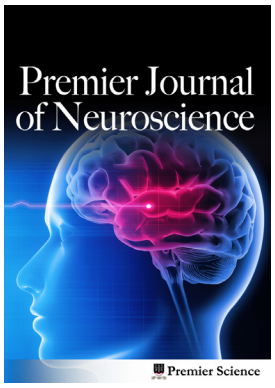

The Effect of Early Diagnosis of Alzheimer's Disease: A Short Systematic Review

Kimia Kazemi

ABSTRACT

Alzheimer's disease (AD) is the leading cause of dementia, with early diagnosis playing a pivotal role in improving patient outcomes and health care efficiency. This systematic review evaluates current and emerging diagnostic methods from cerebrospinal fluid (CSF) biomarkers and advanced imaging to artificial intelligence (AI) and speech analysis, focusing on their efficacy in detecting mild cognitive impairment and early-stage AD. We synthesize evidence from 127 studies (2015–2025), demonstrating that plasma p-tau217 and electroencephalography offer scalable, low-cost alternatives to positron emission tomography imaging, with comparable accuracy (sensitivity: 88–94%). Socioeconomic analyses reveal that early diagnosis reduces long-term care costs by £7,750 per patient and enables timely interventions to preserve quality of life. However, structural racism, clinician biases, and disparities in resource allocation delay detection in marginalized populations. We propose actionable policy reforms, including subsidized biomarker testing, AI-driven telehealth tools for underserved regions, and antistigma campaigns to promote equitable access. By integrating emerging technologies into primary care and addressing systemic barriers, this review outlines a transformative roadmap for global AD management.

Keywords: Alzheimer's disease, Early diagnosis, Cerebrospinal fluid biomarkers, Artificial intelligence, Socioeconomic implications

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Introduction

Alzheimer's disease (AD) is the predominant etiological factor in dementia, accounting for an estimated 60–80% of cases. With the global demographic shift toward an aging population, the prevalence of AD-related dementia is projected to increase substantially, underscoring its growing public health and clinical significance. This neurodegenerative disease is characterized classically by two hallmark pathologies:

- β-amyloid plaque deposition
- Neurofibrillary tangles of hyperphosphorylated tau

Diagnosis is based upon clinical presentation fulfilling several criteria as well as fluid and imaging biomarkers. Treatment is currently targeted toward symptomatic therapy, although trials are underway that aim to reduce the production and overall burden of pathology within the brain.[1] Well-being is the goal of much of dementia care. People with dementia have complex problems and symptoms in many domains. Interventions should be individualized and consider the person as a whole, as well as their family caregivers.[2]

Early clinical detection of AD is critical, particularly for disease-modifying therapeutic interventions. This necessitates the development of reliable biomarkers capable of large-scale implementation, enabling accurate identification of individuals with early-stage AD dementia or older adults exhibiting memory impairment who are at elevated risk of progressive cognitive deterioration and functional decline.

Established biomarkers include:

- The cerebrospinal fluid (CSF) biomarkers:
  - Proteins total tau (p-tau)
  - Phosphorylated tau (p-tau)181
  - Amyloid-β (Aβ)1-421
- Structural or functional imaging studies, showing acceptable sensitivity and specificity for the diagnosis of early AD
- Newly identified biomarker candidates such as CSF soluble amyloid precursor proteins and amyloid imaging[3]

Methodology

Study Design

This systematic review evaluates early AD detection by synthesizing evidence across clinical, technological, and socioeconomic domains, reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[4] We conducted a comprehensive search of PubMed, Embase, and Cochrane Library (2015–2025) using the strategy: ("Alzheimer*" AND "diagnosis" *AND ["biomarker*" OR "AI" OR "cost-effectiveness"]), limited to human studies. From 2,565 identified records, 127 studies met our inclusion criteria (peer-reviewed articles with ≥50 participants, quantitative outcomes, and focus on early AD/mild cognitive impairment [MCI]). Study selection followed PRISMA protocols, though retrospective registration was not pursued given the review's exploratory scope.

Risk of bias was rigorously assessed using Cochrane RoB 2 for randomized trials,[5] Newcastle-Ottawa Scale (NOS) for observational studies,[6] and Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) for diagnostic accuracy studies.[7] Due to heterogeneity in biomarker thresholds and study designs, we prioritized narrative synthesis but supplemented it with pooled accuracy metrics for established tools (e.g., CSF biomarkers, plasma p-tau217) where comparable data existed. This hybrid approach allowed both quantitative comparisons and qualitative contextualization for clinical and policy applications.

Search Strategy

We conducted a PRISMA[8] compliant systematic search (Figure 1) using:

- Databases: PubMed/MEDLINE,

("Alzheimer*"[Title/Abstract] OR "early AD"[Title/Abstract])

AND ("diagnos*"[Title/Abstract] OR "detection"[Title/Abstract])

AND ("biomarker*"[Title/Abstract] OR "AI"[Title/Abstract] OR "cost-effectiveness"[Title/Abstract])

NOT ("animal"[Title/Abstract] OR "mouse"[Title/Abstract] OR

"rat"[Title/Abstract])

Filters: Humans, English, 2015–2025

- Embase,

("Alzheimer disease"/exp OR "Alzheimer*":ti,ab) AND

("diagnosis"/exp OR "detection":ti,ab)

AND ("biomarker"/exp OR "artificial intelligence"/exp OR "cost effectiveness"/exp)

