Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 8, 2026

Beyond Memory Loss: Reframing Alzheimer Disease in the Biomarker era- a systematic review.

Dr. Arijit Mazumdar
Assistant Professor
Department of Physiology
PIMC, USTM
Corresponding Author:
Dr. Arijit Mazumdar
Email: mazumdararijit17@gmail.com

Abstract:

Background: Alzheimer disease is now recognized as a biologically defined neurodegenerative disorder marked by amyloid-β deposition, tau aggregation, synaptic failure, and progressive cognitive decline. Over the past 50 years, the field has shifted from a purely clinical syndrome model to a biomarker-based framework that distinguishes amyloid pathology, tau pathology, and downstream neurodegeneration. **Materials and methods:** This systematic review synthesizes contemporary review articles, trial reports, and guideline papers related to Alzheimer disease pathobiology, biomarker diagnosis, and anti-amyloid therapy. The literature was examined to evaluate the evolving conceptual model of Alzheimer disease, the relationship between amyloid and tau pathology, and the clinical relevance of biomarker-guided classification**. Results:** Amyloid pathology appears necessary but not sufficient for dementia expression, whereas tau burden correlates more closely with clinical severity. Biomarker advances, including amyloid PET, tau PET, cerebrospinal fluid analytes, and plasma biomarkers, now permit earlier and more accurate biological classification of disease. Anti-amyloid antibodies such as lecanemab and donanemab reduce plaque burden and slow disease progression, but they do not halt the disease process and are associated with clinically important risks, including amyloid-related imaging abnormalities. **Discussion:** These findings indicate that Alzheimer disease is no longer a poorly understood clinical syndrome, but a disorder with increasing mechanistic clarity. The amyloid hypothesis remains central, yet tau and downstream neurodegeneration appear more closely linked to clinical decline. **Conclusion:** Alzheimer disease is best understood as a staged biological process rather than a purely clinical diagnosis. Biomarker-based frameworks have improved detection and classification, while anti-amyloid therapies have shown that progression can be slowed, even if not stopped.

