken, B. M., et al. (2025). Sex and ethnicity in early-onset Alzheimer's disease biomarkers and global function. *Alzheimer's & Dementia*. <https://doi.org/10.1002/alz.12340424>
7. Bagaria, J., et al. (2022). Genetics, functions, and clinical impact of presenilin-1 (PSEN1) gene. *Cureus*, 14, e29393. <https://doi.org/10.7759/cureus.29393>

8. Barnett, K., et al. (2024). How the arts heal: A review of the neural mechanisms behind the therapeutic effects of creative arts on mental and physical health. *Frontiers in Psychology*, 15. <https://doi.org/10.3389/fpsyg.2024.11480958>
9. Bettcher, B. M., et al. (2018). CSF and plasma levels of inflammation differentially relate to CNS markers of Alzheimer's disease pathology and neuronal damage. *Journal of Alzheimer's Disease*, 62(1), 385–397. <https://doi.org/10.3233/JAD-170602>
10. Berg-Werger, M., & Stewart, D. B. (2017). Non-pharmacologic interventions for persons with dementia. *Missouri Medicine*, 114(2), 116–119.
11. Bharadwaj, P. R., et al. (2009). A β aggregation and possible implications in Alzheimer's disease pathogenesis. *Journal of Cellular and Molecular Medicine*, 13(3), 412–421.
12. Birks, J. (2006). Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database of Systematic Reviews*, 2006(1), CD005593. <https://doi.org/10.1002/14651858.CD005593>
13. Bouter, C., et al. (2019). 18F-FDG PET detects drastic changes in brain metabolism in the Tg4-42 model of Alzheimer's disease. *Frontiers in Aging Neuroscience*, 10, 425. <https://doi.org/10.3389/fnagi.2018.00425>
14. Caldera, S., et al. (2025). Financial pressures of family caregiving. *Journal of Alzheimer's Disease*.
15. Chapleau, M., et al. (2022). The role of amyloid PET in imaging neurodegenerative disorders: A review. *Journal of Nuclear Medicine Technology*, 50(3), 204–211.
16. Cho, H., et al. (2024). Amyloid and tau PET in early-onset Alzheimer's disease: Baseline data from the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS). *Alzheimer's & Dementia*.
17. Crimins, J. L., et al. (2013). The intersection of amyloid beta and tau in glutamatergic synaptic dysfunction and collapse in Alzheimer's disease. *Ageing Research Reviews*, 12(3), 757–763.
18. Crutch, S. J., Schott, J. M., Rabinovici, G. D., et al. (2017). Consensus classification of posterior cortical atrophy. *Alzheimer's & Dementia*, 13(8), 870–884. <https://doi.org/10.1016/j.jalz.2017.01.014>
19. de la Vega, M. P., et al. (2021). The Uppsala APP deletion causes early-onset autosomal dominant Alzheimer's disease by altering APP processing and increasing amyloid- β fibril formation. *Science Translational Medicine*, 13(606), eabc6184. <https://doi.org/10.1126/scitranslmed.abc6184>
20. Dehbozorgi, B., et al. (2022). Barriers to family involvement in the care of patients with chronic mental illnesses: A qualitative study. *BMC Psychiatry*, 22, 700. <https://doi.org/10.1186/s12888-022-04325-7>
21. D'Alessandro, M., et al. (2025). Mitochondrial dysfunction in Alzheimer's disease. *Mechanisms of Ageing and Development*. <https://doi.org/10.1016/j.mad.2025.112360>
22. Griffin, P., et al. (2024). Developments in understanding early-onset Alzheimer's disease. *Brain Communications*, 6(1), fcae019. <https://doi.org/10.1093/braincomms/fcae019>
23. Egleston, B. L., et al. (2015). Characteristics of clinical trials that require participants to be fluent in English. *Clinical Trials*, 12(6), 618–626. <https://doi.org/10.1177/1740774515609609>
- 24.