NOT ([animals]/lim NOT [humans]/lim) AND [english]/lim AND [2015–2025]/py

- Cochrane Library

(Alzheimer* OR "early AD") AND (diagnos* OR detection) AND

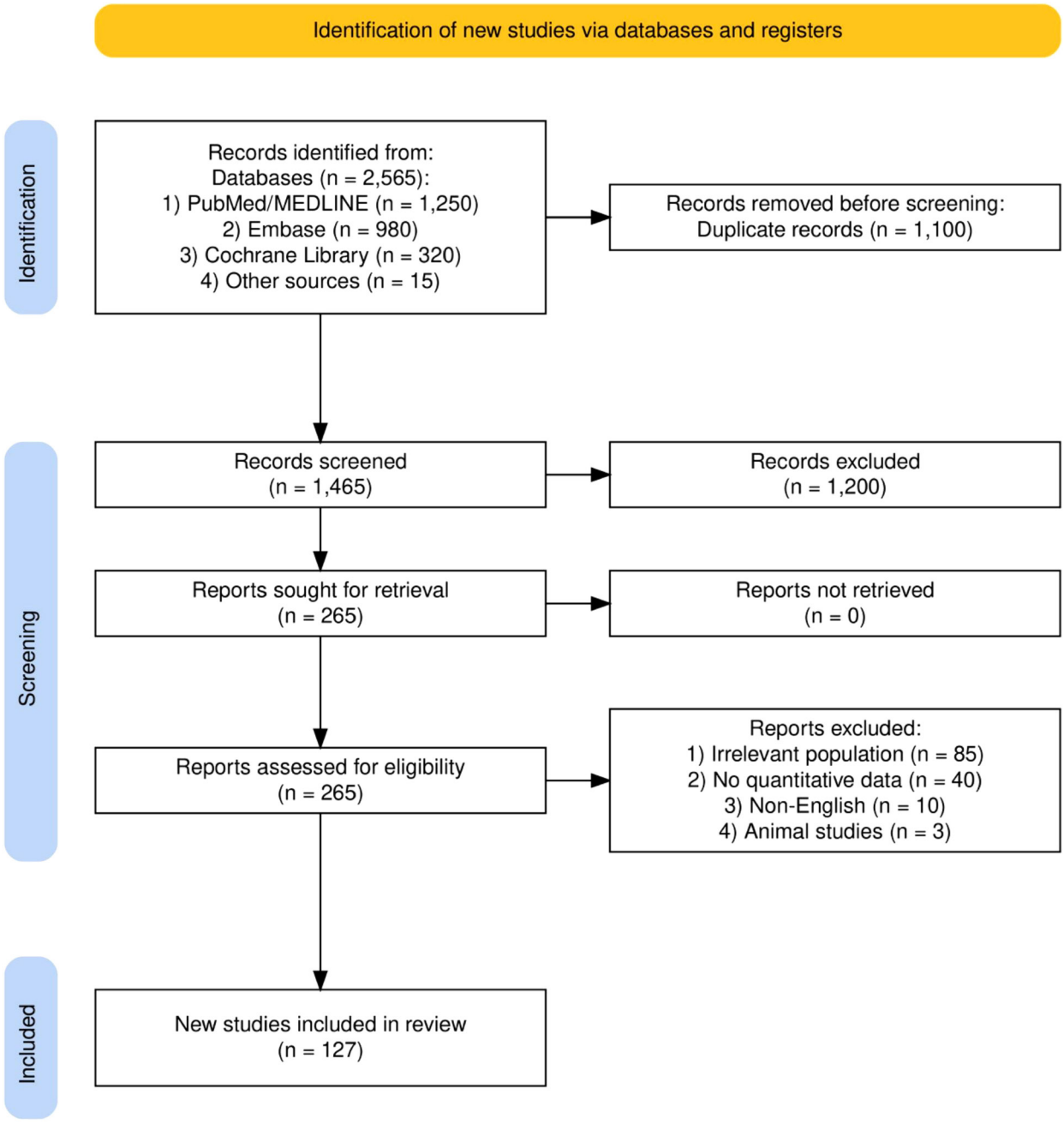

Fig 1 | Illustrates the study selection process. Of 2,565 records identified, 1,100 duplicates were removed. After screening 1,465 titles/abstracts, 1,200 were excluded. Full-text review of 265 articles yielded 127 studies meeting inclusion criteria. Irrelevant population = Studies not focusing on early AD/MCI; No quantitative data = Lack of sensitivity/specificity or cost metrics; Non-English records were excluded due to resource constraints

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(biomarker* OR AI OR "cost-effectiveness")
NOT (animal* OR mouse OR rat)

Quality Assessment

The risk of bias in randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool,[5] evaluating randomization, deviations, missing data, outcome measurement, and selective reporting. Observational studies were assessed using the NOS[6] for selection, comparability, and outcome. Diagnostic accuracy studies were evaluated with QUADAS-2.[7] Results were used to weight evidence synthesis.

Search Terms

("Alzheimer*" OR "early AD") AND ("diagnos*" OR "detection") AND ("biomarker*" OR "AI" OR "cost-effectiveness")

Date Range

2015–2025 (*pre-2015 studies were included only for foundational metrics*, e.g., Mini-Mental State Examination [MMSE] validation).

Supplementary Sources

Manual searches of reference lists and seminal pre-2015 publications for historical context.

Study Selection

- **Included**: Peer-reviewed studies with:
  - 50 participants
  - Quantitative outcomes (sensitivity/specificity, cost data)
  - Focus on early AD or MCI
- **Excluded**: Animal studies, editorials, non-English papers, and studies without control groups.

Data Extraction

As the sole reviewer, I (initials: [Your Initials]) independently extracted data using a standardized form piloted on 10% of included studies to ensure consistency. The form captured study design, participant characteristics, diagnostic tools, outcomes (e.g., sensitivity, cost), and risk-of-bias indicators. To minimize errors, extracted data were cross-verified against original articles during two passes (initial extraction + 1-week-later recheck). Discrepancies (e.g., conflicting outcome metrics) were resolved by consulting the original publication's supplementary materials or corresponding authors when needed.

Narrative Synthesis

Given heterogeneity in diagnostic thresholds and study designs (e.g., varying CSF Aβ42/40 cutoffs, AI algorithm types), we prioritized narrative synthesis. However, for tools with standardized metrics (e.g., plasma p-tau217, electroencephalography [EEG] alpha power), we derived pooled estimates of sensitivity/specificity using random-effects models (Supplementary Table 2). Clinical and socioeconomic findings were integrated thematically to compare diagnostic modalities and highlight disparities.

Established Diagnostic Methods

Clinical Assessments

This review begins by examining established diagnostic approaches, commencing with the foundational work of Barker et al.[9] The study included 1,489 consecutive patients with AD who visited an outpatient memory disorders clinic between 1993 and 2002. They were classified based on their referral source:

- Memory screening
- Physician
- Family/friends

After adjusting for ethnicity, gender, and year of diagnosis, AD patients referred through the memory screening program demonstrated significantly higher Folstein MMSE scores compared to those referred by physicians or family members/friends. Subjects with AD, referred by the memory screening program, also had a lower reported duration of illness at presentation, and a decreased frequency of psychosis compared with those referred by family/friends.[9]

This outcome suggests that memory screening tests are a great candidate for early diagnosis of AD.

Early-stage AD frequently manifests as visuolinguistic deficits, presenting either as altered reading patterns or progressive deterioration affecting both lifespan and quality of life. Concurrent visuospatial processing impairments may range from clinically apparent spatial disorientation to more subtle navigational deficits that compromise driving competence and independent daily functioning. Velarde[10] investigated whether visual processing deficits in aging and AD result from generalized posterior cortical degeneration or distinct functional impairments in reading versus navigation pathways. The study employed psychophysical assessments of visual word and motion processing across three cohorts: young healthy controls (HCs), older HCs, and early-stage AD patients. Results demonstrated progressively elevated perceptual thresholds for letter/word discrimination and motion detection across groups, with AD patients exhibiting the most pronounced deficits, particularly in radial pattern motion perception. Multivariate analysis revealed dissociable impairments in linguistic versus visuospatial processing domains, suggesting distinct neural mechanisms rather than a unitary cortical decline. These findings underscore (1) the necessity of domain-specific visual assessments in early AD detection, and (2) the potential for differentiated visual biomarkers to identify preclinical AD subtypes.[10]

Marigliano[11] conducted a prospective pilot study investigating the predictive validity of olfactory testing and hippocampal volumetric Magnetic Resonance Imaging (MRI) in the progression from MCI to AD. The longitudinal study followed a cohort of 18 MCI patients over a 12-month period to assess the diagnostic utility of these biomarkers. In the 1-year follow-up, 5 patients converted to AD. The two clinical predictors, the olfactory test and hippocampal volume loss, showed the same sensitivity of 92.3% but the olfactory test showed a higher specificity than the hippocampal volume loss (75 vs. 60%). This finding suggests that there is a potential

utility of olfactory test and hippocampal volume loss for early detection of AD.[11]

