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Bibliometric Analysis

Global mapping of early diagnostic tools for Alzheimer's disease: Integrating bibliometric analysis, SWOT strategy, and a novel Relative Effectiveness Index

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Abstract

Alzheimer's disease (AD) remains a major cause of dementia worldwide, but early detection strategies are diverse and context-specific. This study aimed to map early diagnostic modalities for AD, assess their coverage across populations and comorbidities, evaluate their relative effectiveness, and examine their strategic feasibility using an integrated bibliometric–SWOT approach. We analyzed Scopus-indexed studies published from 2015 to 2025 and classified them by primary modality, supporting techniques, target population, and comorbidities. A novel Relative Effectiveness Index (REI) and adjusted REI were developed to evaluate 108 modality–population–comorbidity combinations. Keyword co-occurrence analysis identified major thematic clusters, while chord diagrams and SWOT analysis illustrated methodological pairings and contextual feasibility across high-income countries (HICs) and low- and middle-income countries (LMICs). Data indicated that biomarkers and neuroimaging were predominantly applied in elderly populations and in comorbidities such as Parkinson's disease, diabetes, and stroke. Scoring tools were most common in studies involving depression and cardiovascular disease, whereas functional tests were least used overall, with limited application in Parkinson's disease and epilepsy. Blood-based methods and machine learning were frequently paired with biomarkers and neuroimaging, reflecting a shift toward non-invasive and precision diagnostics. Thematic clustering highlighted research concentrations on neurodegenerative mechanisms, AI-based neuroimaging, and blood biomarker discovery. Adjusted REI was highest for neuroimaging in elderly populations (1.03), while machine learning–integrated approaches consistently outperformed others across modalities (adjusted REI>1.1). In contrast, combinations involving younger populations, anthropometric methods, and some comorbidities showed little or no supporting evidence. SWOT analysis indicated that scoring tools remain accessible and interpretable, whereas biomarker- and neuroimaging-based strategies offer greater diagnostic precision but face implementation barriers, particularly in LMICs. Overall, this study provides an integrative evidence map of early AD detection, highlighting both well-supported strategies and critical evidence gaps.

Keywords: Neurodegenerative disorder, Alzheimer's disease, bibliometric analysis, early detection, Relative Effectiveness Index

Received: January 10, 2026 - Accepted: April 13, 2026 - Published online: April 14, 2026

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that constitutes the most common cause of dementia globally [1]. With over 55 million people affected and numbers projected to rise steeply in aging populations, AD presents a growing public health concern [2]. Beyond cognitive decline, AD significantly impairs daily functioning, emotional well-being, and quality of life, not only for patients but also for caregivers and families [2]. While traditionally viewed as a disease of the elderly, mounting evidence indicates that AD pathology may begin decades earlier, with subtle cognitive and behavioral changes detectable in younger individuals [3]. Moreover, chronic low-grade systemic inflammation from comorbid conditions such as diabetes, hypertension, and cardiovascular disease may accelerate the progression of AD [1,4,5], underscoring the urgency of early detection in at-risk populations [6].

Recent research has explored a wide array of early diagnostic modalities for AD, including neuroimaging techniques (e.g., magnetic resonance imaging (MRI), positron emission tomography (PET)), molecular biomarkers (e.g., amyloid, tau, blood-based proteins) [7], cognitive scoring systems (e.g., Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA)), and functional tests (e.g., gait, speech, eye tracking) [8,9]. Parallel advances in artificial intelligence (AI) and machine learning have further enhanced diagnostic accuracy [10-12], especially when integrated with imaging or fluid biomarkers [13]. These tools offer potential for earlier intervention, better prognostication, and more efficient clinical trial enrollment [14]. However, global disparities in resource availability and health infrastructure have shaped the deployment of these modalities differently. In low- and middle-income countries (LMICs), challenges include limited access to high-cost technologies, shortage of trained personnel, and the need for innovative, low-cost screening approaches [15,16]. Meanwhile, high-income countries (HICs), despite having advanced diagnostic systems, often face stagnation in converting economic growth into improved health outcomes, compounded by the rising burden of aging populations [17]. Despite the growing volume of research, the evidence base remains fragmented and imbalanced. Most studies are siloed by method, comorbidity, or population, limiting the ability to draw comprehensive comparisons and identify scalable, context-specific diagnostic strategies [18-20].

