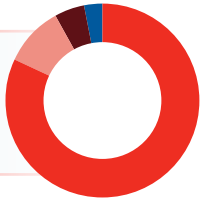
ALZHEIMER'S DISEASE (AD) FUNDAMENTALS

The Hidden Pathological Progression of AD

AD is a progressive neurodegenerative disorder that is thought to begin with the aberrant accumulation of amyloid plaques and neurofibrillary tangles (NFTs) in the brain, ultimately leading to cell death and increasingly debilitating cognitive, functional, and behavioral impairments.[2]

AD is the most common type of dementia, shown by percentage distribution of cases.[1]



- **60-80% AD**
- 5-10% Vascular dementia
- 5% Lewy body disease
- 3% Frontotemporal degeneration

>50% Mixed pathologies

AD Exists Along a Progressive Continuum[2-4]

Stages 1-2 — Preclinical AD

- Normal performance within expected range on objective cognitive tests
- Potential subjective cognitive decline or change in mood, anxiety, or motivation not explained by life events (Stage 2)
- Remains fully independent with no or minimal (Stage 2) functional impact on activities of daily living (ADLs)

Stage 3 — Mild cognitive impairment (MCI) due to AD

- Performance in the impaired/abnormal range on objective cognitive tests
- Performs ADLs independently, but functional impact on complex ADLs may be detectable

Stage 4 — Mild dementia due to AD

- Progressive cognitive and mild functional impairment on instrumental ADLs, with independence on basic ADLs

Stage 5 — Moderate dementia due to AD

- Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance

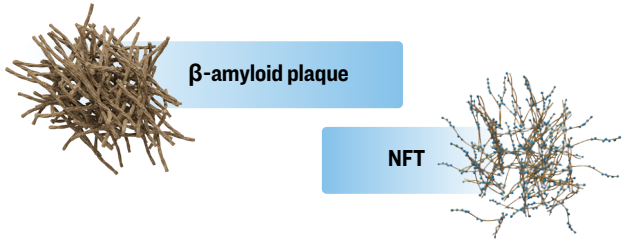
Stage 6 — Severe dementia due to AD

- Progressive cognitive and functional impairment, and complete dependence for basic ADLs

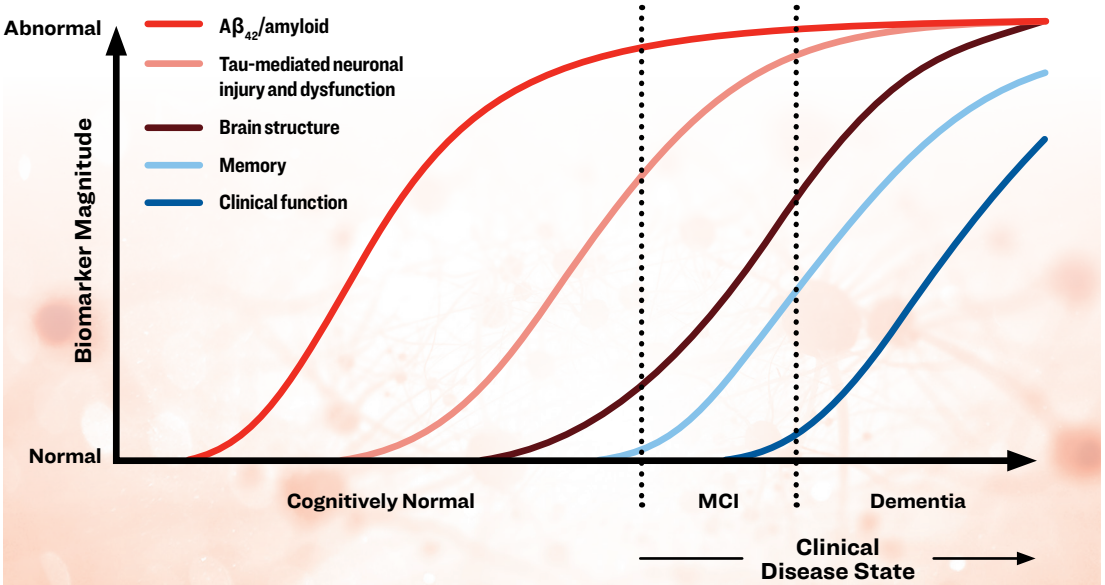
Neuropathological changes in AD are present in all stages from Stage 1 to Stage 6.