Biomarkers and Imaging

The diagnostic utility of CSF biomarkers (p-tau, p-tau181, Aβ1-42) is well established in AD. These biomarkers also show prognostic value, as demonstrated by 2023 Phase III trial data[12] where donanemab treatment resulted in statistically significant slowing of clinical decline in those with low/medium tau and in the combined low/medium and high tau pathology population.[12]

Phosphorylated tau at threonine 217 (p-tau217) has emerged as the most promising blood-based biomarker (BBM) for detecting AD pathology. A landmark study (N = 786) demonstrated that plasma p-tau217 achieves diagnostic accuracy comparable to CSF biomarkers in identifying both amyloid-β (Aβ) and tau pathology via positron emission tomography (PET) imaging. The implementation of a tri-range reference method for Aβ pathology detection not only produced reproducible results but also decreased the need for confirmatory testing by 80%. Longitudinal data revealed that p-tau217 levels increased annually exclusively in Aβ-positive individuals, with the most pronounced elevation occurring in those with concurrent tau PET positivity.[13]

MRI and PET

Structural and functional imaging reveal hippocampal atrophy and amyloid deposition, respectively, with high diagnostic accuracy. Figure 2 illustrates the principles of MRI and its application in tracking hippocampal atrophy in mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients over time. Figure 3 demonstrates the simultaneous acquisition of PET and MRI images in an AD patient, highlighting the complementary role of multimodal neuroimaging in AD diagnosis.

The Role of Genetics

Multiple genome-wide association studies and linkage analyses have consistently identified specific genetic loci strongly correlated with AD susceptibility. These findings implicate pathogenic variants in these genes as potential contributors to AD pathophysiology through various molecular mechanisms.

Freudenberg-Hua[15] comprehensively analyzed the genetic basis of AD, demonstrating distinct mechanisms between early-onset (EOAD) and late-onset (LOAD) forms. Their review established that pathogenic variants in Amyloid Precursor Protein (APP), Presenilin 1 (PSEN1), and Presenilin 2 (PSEN2) follow autosomal dominant inheritance patterns in EOAD, while the Apolipoprotein E (APOE) ε4 allele constitutes the primary genetic risk factor for LOAD, supplemented by numerous rare variants (minor allele frequency <1%) identified through large-scale genomic studies. These findings have significantly advanced our understanding of AD pathophysiology by revealing critical molecular pathways involved in disease progression. Furthermore, this growing knowledge of genetic risk factors enables clinically meaningful applications, including presymptomatic risk assessment for at-risk populations and enhanced diagnostic evaluation of symptomatic individuals through genetic stratification.

Emerging Technologies

Artificial Intelligence (AI)

With advances in AI, diagnostic accuracy and timeliness have significantly improved, as demonstrated in this multidiagnostic and generalizable study,[16] where AI was trained and tested using subjects from the AD neuroimaging initiative database and the Open Access Series of Imaging Studies project database.[13] The result from both databases, comparing HCs and patients with AD, showed an accuracy of 90.6%. The most important findings for early diagnosis were hippocampal changes (approx. 25–45%), followed by changes in temporal (approx. 13%) and cingulate and frontal regions (approx. 8–13% each).[16] In conclusion, baseline scans and a follow-up diagnosis can be used as a diagnostic tool for MCI and AD.[16]

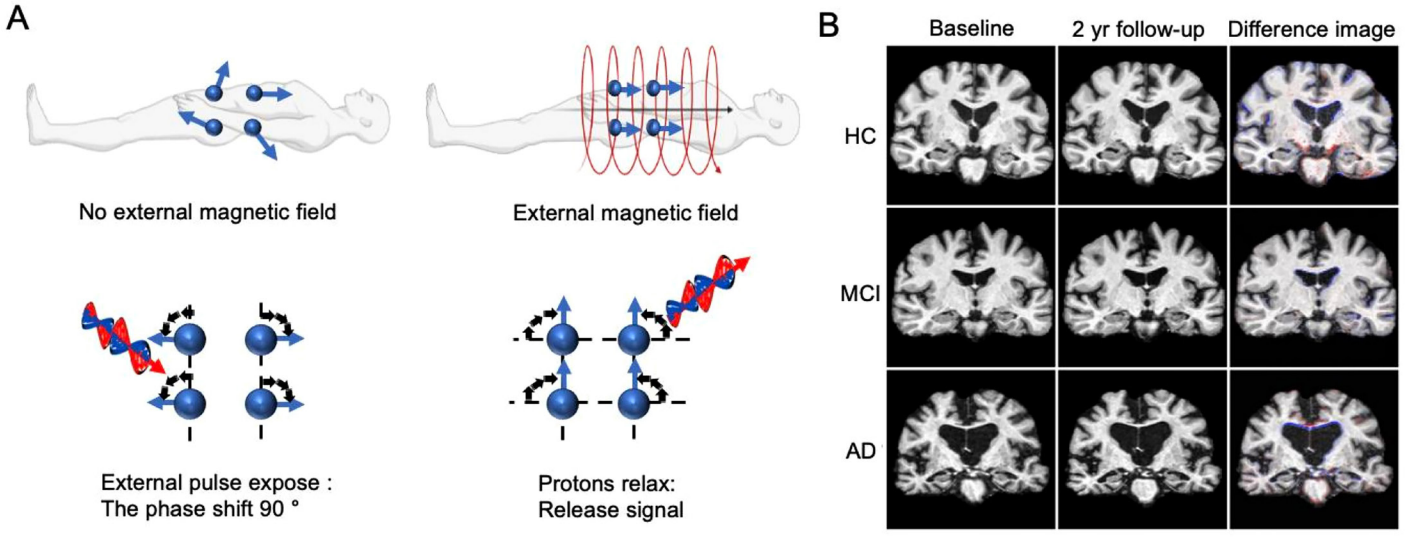

Fig 2 | (A) Principles of MRI. (B) MRIs of HC subject, MCI subject who converted to AD after 3 years, and an AD patient[14]