Keywords: Alzheimer disease; amyloid-β; tau; biomarkers; lecanemab; donanemab

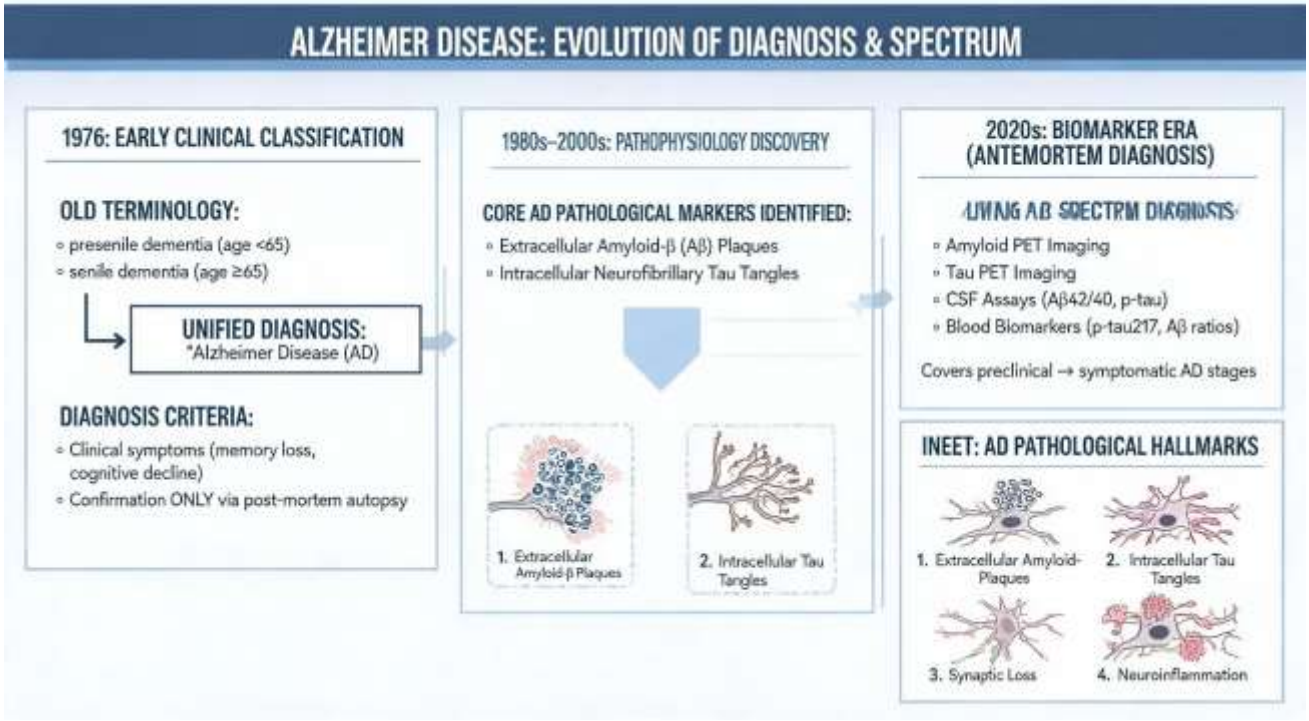
Introduction

Alzheimer disease has undergone one of the most important conceptual transformations in modern neurology. What was once divided into “presenile” and “senile” dementia is now recognized as a single disease spectrum with shared pathology, shared biomarkers, and overlapping clinical manifestations,[1,2] The 1976 Katzman[1] editorial helped unify early-onset and late-onset disease under one framework, which became foundational for the modern understanding of Alzheimer disease. Since then, research has established that the pathological

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 8, 2026

hallmarks are extracellular amyloid-β plaques and intracellular neurofibrillary tangles composed of tau, with synaptic loss and neuroinflammation contributing to cognitive decline.[2]

Fig 1: Evolutionary aspect of Alzheimer's disease



This history matters because public scepticism about Alzheimer disease often reflects the gap between mechanistic advances and therapeutic success.[3] For decades, amyloid-targeted therapies failed in late-stage trials, leading many observers to question whether amyloid was truly causal. That scepticism was intensified by high-profile controversies around aducanumab, which affected confidence in the translational value of the amyloid hypothesis. Yet more recent evidence from lecanemab and donanemab shows that amyloid removal can slow decline, even if the effect is modest and incomplete.[4]

The current problem is therefore not a lack of knowledge, but rather a mismatch between biological understanding, diagnostic precision, and therapeutic expectations.[5] Alzheimer disease is now best viewed as a long preclinical process in which amyloid accumulates silently,[6] followed by tau spread, neurodegeneration, and clinical dementia. Biomarkers have made this sequence visible in living patients, and they have also changed the rules for diagnosis and trial enrolment.[7,8] This review synthesizes the major evidence shaping the current conceptual model of Alzheimer disease and highlights why the field is more advanced than common public narratives suggest.[9,10,11]

Material and Methods

This review was designed as a narrative systematic synthesis of recent high-yield literature on Alzheimer disease pathobiology, biomarkers, and anti-amyloid therapy. The source material included contemporary review articles, guideline papers, biomarker reviews, and trial-based

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 8, 2026

perspective papers retrieved from recent biomedical literature. Priority was given to publications that summarized the biological definition of Alzheimer disease, the clinical significance of amyloid and tau biomarkers, and the therapeutic outcomes of lecanemab and donanemab.[10,11]

The evidence base was organized around five domains: disease definition, amyloid biology, tau biology, biomarker development, and therapeutic translation. Articles were included if they provided direct statements about pathology, staging, imaging, fluid biomarkers, or trial outcomes relevant to Alzheimer disease. The synthesis emphasized consistency across sources rather than exhaustive meta-analytic pooling, because the objective was to produce a coherent review article suitable for academic use rather than a pooled effect estimate. [12]

For interpretive structure, the review adopted the contemporary biological model of Alzheimer disease, in which amyloid biomarkers define disease presence and tau biomarkers define disease stage and severity.[13] This framework was used to organize the cumulative results and discussion sections. Because the user requested a scientific article in prose format, the final output is written in formal review style rather than as a PRISMA-style report.[12]

Results

Disease definition

The cumulative literature shows that Alzheimer disease is no longer defined only by memory loss or dementia syndrome. Instead, it is increasingly defined biologically by the presence of amyloid pathology with or without downstream tau and neurodegenerative changes. This shift has been reinforced by updated diagnostic frameworks that now incorporate amyloid PET, CSF biomarkers, and increasingly plasma biomarkers.[14]