To address this gap, a comprehensive mapping of early diagnostic approaches using bibliometric data provides a rapid and scalable means to quantify research patterns, identify underexplored combinations, and highlight trends over time. Coupling this with a curated Relative Effectiveness Index (REI)—which integrates performance metrics and study volume—allows for a more nuanced appraisal of diagnostic utility across diverse contexts. Finally, applying a SWOT analysis framework facilitates the interpretation of findings within real-world feasibility constraints, particularly across low- and high-income settings. Together, these methods offer a powerful approach to guiding evidence-based implementation and identifying research priorities for the early detection of AD. Therefore, the aim of this study was to comprehensively map early diagnostic tools for AD, evaluate their relative effectiveness across populations and comorbidities, and assess their strategic feasibility in different health system settings using an integrated bibliometric, REI, and SWOT-based approach.

Methods

Search strategy

A comprehensive literature search was conducted on 17 July 2025 using the Scopus database. Scopus was selected due to its accessibility to the authors and its indexing of high-quality peer-reviewed journals. The search was restricted to articles published between 2015 and 2025, with the document type limited to "Article" and source type restricted to "Journal" to ensure relevance and scholarly rigor. The following Boolean query was used: TITLE-ABS-KEY ("Alzheimer's disease" OR "Alzheimer disease") AND TITLE-ABS-KEY ("early detection" OR "early diagnosis" OR "screening" OR "presymptomatic" OR "preclinical" OR "subclinical" OR "prodromal")

This query was designed to identify studies on the early detection of AD using a broad range of conceptual and clinical terms. The retrieved metadata included citation details, such as article

title, authors, year of publication, DOI, source title, volume and issue, citation count, publication stage, document type, and open-access status. Bibliographic information included author affiliations, ISSN, publisher, editors, language, and corresponding author details. The dataset also contained abstracts, author keywords, and indexed keywords, as well as funding information, including grant numbers, funding acronyms, sponsoring organizations, and related statements. Additional metadata, such as tradenames, manufacturer information, accession numbers, conference details, and cited references, were also collected. These data served as the basis for the subsequent extraction and classification of diagnostic modalities, target populations, comorbidities, and reported effectiveness.

Co-occurring keywords network analysis

This bibliometric analysis was performed using VOSviewer version 1.6.20 (Centre for Science and Technology Studies, Leiden University, The Netherlands). The dataset was obtained by exporting metadata in .csv format from the Scopus database. The analysis focused on identifying keyword co-occurrence patterns related to early detection in AD [21].

The type of analysis was set to co-occurrence, with the unit of analysis defined as author keywords. A full counting method was applied, where each keyword occurrence was counted equally across documents. A minimum threshold of 30 occurrences was used, resulting in the inclusion of 230 keywords, which generated 7276 links and a total link strength (TLS) of 36,543. Co-occurrence links between keywords were normalized using the association strength method, which adjusts for the overall frequency of individual keywords and emphasizes stronger, meaningful associations [22]. TLS of a keyword represents the sum of the strengths of all its co-occurrence links with other keywords. Mathematically, TLS was calculated based on the formula given by a previous study [22]. This approach helps prevent frequent keywords from dominating due to volume alone. In this study, TLS was used to identify the core keyword in each cluster—the one with the highest overall connectivity to other keywords in that group [22].

To generate the map layout, advanced parameters were set as follows: random starts=1, maximum iterations=1000, initial step size=1.00, step size reduction=0.75, step size convergence=0.001, and random seed=0 to allow reproducibility. Clustering was performed with a resolution of 1.00 and a minimum cluster size of 1, with the merge small clusters option enabled to reduce fragmentation and enhance thematic coherence.

Systematic classification of studies

A structured content extraction from eligible studies was conducted to classify diagnostic approaches and contextual parameters relevant to early detection strategies in AD. Titles and abstracts were extracted from the dataset and systematically reviewed by authors, where discrepancies were resolved through discussion. Four key classifications were derived. First, the main diagnostic modality used, including neuroimaging (e.g., MRI, functional MRI (fMRI), PET, computed tomography (CT)), biomarker assays (e.g., cerebrospinal fluid (CSF), amyloid, tau, protein), cognitive scoring systems (e.g., MMSE, MoCA, questionnaire), and functional tests (e.g., eye tracking, gait analysis, speech assessment). Second, supporting or complementary diagnostic modality identified from the abstract, such as AI-based methods (machine learning, deep learning, neural networks), blood-based measurements (complete blood count (CBC), glucose), and anthropometric parameters (body mass index (BMI), height, weight). Third, coexisting conditions explicitly mentioned in the abstract, including but not limited to diabetes, hypertension, cardiovascular disease, or depression. If multiple comorbidities were reported in a single study, each was recorded as a separate entry. Fourth, target population characteristics were inferred, including elderly, adults, children, or adolescents, based on age-related descriptors found in the abstract.