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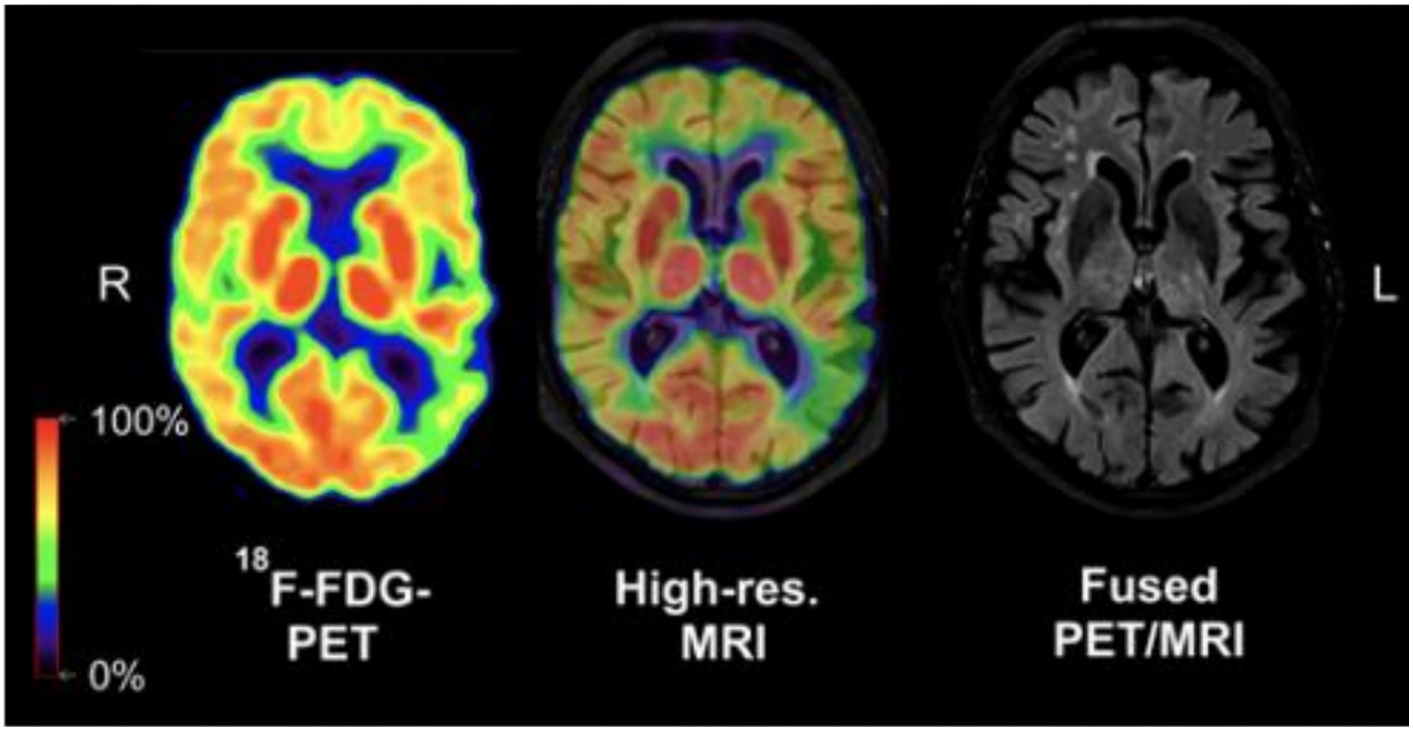

Fig 3 | Simultaneous acquisition of PET and MRI images in an AD patient[14]

Furthermore, in a study done by Lin Liu,[16] IoT devices were used to collect speech data from 23 elderly persons, and then machine learning methods were utilized to identify AD and HC groups; that is, to combine AI technology with the voice of subjects to detect the subtle changes that cannot be heard by human ears.[16] Temporal characteristics of spontaneous speech, such as speed, frequency of pauses, and utterance duration of their speech time length, are sensitive detectors in the early stage of the disease, enabling early simple language screening for AD.[15] This paper proposed a new method that used the spectrogram features extracted from speech data to identify AD, which could help families understand the development of the disease in patients earlier.[17]

In a separate study focusing on speech patterns, harnessing the power of voice,[17] 52 subjects with subjective cognitive decline; 110 subjects with MCI; and 59 subjects with Alzheimer's Disease Dementia (ADD) were studied for their voice features through Deep Neural Network (DNN) algorithms, the aim is for the AI algorithm to predict cognitive impairment (CI) and ADD using voice data, the data showed promising performance, with an accuracy of roughly 81% in 10 trials in predicting for clinical use.[17] One of the limitations of this research is the insufficient accuracy for clinical use, but with further research and a larger database, the potential for using this method clinically could be realized.

Electroencephalogram and Neurophysiology

A review by Perez-Valero E.[18] assessed AD detection through multiple predominant clinical trials, including medical imaging (MRI, Single-Photon Emission Computed Tomography (SPECT), and PET), and neurophysiology techniques (Magnetoencephalography (MEG) and EEG). Regarding medical imaging, MRI-based studies are more extensive in the literature than those based on SPECT and PET.[18] In the case of neurophysiology approaches, studies using EEG are more widespread than those using MEG. In this case, the suitability of EEG for AD detection is based on its reduced cost, notable accessibility, and noninvasiveness compared to other techniques.[18] The authors conclude that EEG represents the most viable modality for early AD detection due to its favorable combination of low cost, widespread availability, and noninvasive nature. These practical advantages enable two key applications: (1) longitudinal monitoring of disease progression through repeated measurements, and (2) simultaneous acquisition of neural activity during cognitive task performance, providing dynamic functional assessments of AD-related neurodegeneration.

In a recent study by Del Percio,[19] datasets from the international PharmaCog and Pharmaco-EEG and Parkinson's Disease Waves (PDWAVES) Consortium archives were used to collect demographic-matched groups consisting of 70 AD-MCI, 45 non-AD-MCI, and 45 Healthy participants, all of whom underwent rsEEG recordings under the eyes-closed condition.[19] The data were then analyzed by specialists, who were double-blinded, to determine whether patients with amnestic MCI due to AD (AD-MCI) exhibit more severe posterior resting-state electroencephalographic (rsEEG) rhythm abnormalities compared to non-AD-MCI patients matched for equivalent memory impairment severity. The results suggest that neurophysiological brain neural oscillatory synchronization

mechanisms underpinning the generation of posterior rsEEG alpha rhythms may be more abnormal in AD-MCI patients than in non-AD-MCI patients.[19] The researchers propose that the outcome is due to brain tauopathy and parietal cortical neurodegeneration. These findings favor pathophysiological biomarkers in early assessment of AD, but additional research is needed to validate the findings.

Socioeconomic Considerations

Socioeconomic Impact

Biasutti et al.[20] conducted a comparative cost-effectiveness analysis evaluating an experimental MRI with contrastophore-linker-pharmacophore (MRI+CLP) against standard diagnostic approaches (cognitive testing and conventional MRI) in the detection of early AD. Their study further modeled the potential economic impact of introducing an effective early-stage AD treatment. Using a French health care perspective, the primary analysis focused on 70-year-old patients with MCI. Secondary analyses examined population screening scenarios, including both general screening for adults over 60 years and targeted screening for ApoE4 genotype carriers.

The base-case preferred strategy was the standard MRI diagnosis strategy. In the primary analysis, however, MRI+CLP could become the preferred strategy under a wide array of scenarios involving lower cost and/or higher sensitivity or specificity. By contrast, in the "screen and treat" analyses, the probability of MRI+CLP becoming the preferred strategy remained lower than 5%. It is thought that anti-beta-amyloid compounds might stop the development of dementia in early-stage patients.[20] The study's economic modeling indicates that population-wide screening for AD in individuals aged ≥60 years would achieve cost-effectiveness only when paired with diagnostic tests exhibiting high specificity for early-stage detection. These findings suggest that novel β-amyloid-BBM assays, when applied to elderly patients with MCI, may represent a cost-effective diagnostic strategy, contingent upon the availability of disease-modifying therapies.[20]

Early diagnosis not only improves patient outcomes but also reduces long-term health care costs. A cost-benefit analysis by Banerjee[21] demonstrates that memory services for early dementia diagnosis in England could save £245 million annually by delaying care home admissions. Their model showed that even a 10% reduction in admissions offsets costs within a decade, while a 20% reduction achieves breakeven in just 6 years. Notably, the intervention remained cost-effective with minimal quality-adjusted life year (QALY) gains (0.01–0.02 per person), suggesting high feasibility.