25. Elliott, V., et al. (2019). Health-related stigma of noncommunicable neurological disease in rural adult populations: A scoping review. *Health & Social Care in the Community*, 27(4), e158–e188. <https://doi.org/10.1111/hsc.12677>
26. Fakorede, S., et al. (2025). Dual impact of neuroinflammation on cognitive and motor impairments in Alzheimer's disease. *Frontiers in Aging Neuroscience*. <https://doi.org/10.3389/fnagi.2025.12130662>
27. Filippi, M., et al. (2026). Anti-amyloid therapies and the transformation of Alzheimer's care pathways: Early lessons from the frontline. *Alzheimer's & Dementia*. <https://doi.org/10.1002/alz.12925121>
28. Galilee, J., et al. (2025). Facets of language performance in early-onset and late-onset Alzheimer's disease dementia. *Alzheimer's & Dementia*. <https://doi.org/10.1002/alz.40990522>
29. Gibson, A., et al. (2014). Exploring the service and support needs of families with early-onset Alzheimer's disease. *Dementia*, 13(6), 806–824. <https://doi.org/10.1177/1471301213482258>
30. Giebel, C., et al. (2024). A systematic review on the evidence of misdiagnosis in dementia and its impact on accessing dementia care. *Age and Ageing*, 53(11), afae263. <https://doi.org/10.1093/ageing/afae263>
31. Goate, A. M., et al. (2017). Genetics of β -amyloid precursor protein in Alzheimer's disease. *Cold Spring Harbor Perspectives in Medicine*, 7(6), a024539. <https://doi.org/10.1101/cshperspect.a024539>
32. Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., Ogar, J. M., Rohrer, J. D., Black, S., Boeve, B. F., Manes, F., Dronkers, N. F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B. L., Knopman, D. S., Hodges, J. R., Mesulam, M. M., & Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology*, 76(11), 1006–1014. <https://doi.org/10.1212/WNL.0b013e31821103e6>
33. Gulyaeva, N. V., et al. (2025). The potential regulators of amyloidogenic pathway of APP processing in Alzheimer's disease. *International Journal of Molecular Sciences*, 26. <https://doi.org/10.3390/ijms261212292>
34. Hamel, L. M., et al. (2016). Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. *Cancer Control*, 23(4), 327–337. <https://doi.org/10.1177/107327481602300404>
35. Hammers, D. B., et al. (2024). Profiling baseline performance on the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) cohort near the midpoint of data collection. *Alzheimer's & Dementia*, 20(Suppl. 16). <https://doi.org/10.1002/alz.10806768>
36. Henstridge, C. M., et al. (2016). Synaptic pathology: A shared mechanism in neurological disease. *Ageing Research Reviews*, 28, 72–84. <https://doi.org/10.1016/j.arr.2016.04.005>
37. Honda, A., et al. (2025). Impact of financial burden on family caregivers of older adults using long-term care insurance services. *BMC Geriatrics*. <https://doi.org/10.1186/s12877-025-12511701>
38. Howe, E. G. (2012). Informed consent, participation in research, and the Alzheimer's patient. *Innovations in Clinical Neuroscience*, 9(5–6), 47–51.

39. Illán-Gala, I., et al. (2018). Challenges associated with biomarker-based classification systems for Alzheimer's disease. *Journal of Alzheimer's Disease*, 64(S1), S3–S14.