Pairings were then generated between: (1) main and supporting diagnostic modalities, (2) diagnostic modality and comorbidities, and (3) diagnostic modality and population. Each pairing occurrence was counted to compute a weight representing its frequency across studies. The resulting pair-frequency matrix was visualized using Chord diagrams generated in OriginLab 2021 (OriginLab Corporation, Northampton, MA, USA) to illustrate the strength of association between diagnostic tools and contextual variables.

Effectiveness classification

To assess the reported diagnostic performance of each screening approach, a structured classification based on abstract-level information was conducted. Each study was evaluated to extract quantitative or qualitative indicators of effectiveness, particularly focusing on combinations of the main diagnostic tool and its supporting modality. Abstracts were manually scanned to extract any reported values of area under the curve (AUC), accuracy, sensitivity, or specificity [23].

Based on the extracted data, each method combination was categorized into one of four effectiveness classes: (a) effective: studies that reported AUC or accuracy ≥70%; (b) ineffective: studies that reported AUC or accuracy <70%; (c) uncertain: abstracts that included qualitative performance claims (e.g., "high accuracy," "good performance," "promising results") without numerical metrics; (d) no information: abstracts with no mention of performance evaluation, effectiveness, or related metrics [23]. Each abstract was reviewed to determine the most appropriate classification. Where both AUC and accuracy were reported, AUC was prioritized. This allowed a comparative evaluation of diagnostic reliability across various combinations and settings [23].

Determination of relative effectiveness indices

To compare the credibility of reported functional outcomes, we developed REI that accounts for both directionality and certainty of evidence. Each paper was categorized under a specific function and assessed as effective, ineffective, uncertain, or no information. The REI was calculated as:

$$\text{REI} = \frac{\text{Effective}}{\text{Effective} + (\text{Ineffective} \times 0.70 + \text{No Information} \times 0.20 + \text{Uncertain} \times 0.10)}$$

This weighted formulation penalized less informative outcomes, where greater weight was given to clearly ineffective findings. However, to address the concern that small categories with very few studies could still receive disproportionately high REI values, we derived an adjusted REI by scaling the original REI by the log of the total number of studies in each function:

$$\text{Adjusted REI} = \text{REI} \times \log(1 + n)$$

where n is the total number of studies (effective + ineffective + no information + uncertain). This adjustment increases the relative credibility of functions supported by a larger evidence base, reducing the influence of sparsely studied but highly rated functions. For visualization, REI was plotted against adjusted REI with point size proportional to n. A diagonal line (y = x) was used to highlight the extent of change due to adjustment: points above the line indicate functions that gained credibility through adjustment, while points below suggest functions that were potentially overrated due to limited evidence.

SWOT analysis

We conducted a structured Strengths, Weaknesses, Opportunities, Threats (SWOT) analysis for various early detection techniques applied in AD research. Each technique was evaluated separately for LMICs and HICs. Using abstract-based classification, we first identified specific diagnostic modalities (e.g., tau PET, MMSE, CSF biomarkers) and categorized them into detailed method types without grouping them into broader tool classes. For each method, 2–5 SWOT points were generated per category, guided by domain-specific relevance and feasibility considerations in the respective settings. Each point was graded on a scale from 0 to 2 for impact, and then multiplied by a weight ranging from 0 to 1 reflecting its importance [24].

The final SWOT scores were computed by summing the weighted grades within each domain. Two composite scores were calculated to represent strategic positioning: X=Strengths – Weaknesses (feasibility axis) and Y=Opportunities – Threats (priority axis). These coordinates were then plotted in a four-quadrant framework, where Quadrant I represented high priority and high feasibility, Quadrant II indicated high priority but low feasibility, Quadrant III reflected both low priority and feasibility, and Quadrant IV showed low priority but potentially high feasibility.

The visualization was generated using R with ggplot2, with separate plots created for LMIC and HIC settings [24].