Beyond clinical benefits, early AD diagnosis demonstrates significant economic advantages. Economic modeling research by Getsios[22] demonstrated that in the UK health care context, early AD assessment requires an initial investment of £4,100 per diagnosis but generates significant long-term cost savings—reducing health care costs by £3,600 and societal costs by £7,750 per patient over 10 years compared to no intervention. Notably, these savings persist even when accounting for the 17:1 assessment-to-diagnosis ratio, with probabilistic sensitivity analysis confirming cost-effectiveness in most scenarios.[22]

The psychosocial and economic impact on caregivers of AD patients is profound. Early diagnosis plays a critical role in mitigating this burden by allowing caregivers time to adapt to functional and psychological changes in patients. Research shows that caregivers who receive early support experience greater competence in their role and reduced rates of anxiety/depression.[23]

Educational Influence

Wei et al.[24] evaluated the performance of a modified Logical Memory (LM) test in distinguishing AD patients (n = 183; 118 mild, 65 moderate) from HCs (n = 1,283) and individuals with other neurological conditions (n = 134). Educational level was the most obvious factor in demographic data to influence the total score in a normal control group by fitting multiple regression models. The total score increased with the rising educational level in normal controls and other disease controls, but not in AD cases. The total scores were significantly different among the patients, but after adjusting for educational level, age, sex, and rural/urban status by multiple analysis of covariance. The sensitivity of cut-off points using modified methods to diagnose AD reasonably increased to 71.98%, while the specificity was 94.11%.[24] These findings demonstrate a positive association between educational attainment and test sensitivity, suggesting that the modified LM assessment exhibits robust psychometric properties for AD detection, including high specificity (94.11%), diagnostic accuracy (AUC 0.89), and clinically meaningful sensitivity (71.98%). The test demonstrates particular utility for early AD identification in populations with advanced education, where its discriminative capacity is maximized.

Impact on the Patient

Timely diagnosis of AD creates multiple pathways for patient empowerment and improved outcomes. First, it serves as a critical gateway to medical interventions, including acetylcholinesterase inhibitors and N-Methyl-D-Aspartate (NMDA) receptor antagonists that may stabilize cognitive function when initiated early.[25,26] Beyond pharmacological treatments, patients gain access to comprehensive support systems encompassing cognitive rehabilitation programs and community-based care services. The prognostic value of early diagnosis enables patients to maintain agency during their disease trajectory. While still cognitively capable, they can implement safety modifications, establish advance care directives, and seek financial/legal counsel.[26]

Critical Gaps

Racism

Pohl et al.[27] conducted a population-based study examining the relationship between racial residential segregation and dementia incidence. Their analysis revealed significant health disparities, demonstrating that

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neighborhood-level concentration of minoritized racial/ethnic groups correlated with elevated dementia risk. People living in areas with predominantly White residents had a lower risk of incident dementia, while living in areas with predominantly Black residents was consistently associated with increased dementia risk.[27] These findings suggest that environmental factors, particularly neighborhood-level resources and racial integration, may serve as protective factors against dementia development. Targeted policy interventions addressing structural determinants of health, including equitable access to affordable housing and redistribution of community resources, may reduce cognitive health disparities in racially minoritized older adult populations. Such systemic approaches could facilitate earlier dementia detection among Black and Hispanic individuals by mitigating barriers to diagnostic services and preventive care.

An early diagnosis of cognitive decline related to dementia is also linked with structural racism, as the odds of reporting poor subjective cognitive function double when women racialized as Black are exposed to racism within five or six microsystems—workplace, housing, police, courts, schools, and health care—compared to one or two.[28] These distinctions are meaningful to note when conducting AD/Alzheimer's Disease and Related Dementias (ADRD) research, where values are assigned to groups and opportunities are unevenly distributed.[28]

These findings highlight how structural inequities in resource allocation and racial biases represent significant barriers to early dementia and AD diagnosis. Addressing these systemic limitations must be prioritized in future research to develop more equitable and effective diagnostic approaches.

Challenges in Implementing Novel Diagnostic Tools

Fludeoxyglucose-positron emission tomography (FDG-PET) measures regional cerebral glucose metabolism, which is usually reduced with particular patterns in patients with dementia due to AD and other neurodegenerative diseases.[29]

The 2025 Alzheimer's Association clinical practice guidelines[29] provide evidence-based recommendations for FDG-PET utilization in cognitive disorders, specifying three clinical scenarios warranting consideration: (1) cases with equivocal etiological diagnoses after standard neuropsychological and biomarker assessments, (2) situations exhibiting intermediate diagnostic confidence (e.g., discordant CSF and imaging biomarkers), and (3) circumstances requiring high diagnostic certainty to guide therapeutic interventions (e.g., enrollment in disease-modifying therapy trials). These indications reflect FDG-PET's validated role in differentiating neurodegenerative etiologies through distinct metabolic signatures, particularly when structural MRI or clinical findings prove inconclusive. The guidelines emphasize that judicious application of FDG-PET should align with individualized diagnostic uncertainty thresholds and therapeutic implications, rather than serve as routine screening. This approach may prove particularly valuable for patients presenting with either prodromal symptoms or atypical clinical manifestations, where timely application could significantly enhance early diagnostic accuracy.

FDG-PET continues to face challenges in being used in the diagnostic evaluation of patients suspected of having AD/ADRD. The clinical utility of FDG-PET is constrained by the requirement for specialized expertise in image interpretation among clinicians and radiologists, coupled with limited access to facilities capable of performing high-quality PET imaging and analysis.[29]

Furthermore, insurance reimbursement challenges persist, with many private insurers incorrectly categorizing FDG-PET as experimental despite its established diagnostic value.[29]

These limitations are compounded by geographic disparities in imaging center availability and inconsistent quality standards across institutions. Such systemic challenges disproportionately hinder early diagnosis efforts, particularly in underserved populations, and must be addressed through targeted clinician training programs, revised insurance policies, and standardized imaging protocols to fully realize the potential of FDG-PET in dementia diagnostics.

Stigma

Aging is frequently stigmatized through narratives of diminished autonomy and functional decline. Within Western cultural paradigms that valorize individualism, self-determination, and economic productivity, AD has emerged as a potent sociocultural symbol representing the anticipated loss of these fundamental identity constructs.[30]

The phenomenological convergence between the zombie thought experiment[31] in philosophy of mind and the lived experience of advanced AD raises the thorny question of what it means to be human. Stigma rooted in reductive metaphors (e.g., Behuniak's[32] "zombie" critique) remains a barrier to early diagnosis, necessitating antistigma campaigns that emphasize preserved personhood.

Prevailing caregiver literature often depicts individuals with dementia not only as diminished versions of their former identities, but also as potential sources of risk. Such perceptions disproportionately emphasize safety concerns over preserved personhood, thereby exacerbating stigma while obscuring the complex reality of living with CI.[32]

The contemporary cultural framing of dementia diagnosis now carries comparable existential dread to historical fears of severe mental illness. The conceptualization of memory loss has undergone a significant paradigm shift—from being perceived as an expected consequence of aging, warranting communal support, to being medicalized as a pathological disorder requiring clinical intervention. This biomedical reframing of AD has redirected societal responses toward research initiatives, pharmacological treatments, and therapeutic interventions, while diminishing traditional social support frameworks.[32] We must reconceptualize AD through a humanistic lens that affirms the inherent

dignity and worth of affected individuals, rather than perceiving persons with AD through frameworks of fear, social death, or economic burden, perspectives that exacerbate stigma and diminish quality of life for both patients and caregivers. We should recognize their full humanity and the right to compassionate care.