<https://doi.org/10.3233/JAD-179907>
40. Jones, D. (2025). Atypical presentations of Alzheimer's disease. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12175143/>
41. Jost, Z. (2025). Understanding cognitive decline in aging: Mechanisms and mitigation strategies – A narrative review. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12009036/>
42. Kalampokini, S. (2021). The Greek variant in APP gene: The phenotypic spectrum of APP mutations. National Library of Medicine. <https://pubmed.ncbi.nlm.nih.gov/34830236/>
43. Kang, L. (2022). Lifestyle mental wellbeing for the primary care visit. National Library of Medicine. <https://www.ncbi.nlm.nih.gov/books/NBK587344/>
44. Kim, S. (2015). Ethics of genetic and biomarker test disclosures in neurodegenerative disease prevention trials. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC4395889/>
45. Kuo-Wu, C. (2025). A 2025 update on treatment strategies for the Alzheimer's disease spectrum. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12637128/>
46. Ioannou, K. (2024). Tau PET positivity predicts clinically relevant cognitive decline driven by Alzheimer's disease compared to comorbid cases: Proof of concept in the ADNI study. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC11746147/>
47. Kalampokini, S. (2021). The Greek variant in APP gene: The phenotypic spectrum of APP mutations. National Library of Medicine. <https://pubmed.ncbi.nlm.nih.gov/34830236/>
48. Kvello-Alme, M. (2021). Time to diagnosis in young onset Alzheimer's disease: A population-based study from Central Norway. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC8461696/>
49. Langbaum, J. (2024). Recommendations to address key recruitment challenges of Alzheimer's disease clinical trials. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9911558/>
50. Lanoiselée, H.-M. (2017). APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. *PLOS Medicine*.
<https://doi.org/10.1371/journal.pmed.1002270>
51. Lavis, S. (2020). Increased microglial activation in patients with Parkinson disease using [18F]-DPA714 TSPO PET imaging. National Library of Medicine. <https://pubmed.ncbi.nlm.nih.gov/33242662/>
52. Leochico, C. F. D. (2025). A novel PSEN2 mutation in amnesic early-onset Alzheimer's disease (EOAD): A familial case series. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12198541/>
53. Lepennetier, G. (2019). Cytokine and immune cell profiling in the cerebrospinal fluid of patients with neuro-inflammatory diseases. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6857241/>

54. Levin, J. (2023). Testing the amyloid cascade hypothesis: Prevention trials in autosomal dominant Alzheimer disease. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9399299/>
55. Li, X. (2022). Non-drug therapies for Alzheimer's disease: A review. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9837368/>
56. Lin, C.-Y. (2025). Global trends in prevalence, disability adjusted life years, and risk factors for early onset dementia from 1990 to 2021. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12008207/>
57. Lin, Z. (2026). Racial and ethnic reporting and representation in US Alzheimer clinical trials. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC13032159/>
58. Liu, Y. (2022). Clinical characteristics and genotype-phenotype correlation analysis of familial Alzheimer's disease patients with pathogenic/likely pathogenic amyloid protein precursor mutations. *Frontiers in Aging Neuroscience*. <https://doi.org/10.3389/fnagi.2022.1013295>
59. Margetis, K. (2025). Physiology, cerebral spinal fluid. National Library of Medicine. <https://www.ncbi.nlm.nih.gov/books/NBK519007/>
60. Martín-Maestro, P., et al. (2017). Mitophagy failure in fibroblasts and iPSC-derived neurons of Alzheimer's disease-associated presenilin 1 mutation. *Frontiers in Molecular Neuroscience*, 10, 291. <https://doi.org/10.3389/fnmol.2017.00291>
61. Martinez, D. (2025). Uncovering barriers to early diagnosis of Alzheimer's disease: A European perspective. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12715703/>
62. Mendez, M. F. (2012). Nonamnesic presentations of early-onset Alzheimer's disease. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC3625669/>
63. Mendez, M. F. (2019). Early-onset Alzheimer disease and its variants. *Continuum (Minneapolis, Minn.)*, 25(1), 34–51. <https://doi.org/10.1212/CON.0000000000000687>
64. Mendez, Mario F. (2018, May 1). Early-Onset Alzheimer's Disease. National Library of Medicine. Retrieved May 25, 2-26, from <https://pmc.ncbi.nlm.nih.gov/articles/PMC5407192/>.