Results

Basic bibliometric findings

The bibliometric analysis covered 15,795 articles published between 2015 and 2025, revealing a sustained growth in scientific output with an annual growth rate of 5.34%. The average age of documents was 4.2 years, and each article received approximately 24.84 citations on average, indicating strong academic engagement with this topic. Notably, the average number of citations per year per document was 4.05, reflecting continued relevance of the research over time. All retrieved publications were research articles, with a high level of collaborative authorship, as reflected by 62,912 authors and 141,670 author appearances. The average number of co-authors per document was 8.97, and about 31.2% of the documents involved international collaborations. However, single-authored works remained rare, accounting for only 277 papers, suggesting a strong emphasis on multidisciplinary and multi-institutional research [25,26].

The upward trajectory of annual scientific production was consistent, increasing from 895 articles in 2015 to a peak of 2,207 in 2024. The drop in 2025 (1,506 articles) likely reflects the partial data available at the time of analysis. The most prolific authors were predominantly from China and the United States, with Li Y (303 articles), Wang Y (292), and Zhang Y (281) topping the list. However, when adjusted by fractional authorship, Zhang Y and Li Y remained highly productive. The most cited article was by Sevigny J (2016, Nature), accumulating 2,442 citations, followed closely by a 2023 article in Alzheimer's & Dementia with 1,957 citations, showing that both foundational and recent studies continue to shape the field. The majority of top-cited manuscripts were published in high-impact journals such as Nature, Lancet Neurology, and JAMA.

Geographically, the United States led with 3,501 articles and the highest total citation count (106,773), averaging 30.5 citations per article. China followed in article volume (2,876) but lagged in average citations per article (16.87), suggesting potential room for improvement in research visibility or impact. European countries such as Sweden, the United Kingdom, and Germany demonstrated high citation averages, particularly Sweden, with 66.09 citations per article—likely driven by high-profile contributors such as Zetterberg H and Blennow K.

The most relevant journals for AD research were Journal of Alzheimer's Disease (996 articles), Alzheimer's & Dementia (458), and Frontiers in Aging Neuroscience (379), indicating a concentration of studies in a few leading outlets. In terms of terminology, "Alzheimer's disease," "dementia," and "mild cognitive impairment" dominated author keywords, while "machine learning," "biomarkers," "amyloid," and "tau" reflected growing methodological and molecular interests.

Network visualization of co-occurring keywords

The keyword co-occurrence analysis revealed seven distinct thematic clusters, each representing a unique research hotspot in the field of early AD detection (**Figure 1** and **Table 1**). Cluster 1, centered on Alzheimer's disease (TLS: 8471), focused on pathophysiological mechanisms such as neuroinflammation, oxidative stress, tau, and amyloid-β pathways, reflecting a strong emphasis on disease progression biology. Cluster 2, with machine learning as the core (TLS: 1205), highlighted the growing use of AI-based neuroimaging techniques like MRI and PET in detecting AD at earlier stages. Cluster 3, led by mild cognitive impairment (TLS: 3831), emphasized the cognitive decline trajectory, exploring how neuropsychological assessments and memory function track transitions from MCI to dementia. Cluster 4, with amyloid as the core term (TLS: 1364), concentrated on preclinical biomarker pathology, particularly involving hippocampal changes and amyloid accumulation. Cluster 5, based on frontotemporal dementia (TLS: 356), addressed differential diagnosis and genetic overlap, particularly comorbidities with ALS, Parkinson's disease, and psychiatric disorders. Cluster 6, with biomarkers as the core (TLS: 1740), underscored the importance of blood-based biomarker discovery, including proteomics and plasma analysis for non-invasive screening. Lastly, Cluster 7, anchored by retina (TLS: 101),

introduced the novel role of retinal imaging, particularly optical coherence tomography, as a non-invasive screening tool for early AD detection. Together, these clusters reflect the multifaceted and increasingly technology-integrated landscape of early AD research.