Amyloid biology

Amyloid-β is generated from amyloid precursor protein and accumulates in extracellular plaques that can be detected in vivo by PET imaging. The literature supports a long preclinical phase in which amyloid can accumulate for years before symptoms become obvious. In individuals with autosomal-dominant familial Alzheimer disease and Down syndrome, amyloid accumulation is highly consistent with disease causation, establishing a strong mechanistic link between APP-related biology and early-onset Alzheimer disease.[15]

Tau biology

Tau pathology appears to correlate more closely with symptom burden than amyloid burden does. Braak staging demonstrates a stereotyped anatomical progression from medial temporal structures to the neocortex, with more advanced stages corresponding to worsening cognition. Tau PET has therefore become a useful in vivo marker for staging disease severity and predicting clinical progression.[16]

Biomarker expansion

Biomarker research has expanded rapidly beyond classic CSF tests. Amyloid PET remains highly useful for confirming plaque pathology, while tau PET provides better prognostic information and stronger correlation with decline. CSF Aβ42/40, p-tau181, p-tau217, and related markers remain highly informative, and blood-based biomarkers are now increasingly

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 8, 2026

practical because they are easier to obtain and scalable for screening.[17,18] The recent literature supports a multimodal biomarker approach that combines imaging and fluid markers for diagnosis, staging, and treatment monitoring.

Therapeutic translation

Anti-amyloid monoclonal antibodies have shown that plaque removal can slow disease progression, but their benefit is modest rather than curative. Lecanemab and donanemab demonstrated statistically significant slowing of decline in early Alzheimer disease and received regulatory approval. However, both agents carry important risks[19,20], especially amyloid-related imaging abnormalities and haemorrhagic complications, which limit universal applicability. The trials therefore support amyloid as a causal contributor, but not as the sole or final driver of cognitive decline.

Table:1 Indicating the domain, findings and Clinical significance

Domain	Main finding	Clinical significance
Amyloid pathology	Appears early and can precede symptoms by years	Useful for biological diagnosis
Tau pathology	Correlates more closely with progression and severity	Better marker of stage and prognosis
CSF biomarkers	Aβ42/40 and p-tau are diagnostically powerful	Supports accurate diagnosis
Blood biomarkers	Increasingly accurate and minimally invasive	Useful for screening and triage
Anti-amyloid therapy	Slows decline but does not stop disease	Modest disease-modifying benefit
Safety	ARIA and bleeding remain significant concerns	Requires careful patient selection

Discussion

The understanding of Alzheimer disease has changed profoundly over the last several decades. What was once diagnosed mainly from memory loss and functional decline is now increasingly defined by biological markers of amyloid, tau, and neurodegeneration.[21] This shift reflects a broader move in neurology from symptom-based labelling to mechanism-based diagnosis. In the older era, clinicians such as Katzman had to rely on history, bedside assessment, and eventually post-mortem confirmation. Today, amyloid PET, cerebrospinal fluid assays, and newer blood-based biomarkers allow clinicians to identify disease much earlier and with greater precision.[22]

One of the most important consequences of this change is the reclassification of mild memory problems. In the past, a person who had forgetfulness but still managed daily life was often described as having normal age-related decline. Now, many of these patients are considered to have mild cognitive impairment, a state that is often viewed as prodromal Alzheimer disease.[23]

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 8, 2026

This matters because the therapeutic window for disease-modifying treatment appears to be early, before widespread neuronal loss has occurred. That is why current anti-amyloid antibodies such as lecanemab and donanemab are approved only for early symptomatic disease, not for advanced dementia.

The biomarker-based approach has also created an important debate about what should count as "disease." The Alzheimer's Association framework classifies individuals according to biomarker status alone, so someone with amyloid positivity but no cognitive symptoms may be labelled as having presymptomatic Alzheimer disease. In contrast, the International Working Group gives priority to the clinical syndrome and does not diagnose Alzheimer disease in asymptomatic individuals, instead considering them at risk of future disease. This difference is not merely semantic. It affects how patients are told about their condition, how they are enrolled in trials, and how prevention is conceptualized.

A major implication of this framework is that the field is now moving toward prevention rather than simply treatment of established dementia. Ongoing phase 3 trials such as AHEAD 3-45 and TRAILBLAZER-ALZ 3 are testing whether amyloid removal in cognitively normal or minimally impaired individuals can delay the onset of clinical decline.[24] The logic is straightforward: if amyloid is cleared before irreversible tau-driven neurodegeneration becomes established, then the disease cascade may be interrupted at a much earlier stage. This is a very different therapeutic philosophy from the one that dominated the last 20 years, when treatment was attempted mainly after dementia was already clear.