65. Minculas, D. (2023). Pharmacotherapy evolution in Alzheimer's disease: Current framework and relevant directions. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9818415/>
66. Na Lee, H. (2021). Molecular characteristics of amyloid precursor protein (APP) and its effects in cancer. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC8125876/>
67. Nan, H. (2025). Identification and characterization of variants in PSEN1, PSEN2, and APP genes in Chinese patients with early-onset Alzheimer's disease. National Library of Medicine. <https://pubmed.ncbi.nlm.nih.gov/40016812/>
68. Nilsson, J. (2024). Cerebrospinal fluid biomarker panel of synaptic dysfunction in Alzheimer's disease and other neurodegenerative disorders. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC10102247/>
69. Omar, S. (2020). Advantages and pitfalls in fluid biomarkers for diagnosis of Alzheimer's disease. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC7563364/>
70. Orobets, K. S. (2023). Amyloid precursor protein and Alzheimer's disease. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC10573485/>

71. Pais, M. (2020). Early diagnosis and treatment of Alzheimer's disease: New definitions and challenges. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC7430379/>
72. Park, H. (2025). Job loss and early-onset dementia risk in middle-aged adults: A longitudinal study. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12750296/>
73. Parsons, C. (2013). Memantine and cholinesterase inhibitors: Complementary mechanisms in the treatment of Alzheimer's disease. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC3753463/>
74. Peeters, G. (2021). Sex differences in the incidence and prevalence of young-onset Alzheimer's disease: A meta-analysis. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9290036/>
75. Pérez-Martínez, D. (2025). Uncovering barriers to early diagnosis of Alzheimer's disease: A European perspective. National Library of Medicine. <https://pubmed.ncbi.nlm.nih.gov/41425084/>
76. Pierron, L. (2025). Lessons learned from 30 years of presymptomatic testing in Huntington disease. ScienceDirect. <https://www.sciencedirect.com/science/article/pii/S003537872500582X>
77. Pontecorvo, M. (2011). PET amyloid imaging as a tool for early diagnosis and identifying patients at risk for progression to Alzheimer's disease. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC3226273/>
78. Raphael, D. (2025). Neuropsychiatric symptoms in mild cognitive impairment and early Alzheimer's disease: Clinical pattern and diagnostic implications. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12782946/>
79. Rawat, P. (2022). Phosphorylated tau in Alzheimer's disease and other tauopathies. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9654278/>
80. Roberts, J. (2021). Genetic testing for neurodegenerative diseases: Ethical and health communication challenges. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC7311284/>
81. Ryan, N. S. (2014). Correlating familial Alzheimer's disease gene mutations with clinical phenotype. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC3937872/>
82. Sakata, N. (2017). Job loss after diagnosis of early-onset dementia: A matched cohort study. PubMed. <https://pubmed.ncbi.nlm.nih.gov/29036820/>
83. Sarasija, S. (2018). Presenilin mutations deregulate mitochondrial Ca²⁺ homeostasis and metabolic activity causing neurodegeneration in *Caenorhabditis elegans*. eLife Sciences. <https://elifesciences.org/articles/33052>
84. Sidaappaji, K. K. (2021). Molecular mechanisms in Alzheimer's disease and the impact of physical exercise with advancements in therapeutic approaches. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC8222772/>
85. Sideman, A. (2022). Facilitators and barriers to dementia assessment and diagnosis: Perspectives from dementia experts within a global health context. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC8997042/>
86. Singh, R. (2026). Cholinesterase inhibitors. National Library of Medicine. <https://www.ncbi.nlm.nih.gov/books/NBK544336/>

87. Sobers, T. (2025). A systematic review of the needs of children and young people of a parent diagnosed with young-onset dementia: Informing a nursing intervention. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC13069222/>
88. Summer, C. (2026). Neurodegeneration: Tau protein and neurofibrillary tangles. Cell Signaling Technology. <https://blog.cellsignal.com/neurodegeneration-tau-protein-and-neurofibrillary-tangles>
89. Swerdlow, R. (2014). The Alzheimer's disease mitochondrial cascade hypothesis: Progress and perspectives. ScienceDirect. <https://www.sciencedirect.com/science/article/pii/S0925443913002895>