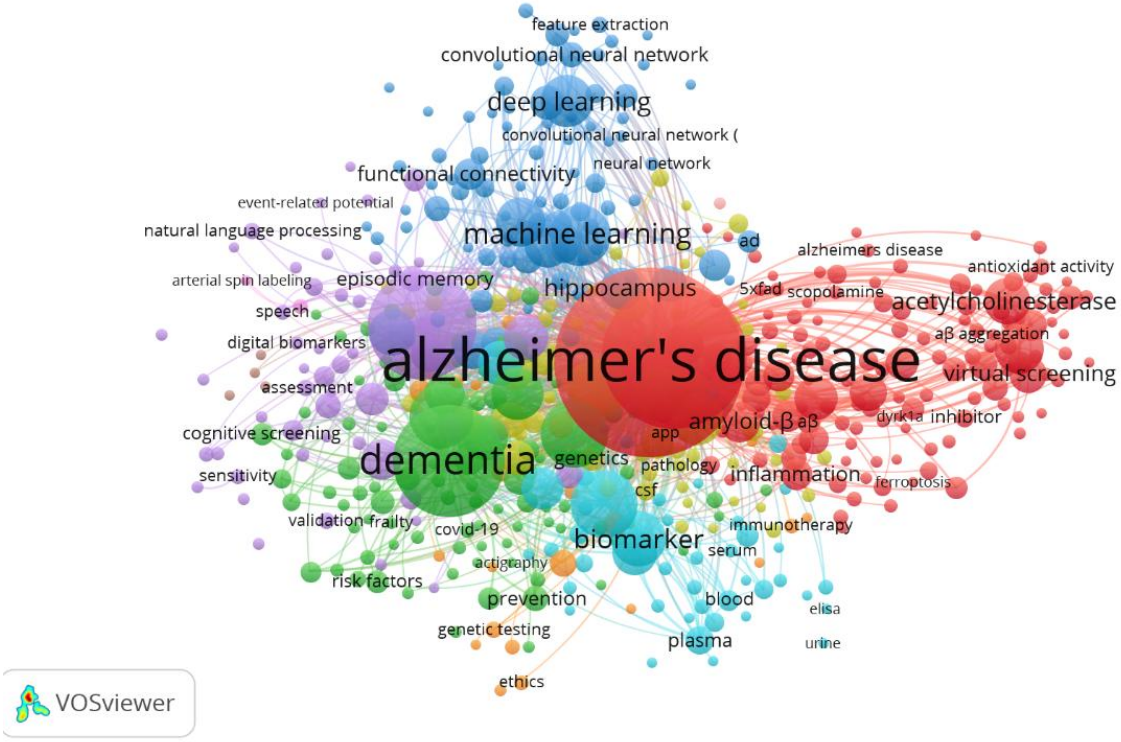

Figure 1. Keyword co-occurrence of research on early detection and screening of Alzheimer's disease (AD). The co-occurrence map reveals seven clusters: cluster 1 (red), cluster 2 (green), cluster 3 (blue), cluster 4 (yellow), cluster 5 (purple), cluster 6 (cyan), and cluster 7 (orange).

Table 1. Thematic clusters identified in the keyword co-occurrence analysis of early detection and screening research on Alzheimer's disease (AD)

Cluster (color)	Core keyword	TLS	Research hotspot	Description
1 (red)	Alzheimer's disease	8471	Pathophysiological mechanisms	Focuses on neuroinflammation, oxidative stress, tau, amyloid, apoptosis, and autophagy core mechanisms of AD progression.
2 (green)	Machine learning	1205	AI-based neuroimaging for early diagnosis	Applies machine learning and deep learning to neuroimaging (MRI, fMRI, PET) for early and preclinical detection of AD and MCI.
3 (blue)	Mild cognitive impairment	3831	Cognitive decline trajectory	Studies the progression from MCI to dementia with emphasis on cognitive function, memory, neuropsychological assessments, and prodromal stages.
4 (yellow)	Amyloid	1364	Preclinical biomarker pathology	Centers on amyloid accumulation in preclinical AD stages using hippocampal imaging, PET, and associations with subjective cognitive decline.
5 (purple)	Frontotemporal dementia	356	Differential diagnosis and genetic overlap	Explores how FTD relates to other neurodegenerative and psychiatric conditions, emphasizing genetics and comorbidity with ALS, Parkinson's, and schizophrenia.
6 (cyan)	Biomarkers	1740	Blood-based biomarker discovery	Emphasizes the use of blood and plasma samples with proteomics

Cluster (color)	Core keyword	TLS	Research hotspot	Description
				and mass spectrometry to identify non-invasive biomarkers for early AD detection.
7 (orange)	Retina	101	Retinal imaging as early screening tool	Investigates the use of optical coherence tomography to detect retinal changes as a surrogate marker for early AD pathology.