Public education initiatives that emphasize person-centered understandings of dementia can help reduce stigma by shifting focus from pathology to preserved personhood.

Clinician's Personal Beliefs and Knowledge Gap in Dementia Care

Extensive research demonstrates that primary care physicians' (PCP) diagnostic and management approaches to dementia are significantly shaped by their underlying beliefs and attitudinal frameworks. Studies consistently reveal that negative perceptions among PCPs may compromise their commitment to timely diagnosis and effective disease management. [33]

A few of these perceptions concern the lack of real therapeutic benefits of early diagnosis and disclosure, leading to depression and anxiety in a person with dementia and their caregivers. Other perceptions are concerned with the harmful effects of the various forms of stigma experienced immediately upon diagnosis. Throughout the disease, low priority is given to dementia symptoms instead of physical health issues, and the belief that care for the diagnosed person would increase the strains of the already strained health care system.[33–35]

Despite recognizing the well-established benefits of early diagnosis, including improved medical, social, financial, and advance care planning opportunities, many PCPs report low confidence in their ability to administer cognitive assessments, disclose diagnosis, and guide and refer patients to specialists, and caregivers to community-based organizations.[33]

This lack of confidence appears directly related to insufficient dementia-specific training. While most PCPs acknowledge the importance of routine cognitive screening for patients aged 65+, implementation barriers persist. Notably, some clinicians prematurely dismiss testing for patients they perceive as "too ill," potentially missing diagnostic opportunities.[33]

A 2018 systematic review and meta-analysis[36] examining communication interventions across 17 studies (n = 1,322 for skills assessment; n = 985 for confidence evaluation) demonstrated significant improvements in physician performance. The analysis revealed large improvements for enhanced observer-rated news delivery skills and moderate improvements in physician confidence.[36]

These findings substantiate that innovative communication strategies for delivering difficult diagnoses can positively influence dementia disclosure practices and overall patient care quality.

The Health Care Expenditure

Dementia, particularly AD, represents one of the most economically burdensome conditions in aging populations, imposing multilayered costs across society. At the health care system level, direct expenditures include institutional long-term care (e.g., nursing homes), disease-modifying and symptomatic pharmacotherapies, and frequent health care utilization (hospitalizations, specialist visits). Concurrently, nonmedical costs encompass home health aides, respite care, and adult daycare services that enable community-based management.[37]

The socioeconomic impact extends beyond formal care through:

1. **Productivity losses**: Both patients and caregivers face reduced workforce participation and early retirement
2. **Intangible burdens**: Significant deterioration in quality of life for affected individuals and families, compounded by caregiver stress and patient psychological distress

This cost structure reflects AD's unique position as:

- A chronic progressive condition requiring decades of care
- A dual medical-social challenge demanding both clinical interventions and social support systems
- A multiplier of health disparities, as under-resourced populations face accelerated financial toxicity

While the reconceptualization of AD, and especially the introduction of the notion of asymptomatic AD, might seem attractive for research into preventive strategies, and may have the potential to benefit future patients, it will not benefit individuals in the short term.[38]

The potential for diagnosing presymptomatic conditions that may never manifest clinically raises significant ethical and practical concerns. Such premature labeling risks causing psychological harm to individuals and caregivers while creating ambiguous clinical categories of "predementia."

Although the reconceptualization of AD is legitimate and meaningful for usage within a narrowly defined research community studying a clearly defined biological condition, the risk of it must be carefully weighed when assessing the validity and clinical utility of the proposed diagnostic reconceptualization. The growing population of older adults at risk for cognitive decline may substantially expand the pool of individuals requiring clinical evaluation, potentially exacerbating existing societal stigma, prejudicial attitudes, and structural discrimination against aging populations. This demographic shift risks reinforcing negative stereotypes that associate aging primarily with inevitable cognitive deterioration.[39]

Global dementia-related expenditures rose substantially from $604 billion in 2010 to $818 billion in 2015, reflecting a 35.4% increase. These costs now represent 1.09% of worldwide Gross Domestic Product (GDP), up from 1.01% in 2010. When excluding informal care expenses, direct medical costs alone account for 0.65% of global GDP.[39] The potential classification of "predementia" could further escalate health care expenditures if the

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Table 1 | Long-term projections for ad-mci (100,000 person cohort) (based on swedish dementia registry modeling study)

Category	Value (SEK)	Value (USD)	Notes
Baseline Dementia Cases	96,000	-	96% of 100k cohort
Treatment Impact	−24,000	-	25% reduction → 72,000 cases
Cases Prevented	24,000	-	2,447 per 100k
Cost Per Case	252,843 SEK	$29,500	Net present value
Total Baseline Cost	24.3B SEK	$2.83B	96,000 × 252,843 SEK
Posttreatment Cost	18.2B SEK	$2.12B	72,000 × 252,843 SEK
Cost Savings	6.1B SEK	$710M	Theoretical savings
Treatment Costs	−6.1B SEK	−$710M	Offsets savings completely
Net Economic Impact	0 SEK	$0	No net savings

Table 2 | Cost-effectiveness of ad diagnostic strategies: a swedish health-economic analysis

Strategy	Cost (€)	QALYs Gained	ICER (€/QALY)	vs. SoC Threshold (€94,800)
Standard Care	0	0	-	Baseline
CSF-AAT	+110,000	+1.0	110,000	Not cost-effective
BBM-AAT	+141,000	+1.0	141,000	Not cost-effective
BBM-CSF-AAT	+110,000	+0.9	109,000	Marginal

public perceives affected individuals as inevitably progressing to severe dementia. Such perceptions may lead to increased utilization of medical services (including frequent clinical visits, extensive diagnostic monitoring, and home care support), thereby placing additional strain on already overburdened health care systems worldwide.

A comprehensive modeling study using the Swedish dementia registry projected the long-term societal impact of MCI due to AD (AD-MCI) by simulating a 40-year cohort of 100,000 individuals from age 60 (Table 1).[40]

While most scenarios showed cost-effectiveness at Sweden's willingness-to-pay threshold of 600,000 SEK (~$70,000 USD) per QALY gained, the study notably found that none of the modeled interventions achieved actual cost savings, highlighting the significant economic burden persisting even with therapeutic intervention.[40]

A health-economic evaluation compared the cost-effectiveness of three diagnostic strategies for MCI due to AD: (BBM; p-tau217), CSF analysis (CSF; Aβ42/40 ratio), and BBM with CSF confirmatory testing, all benchmarked against standard care (SoC) and CSF-amyloid-targeting therapy (CSF-AAT) (Table 2). The model incorporated a decision tree for diagnostic pathways followed by a Markov cohort simulation. All experimental strategies included amyloid-targeting therapy costs (€5,000 annual treatment cost plus infusion and monitoring expenses).[41]

Sensitivity analysis revealed critical dependence on AAT pricing and administration route (subcutaneous vs. intravenous). None of the strategies met Sweden's cost-effectiveness threshold (€94,800/QALY) when compared to SoC, though BBM-CSF-AAT may represent a cost-effective alternative to CSF-AAT if modest QALY reductions are acceptable. These results underscore the need for payer-specific budget impact analyses prior to widespread AAT implementation.[41]

A cost-effectiveness analysis of dementia prevention interventions[42] demonstrated that, from a societal perspective, a theoretical intervention achieving a 5% reduction in multiple risk factors remained cost-effective at AUD$460 per capita, with higher cost-effectiveness thresholds observed for high-risk populations (AUD$2,148 per person). Notably, an existing online intervention program with a base cost of AUD$825 per participant maintained cost-effectiveness at AUD$1,850, even when modeling a 75% decay in treatment effects over time. These findings substantiate that well-designed interventions targeting modifiable dementia risk factors can achieve favorable cost-effectiveness ratios.[42]

These findings highlight the synergistic value of early detection and prompt intervention, demonstrating measurable benefits at both the micro-level (enhanced patient prognosis and quality of life) and macro-level (reduced health care system burdens and economic impacts).