90. Sumontri, S. (2025). Utilizing ADMET analysis and molecular docking to elucidate the neuroprotective mechanisms of a cannabis-containing herbal remedy (Suk-Saiyasna) in inhibiting acetylcholinesterase. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC11989231/>
91. Szigeti, K. (2011). Should EOAD patients be included in clinical trials? National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC3109413/>
92. Tanner, J. (2021). Relationship between tau and cognition in the evolution of Alzheimer's disease: New insights from tau PET. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9364866/>
93. Tenenbaum, J. (2017). Beyond the Genetic Information Nondiscrimination Act: Ethical and economic implications of the exclusion of disability, long-term care and life insurance. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6354179/>
94. TCW, J. (2017). Genetics of β -amyloid precursor protein in Alzheimer's disease. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5453386/>
95. Tomiyama, T. (2020). APP Osaka mutation in familial Alzheimer's disease—Its discovery, phenotypes, and mechanism of recessive inheritance. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC7073033/>
96. Tsao, J. (2013). Genetic testing for early-onset Alzheimer's disease. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC10563974/>
97. Uwishema, O. (2024). Breaking barriers: Addressing inequities in Alzheimer's disease diagnosis and treatment in Africa. *Annals of Medicine & Surgery*. https://journals.lww.com/annals-of-medicine-and-surgery/fulltext/2024/09000/breaking_barriers_addressing_inequities_in.56.aspx
98. Valdez-Gaxiola, C. A. (2024). Early- and late-onset Alzheimer's disease: Two sides of the same coin? National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC11202866/>
99. VandeVrede, L. (2024). Clinical use of biomarkers in the era of Alzheimer's disease treatments. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC11775455/>
100. van Vliet, D., de Vugt, M. E., Bakker, C., Koopmans, R. T. C. M., & Verhey, F. R. J. (2011). Caregivers' perspectives on the pre-diagnostic period in early onset dementia: A long and winding road. *International Psychogeriatrics*, 23(9), 1393–1404. <https://doi.org/10.1017/S1041610211001013>
101. Varte, V. (2025). Early-onset Alzheimer's disease and amyloid precursor protein gene mutations. Springer Nature Link. <https://link.springer.com/article/10.1186/s13064-025-00203-y>

102. Verduzco-Aguirre, H. (2019). Implementation of diagnostic resources for cancer in developing countries: A focus on PET/CT. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6390832/>
103. Vu, M. (2022). Impact of Alzheimer's disease on caregivers in the United States. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC9392839/>
104. Wang, X. (2025). Unraveling the vicious cycle: Oxidative stress and neurotoxicity in neurodegenerative diseases. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12406095/>
105. Wattmo, C. (2017). Early- versus late-onset Alzheimer's disease in clinical practice: Cognitive and global outcomes over 3 years. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5580278/>
106. Wells, C. (2022). An overview of new and emerging technologies for early diagnosis of Alzheimer disease. National Library of Medicine.
107. Whitwell, J. (2024). Atypical clinical variants of Alzheimer's disease: Are they really atypical? National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC10933030/>
108. Wise-Brown, A. (2024). Promoting diversity in clinical trials: Insights from planning the ALUMNI AD study in historically underrepresented US populations with early symptomatic Alzheimer's disease. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC11490654/>
109. Yang, M. (2025). Ethnic disparities in patients with early-onset Alzheimer's disease (EOAD). National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC12734356/>
110. Zapata-Restrepo, L. M. (2025). Case of early onset Alzheimer's disease associated with a novel PSEN1 variant identified in Colombia. *Nature*. <https://www.nature.com/articles/s44400-025-00036-w>
111. Zhang, X. (2018). The early events that initiate β -amyloid aggregation in Alzheimer's disease. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6277872/>
112. Zhang, Z. (2025). Global, regional, and national burden of early-onset Alzheimer's disease and other dementias in young adults aged 40–64 years, 1990–2021: A population-based study. National Library of Medicine. <https://pmc.ncbi.nlm.nih.gov/articles/PMC11921012/>