The Neuropathologic Changes of AD May Begin ~20 Years Before Clinical Symptoms[2,4-7]

Two primary hallmark neuropathologies characterize AD: extracellular β-amyloid plaques comprised of amyloid beta peptides, and intracellular neurofibrillary tangles (NFTs) comprised of aggregated hyperphosphorylated tau protein.[6]



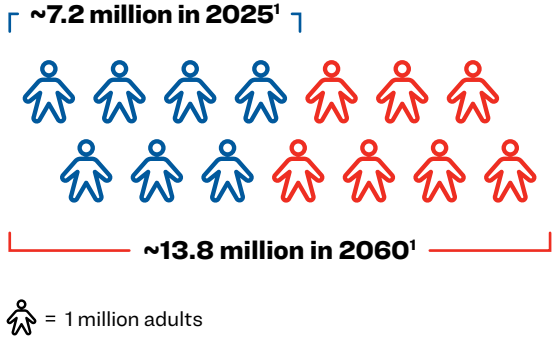
As the disease stages progress, neurodegenerative changes lag behind β-amyloid plaque and NFT accumulation.



Hypothetical model of dynamic biomarkers of the AD pathological cascade, beginning with the abnormal accumulation of amyloid and the subsequent accumulation of tau, which leads to MCI and eventually dementia. Modified from Jack CR Jr, et al.[7]

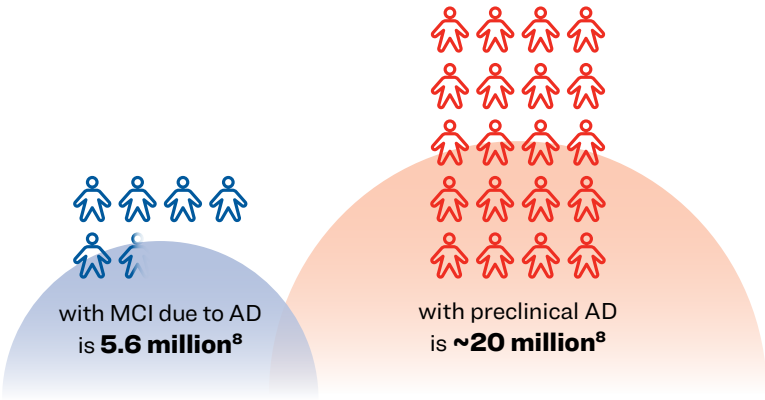
AD Is a Growing Healthcare Crisis[2]

The prevalence of AD dementia in adults aged 65 years and older is projected to almost double in the United States by 2060.[1]



Today millions more people are in the early stages of AD.

The estimated number of people in the United States aged 50 and older*



Explore AD's hidden story and learn more at: medical.lilly.com/us/diseases/cognitivehealth

*There are multiple methods for calculating the prevalence of AD. These estimates are based on individuals who were amyloid positive as determined by positron emission tomography or cerebrospinal fluid assays.[8]

1. Alzheimer's Association. *Alzheimers Dement*. 2025;21(4):e70235. **2.** Porsteinsson AP, et al. *J Prev Alzheimers Dis*. 2021;8(3):371-386. **3.** Jack CR, et al. *Alzheimers Dement*. 2018;14(4):535-562. **4.** Jack CR Jr, et al. *Alzheimers Dement*. 2024;20(8):5143-5169. **5.** McDade E, et al. *Alzheimers Dement (N Y)*. 2020;6(1):1-9. **6.** Aisen PS, et al. *Alzheimers Res Ther*. 2017;9(1):60. **7.** Jack CR Jr, et al. *Lancet Neurol*. 2013;12(2):207-216. **8.** Gustavsson A, et al. *Alzheimer's Dement*. 2023;19:658-670.

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