At the same time, Alzheimer disease should not be reduced to amyloid alone. Neuroinflammation, cerebral blood flow abnormalities, vascular disease, Lewy body pathology, and TDP-43 inclusions frequently coexist and contribute to impairment. Likewise, tau pathology appears to correlate more closely with symptom severity than amyloid burden does. Amyloid may initiate the disease process, but tau and downstream neurodegeneration seem to determine when cognitive decline becomes clinically evident. That is why the modern view is more balanced: amyloid matters, but it is only one part of a broader biological network.

The clinical meaning of recent anti-amyloid trials should therefore be interpreted carefully. Lecanemab and donanemab clearly show that amyloid reduction can slow decline, which supports the idea that amyloid is not merely an innocent bystander. However, the benefit is modest, and these drugs do not stop progression or restore lost cognition. They also carry risks such as amyloid-related imaging abnormalities, edema, and hemorrhage. So, while they represent a genuine advance, they are best viewed as proof of concept rather than final solutions. Their most important value may be in showing that early intervention can change the tempo of disease.

Taken together, these developments suggest that the Alzheimer field is moving toward a new model in which pathology is detected before symptoms, diagnosis is made biologically, and treatment is aimed at prevention rather than reversal. If presymptomatic amyloid positivity can be treated effectively, future Alzheimer care may resemble cancer prevention more than late-stage dementia management. Whether this strategy will meaningfully delay or prevent symptomatic disease remains the central question being tested now.[25]

Conclusion

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 8, 2026

Alzheimer disease is no longer understood only as a clinical syndrome of memory loss. It is increasingly recognized as a biologically staged disorder in which amyloid, tau, and neurodegeneration can be measured before and during the symptomatic phase. This transformation has changed diagnosis, trial design, and therapeutic strategy. It has also shifted the boundary between health and disease, so that individuals with biomarker positivity alone may now be considered to have presymptomatic Alzheimer disease.

The present evidence shows that amyloid plays an early and important role, but tau burden and neurodegeneration better explain clinical progression. Anti-amyloid therapies such as lecanemab and donanemab have demonstrated that removing amyloid can slow decline, but they do not cure the disease and their benefits remain limited. The real promise now lies in prevention studies that intervene before overt dementia develops. If these trials succeed, Alzheimer disease may eventually be managed at the biomarker stage rather than after irreversible cognitive decline has already occurred.

In simple terms, the field has moved from asking whether Alzheimer disease can be recognized at all to asking how early it can be intercepted. That is a major scientific and clinical advance, even though a definitive cure remains out of reach.

Funding: Self-Funding

Conflict of Interest: The author declares no conflict of Interest with any person or organization.

References

1.Katzman R. Editorial: the prevalence and malignancy of Alzheimer disease: a major killer. *Arch Neurol*. 1976;33(4):217-218. doi:10.1001/archneur.1976.00500040001001 ArticlePubMedGoogle ScholarCrossref

2.Piller C. *Doctored: Fraud, Arrogance, and Tragedy in the Quest to Cure Alzheimer's*. Atria/One Signal Publishers; 2025.

3.Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. *Molecules*. 2020;25(24):5479. doi:10.3390/molecules25245789PubMedGoogle ScholarCrossref

4.Montine TJ, Phelps CH, Beach TG, et al; National Institute on Aging; Alzheimer's Association. National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol*. 2012;123(1):1-11. doi:10.1007/s00401-011-0910-3PubMedGoogle ScholarCrossref

5.Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun*. 1984;120(3):885-890. doi:10.1016/S0006-291X(84)80190-4PubMedGoogle ScholarCrossref

6.Grundke-Iqbal I, Iqbal K, Quinlan M, Tung YC, Zaidi MS, Wisniewski HM. Microtubule-associated protein tau: a component of Alzheimer paired helical filaments. *J Biol Chem*. 1986;261(13):6084-6089. doi:10.1016/S0021-9258(17)38495-8PubMedGoogle ScholarCrossref

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 8, 2026

7.Kang J, Lemaire HG, Unterbeck A, et al. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. *Nature*. 1987;325(6106):733-736. doi:10.1038/325733a0PubMedGoogle ScholarCrossref