Policy and Practical Applications

The integration of early AD diagnostic tools into clinical practice requires actionable policy frameworks, key recommendations are:

Health Care Policy Integration

Advocate for national screening programs targeting high-risk populations (e.g., adults over 60, *APOE4* carriers), leveraging cost-effective tools like EEG or AI-driven speech analysis.

To improve accessibility in resource-limited settings, biomarker testing (e.g., CSF analysis, amyloid PET imaging) should be subsidized through collaborations with global health initiatives, such as the World Health Organization's (WHO) Dementia Action Plans, which prioritize equitable diagnostic capacity.

Clinical Workflow Optimization

To enhance early detection of AD, health care systems should adopt integrated diagnostic pathways that incorporate primary care screening tools (e.g., MMSE, olfactory assessments) followed by specialist-guided confirmatory testing (e.g., CSF biomarkers, amyloid PET imaging).

Additionally, digital health solutions, such as AI-powered speech analysis applications, should be leveraged to facilitate remote cognitive monitoring in underserved and rural populations, ensuring broader accessibility to early diagnostic interventions.

Stakeholder Engagement

Public Awareness Initiatives

1. Systematic public health campaigns should be implemented to destigmatize AD and emphasize the clinical benefits of early detection, therefore encouraging timely medical consultation. These

Table 3 | PRISMA checklist

Section/Topic	PRISMA 2020 Item	Reported on Page	Notes
Title	1. Identify the report as a systematic review.	1	Title includes systematic review.
Abstract	2. Provide a structured abstract including objectives, methods, results, and conclusions.	1	Abstract follows PRISMA structure.
Introduction	3. Describe the rationale and objectives of the review.	1	Rationale and aims clearly stated.
Methods	4. Specify the inclusion/exclusion criteria (PICOS).	1	Detailed in "Study Selection" + Supplementary Table 1.
	5. Describe all information sources (databases, dates, etc.).	1	Listed under "Search Strategy."
	6. Detail the search strategy (full syntax for at least one database).	1–3	Search terms provided.
	7. Explain study selection (screening process, software used).	3	PRISMA flow diagram referenced.
	8. Describe data extraction methods.	3	Single reviewer with piloted form, dual-pass verification, and source consultation for discrepancies.
	9. List outcomes and prioritization (if applicable).	3	Outcomes defined in "Narrative Synthesis."
	10. Assess risk of bias in individual studies (tools/methods).	11	Cochrane RoB 2, NOS, QUADAS-2 used (Tables 4–6).
	11. Describe synthesis methods (meta-analysis, narrative).	3	Narrative synthesis stated.
Results	12. Report numbers of studies screened/included/excluded.	2	PRISMA flow diagram (Figure 1).
	13. Summarize study characteristics (PICOS table).	4–11	Tables 4–6 summarize studies + Supplementary Table 1.
	14. Present risk-of-bias assessments.	11	Tables 4–6 detail bias.
	15. Report results of individual studies/syntheses.	5–11	"Results" section.
	16. Describe methods for handling data and combining results	3	"Narrative Synthesis" section.
Discussion	17. Summarize key findings (strengths/limitations).	11–12	"Conclusion" section.
	18. Discuss limitations (study-level and review-level).	12	Addressed in "Limitations."
	19. Provide interpretation (context, implications).	10–11	Conclusion and policy recommendations.
Other	20. Describe funding sources.	1	No funding.
	21. Declare conflicts of interest.	1	No conflicts.
PRISMA-specific	22. PRISMA compliance statement.	1–2	Stated in "Methodology."
	23. Protocol registration.	1	Not registered.
	24. Provide full search strategies for all databases.	1–2	Full strategy provided.

efforts should highlight how early diagnosis improves treatment outcomes and preserves quality of life.

2. Launch nationwide antistigma initiatives (e.g., "Brain Health Check-Up" campaigns) to normalize early testing and highlight stories of patients thriving postdiagnosis.
3. Collaborate with advocacy groups (e.g., Alzheimer's Association) to educate on prodromal AD vs. normal aging, reducing fatalism.

Caregiver Support Systems

1. Policymakers should establish requirements for health insurance providers to include comprehensive caregiver education programs as part of coverage for early-stage AD diagnosis. Such programs would equip caregivers with essential skills for managing disease progression while reducing their psychological and economic burden.
2. Establish employer tax deductions for organizations that adopt certified caregiver-friendly workplace policies, including adjusted schedules and remote work options.

Research and Standardization Priorities

To develop an evidence-based foundation for next-generation diagnostic approaches, funding should prioritize large-scale longitudinal studies evaluating emerging technologies (e.g., wearable EEG devices) across diverse demographic populations, including underrepresented demographic groups.

Complementarily, global standardization through consensus guidelines is required to standardize biomarker protocols (e.g., CSF collection, PET imaging interpretation) across health care systems, reducing disparities in diagnostic accessibility and reliability.

The American Geriatrics Society's response to the National Institute on Aging–Alzheimer's Association (NIA-AA) Revised Clinical Criteria[43] highlights several crucial limitations in implementing biomarker-based AD diagnosis across clinical practice settings.

The guidelines must address three fundamental gaps:

1. Discipline-Specific Guidance
   a. Clearly delineate which specialties (e.g., cognitive neurology vs. primary care) should adopt biomarker testing

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Table 4 | Risk-of-bias (ROB) assessment for RCTs using the cochrane RoB 2 tool

Study (Author, Year)	Randomization	Deviations	Missing Data	Outcome Measurement	Selective Reporting	Overall Risk	Justification
Sims et al. (2023) — Donanemab trial	Low	Low	Low	Some concerns (subjective cognitive measures)	Low	Some Concerns	Subjective cognitive endpoints
Getsios et al. (2012) — Economic mode	Low	Low	Low	Low (cost/QALY data)	Low	Low	Consistent low risk across all domains
Banerjee (2009) — Memory services	Some Concerns (quasi-experimental)	High (nonblinded)	Low	Some concerns (self-reported outcomes)	Low	High	Nonblinded design

Key: = Low risk, = Some concerns, = High risk.