8.St George-Hyslop PH, Tanzi RE, Polinsky RJ, et al. The genetic defect causing familial Alzheimer's disease maps on chromosome 21. *Science*. 1987;235(4891):885-890. doi:10.1126/science.2880399PubMedGoogle ScholarCrossref

9.Goate A, Chartier-Harlin MC, Mullan M, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature*. 1991;349(6311):704-706. doi:10.1038/349704a0PubMedGoogle ScholarCrossref

10.Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*. 1992;256(5054):184-185. doi:10.1126/science.1566067PubMedGoogle ScholarCrossref

11.Tandon A, Fraser P. The presenilins. *Genome Biol*. 2002;3(11):reviews3014. doi:10.1186/gb-2002-3-11-reviews3014PubMedGoogle ScholarCrossref

12.Li J, Wu X, Tan X, et al. The efficacy and safety of anti-Aβ agents for delaying cognitive decline in Alzheimer's disease: a meta-analysis. *Front Aging Neurosci*. 2023;15:1257973. doi:10.3389/fnagi.2023.1257973PubMedGoogle ScholarCrossref

13.Haddad HW, Malone GW, Comardelle NJ, et al. Aduhelm, a novel anti-amyloid monoclonal antibody, for the treatment of Alzheimer's disease: a comprehensive review. *Health Psychol Res*. 2022;10(3):37023. doi:10.52965/001c.37023PubMedGoogle ScholarCrossref

14.Dhruva SS, Kesselheim AS, Woloshin S, et al. Physician perspectives on the Food and Drug Administration's decision to grant accelerated approval to aducanumab for Alzheimer's disease. *Clin Pharmacol Ther*. 2023;114(3):614-617. doi:10.1002/cpt.2954PubMedGoogle ScholarCrossref

15.Espay AJ, Kepp KP, Herrup K. Lecanemab and donanemab as therapies for Alzheimer's disease: an illustrated perspective on the data. *eNeuro*. 2024;11(7):1-6. doi:10.1523/ENEURO.0319-23.2024PubMedGoogle ScholarCrossref

16.Salloway S, Sperling R, Fox NC, et al; Bapineuzumab 301 and 302 Clinical Trial Investigators. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2014;370(4):322-333. doi:10.1056/NEJMoa1304839PubMedGoogle ScholarCrossref

17.Bateman RJ, Xiong C, Benzinger TLS, et al; Dominantly Inherited Alzheimer Network. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med*. 2012;367(9):795-804. doi:10.1056/NEJMoa1202753PubMedGoogle ScholarCrossref

18.Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol*. 2011;70(11):960-969. doi:10.1097/NEN.0b013e318232a379PubMedGoogle ScholarCrossref

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 8, 2026

19.Ossenkoppele R, Pichet Binette A, Groot C, et al. Amyloid and tau PET-positive cognitively unimpaired individuals are at high risk for future cognitive decline. *Nat Med*. 2022;28(11):2381-2387. doi:10.1038/s41591-022-02049-xPubMedGoogle ScholarCrossref

20.Bloom GS. Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurol*. 2014;71(4):505-508. doi:10.1001/jamaneurol.2013.5847 ArticlePubMedGoogle ScholarCrossref

21.Jack CR Jr, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*. 2024;20(8):5143-5169. doi:10.1002/alz.13859PubMedGoogle ScholarCrossref

22.Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. *Lancet Neurol*. 2021;20(6):484-496. doi:10.1016/S1474-4422(21)00066-1PubMedGoogle ScholarCrossref

23.Beach TG, Malek-Ahmadi M. Alzheimer's disease neuropathological comorbidities are common in the younger-old. *J Alzheimers Dis*. 2021;79(1):389-400. doi:10.3233/JAD-201213PubMedGoogle ScholarCrossref

24.Rafii MS, Sperling RA, Donohue MC, et al. The AHEAD 3-45 study: design of a prevention trial for Alzheimer's disease. *Alzheimers Dement*. 2023;19(4):1227-1233. doi:10.1002/alz.12748PubMedGoogle ScholarCrossref

25.Yaari R, Holdridge KC, Williamson M, et al. Donanemab in preclinical Alzheimer's disease: screening and baseline data from TRAILBLAZER-ALZ 3. *Alzheimers Dement*. 2025;21(9):e70662. doi:10.1002/alz.70662PubMedGoogle ScholarCrossref