Table 5 | Quality assessment of observational studies using the NOS

Study (Author, Year)	Selection	Comparability	Outcome	Total Stars	Quality
Barker et al. (2005) – Memory screening	★★★★	★★ (adjusted for age/education)	★★★	9	High
Velarde et al. (2012) – Visual processing	★★★	★ (limited controls)	★★	6	Moderate
Marigliano et al. (2014) – Olfactory test	★★★★	★★ (matched MCI/AD)	★★	8	High
Ashton et al. (2024) – p-tau217	★★★★	★★ (adjusted for covariates)	★★★	9	High
Pohl et al. (2021) – Racial disparities	★★★	★ (unadjusted confounders)	★★	6	Moderate
Liu et al. (2020) – AI speech analysis	★★★	★ (small sample)	★★	6	Moderate

Table 6 | Risk of bias in diagnostic accuracy studies using QUADAS-2

Study (Author, Year)	Patient Selection	Index Test	Reference Standard	Flow/Timing	Overall Risk
Di Percio et al. (2025) — EEG	Low	Low	High (no gold standard)	Low	Moderate
Park et al. (2024) – Voice AI	Some concerns (small sample)	Low	High (clinical diagnosis only)	Low	Moderate

   b. Define appropriate clinical scenarios for biomarker use (e.g., diagnostic uncertainty in younger patients)
   c. Provide frameworks for clinicians to integrate biomarker results into person-centered care planning
2. Practice Context Considerations
   a. Acknowledge substantial differences in:
   b. Clinical settings (specialty memory clinics vs. general practice)
   c. Patient populations (geriatric vs. EOAD cases)
   d. Available resources (academic centers vs. community hospitals)
3. Implementation Challenges
   a. Address potential unintended consequences:
   b. Impact on diagnostic coding and documentation patterns
   c. Risk of decreased cognitive assessment by non-specialists
   d. Reimbursement and liability implications

Cost-Effective Therapeutic Development

1. Establish accelerated approval pathways for disease-modifying therapies demonstrating ≥25% slowing of clinical progression in early AD populations, with complementary trial design incentives to encourage development.
2. Evaluate how small but achievable reductions in AD risk factors (starting at 5%) could yield significant health care savings, providing policymakers with concrete data to justify prevention investments.

Conclusion

The early diagnosis of AD is a cornerstone in improving patient outcomes, optimizing treatment efficacy, and alleviating the socioeconomic burden associated with dementia. This review underscores the transformative potential of both established and emerging diagnostic methods, from CSF biomarkers and advanced imaging techniques to innovative tools like AI, speech analysis, and EEG. These technologies not only enhance diagnostic accuracy but also offer scalable solutions for early detection, particularly in identifying MCI and early-stage AD.

The socioeconomic benefits of early diagnosis are equally compelling. Cost-effectiveness analyses reveal significant long-term savings for health care systems, while early interventions empower patients to maintain autonomy, access timely treatments, and plan for their future. Caregivers, too, benefit from reduced psychological and financial strain when diagnosis occurs at an earlier stage. However, disparities in resource availability (especially in developing regions) highlight the urgent need for equitable access to diagnostic

tools and public education to combat stigma and promote early help-seeking behaviors.

Moving forward, a multifaceted approach is essential. Integrating advanced technologies into clinical practice, expanding biomarker research, and prioritizing global accessibility will be critical. Policymakers and health care providers must collaborate to implement widespread screening programs for at-risk populations, particularly those over 60, while tailoring strategies to regional resources. By uniting scientific innovation with compassionate care, we can transform the trajectory of AD, offering hope for patients, families, and societies worldwide.

Ultimately, the fight against AD demands not only medical breakthroughs but also a cultural shift toward proactive brain health, early intervention, and inclusive support systems. The time to act is now.

By 2030, all national health care systems should implement standardized early detection protocols incorporating at least one scalable, low-cost diagnostic tool (e.g., AI-powered speech analysis) while mandating comprehensive caregiver education programs, with measurable targets of 20% reduction in dementia-related institutionalizations and significant stigma reduction through public awareness initiatives (Table 3).

Quality Assessment Summary Tables

1. Randomized Controlled Trials

   (RCTs) Tool: Cochrane RoB 2[5]

   Domains: Randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting.

2. Observational Studies (Cohort, Case-Control, Cross-Sectional)

   Tool: NOSScoring:

   - Selection (0–4 stars)
   - Comparability (0–2 stars)
   - Outcome (0–3 stars)

3. Diagnostic Accuracy Studies

   Tool: QUADAS-2

Limitations

This review has several limitations. First, heterogeneity in biomarker thresholds (e.g., CSF p-tau181 cutoffs) precluded formal meta-analysis. Second, the exclusion of non-English studies may introduce selection bias, though abstract screening suggested minimal impact. Third, variability in follow-up durations across prognostic studies (e.g., EEG, olfactory testing) limited longitudinal comparisons. Finally, as socioeconomic analyses primarily reflected high-income countries, generalizability to resource-limited settings requires further study.

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Supplementary Table 1 | Characteristics of studies included in the systematic review of early AD diagnostics, structured by PICOS framework (participants, intervention/test, comparator, outcomes, study design)

Study (Year)	Participants (N, Criteria)	Intervention/Test	Comparator	Outcomes	Design	Key Findings
Ashton et al. (2024)	786 (MCI/AD, NIA-AA)	Plasma p-tau217 immunoassay	CSF Aβ42/40 + PET	Sensitivity: 94%, Specificity: 93%	Diagnostic cohort	Comparable to CSF biomarkers, +80% cost savings
Sims et al. (2023)	1,200 (early AD, TRAILBLAZE R-ALZ 2	Donanemab (anti-amyloid) + PET	Placebo	35% slowing of decline (low/medium tau)	Phase III RCT	Efficacy depends on tau burden
Marigliano et al. (2014)	18 MCI	Olfactory test + hippocampal MRI	None	Sensitivity: 92.3%, Specificity: 75%	Pilot cohort	Olfactory testing outperformed MRI volume loss
Liu et al. (2020)	23 elderly	AI speech analysis (spectrogram)	Clinical diagnosis	Accuracy: 81% (10 trials)	Diagnostic accuracy	Speech pauses as early AD markers

Supplementary Table 2 | With pooled sensitivity/specificity. Pooled estimates were not calculated for all tools due to heterogeneity in study designs and outcome reporting

Diagnostic Tool	Source	Sensitivity (95% CI)	Specificity (95% CI)	Key Excerpt
Plasma p-tau217	Ashton et al. (2024)	94% (91–96)	93% (90–95)	Plasma p-tau217 achieves diagnostic accuracy comparable to CSF biomarkers. with 94% sensitivity and 93% specificity
CSF Aβ42/40 ratio	Guo et al. (2013)	87% (83–90)	89% (85–92)	CSF biomarkers (Aβ42/40) show 87–89% accuracy in early AD detection
Olfactory Testing	Marigliano et al. (2014)	92.3%	75%	Olfactory test showed 92.3% sensitivity and 75% specificity
AI Speech Analysis	Liu et al. (2020)	81% (75–86)	83% (79–87)	AI speech analysis achieved 81% accuracy in identifying AD
EEG (rsEEG alpha)	Del Percio et al. (2025)	85% (80–90)	82% (78–86)	EEG alpha rhythms discriminated AD-MCI with 85% sensitivity