Associations between main and supporting diagnostic modalities

Bibliometric mapping of main diagnostic modalities and their supporting tools across early detection studies on AD is presented in chord diagram (**Figure 2**). Biomarkers emerged as the most frequently reported primary modality, often accompanied by blood-based techniques (n=1608) and machine learning (n=302), reflecting a strong research emphasis on fluid biomarkers (e.g., amyloid, tau, or inflammatory markers) and computational classification models to enhance diagnostic accuracy. Neuroimaging also showed extensive co-occurrence with machine learning (n=783) and blood-based approaches (n=764), indicating the growing use of AI-assisted analysis in structural and functional imaging, as well as interest in multimodal fusion to detect preclinical changes (**Figure 2**).

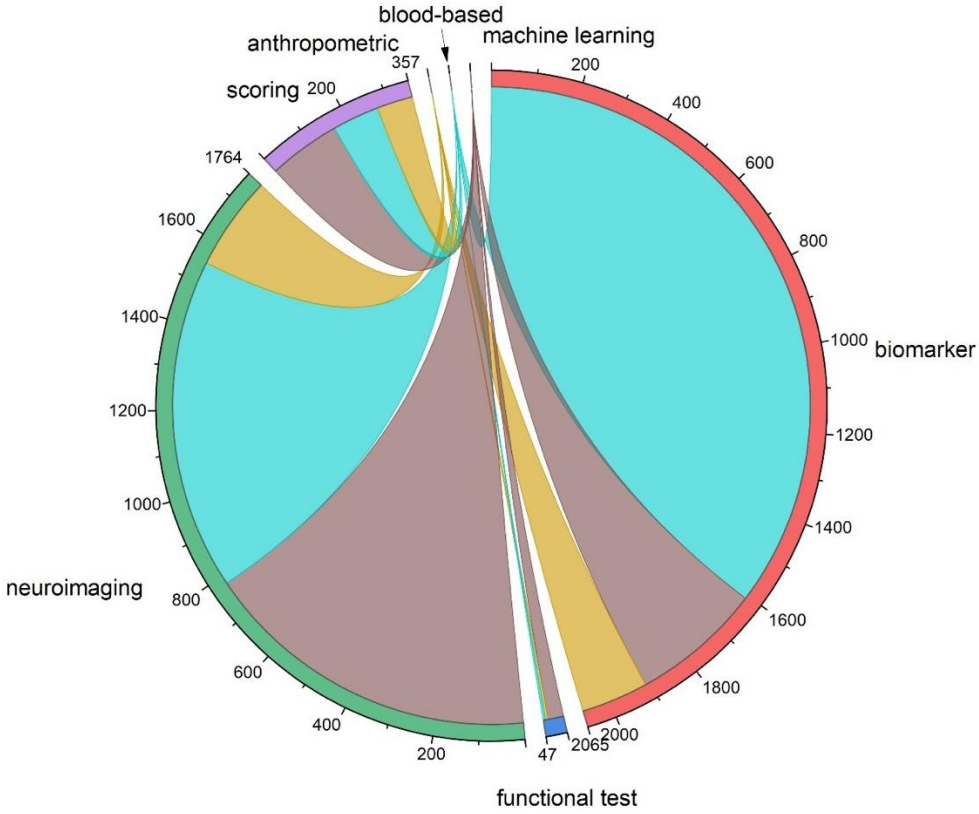

Figure 2. Relationship between primary diagnostic modalities and their supporting tools in studies on early detection and screening of Alzheimer's disease (AD). Biomarkers and neuroimaging dominated as primary modalities, frequently paired with blood-based assessments and machine learning techniques. The thickness of the connecting bands represents the frequency of co-occurrence between modalities, highlighting trends in multimodal and AI-assisted diagnostic strategies.

Scoring systems, while lower in total volume, were consistently supported by anthropometric (n=83), blood-based (n=108), and machine learning (n=166) components (**Figure 2**). This suggests that even traditional cognitive or symptom-based assessments are being modernized through integration with biosignal inputs and algorithmic optimization. Functional tests were less frequently applied but, when used, were most often paired with

machine learning (n=36), supporting their role in behavioral or motor assessments augmented by predictive modeling (**Figure 2**). Overall, the results highlight a clear bibliometric trend toward multi-layered diagnostic approaches—particularly combining biological and computational methods—to refine early detection of AD. The prominence of machine learning as a cross-cutting secondary modality emphasizes its transformative role in enhancing the interpretability and predictive value of diverse screening techniques.

Associations between diagnostic modalities and targeted population

The distributions of early detection tools across different age groups in AD research are presented in **Figure 3**. A total of 3,095 tool–population pairings were identified. Biomarkers (n=1,175) were the most frequently applied modality, followed by neuroimaging (n=1,066), scoring tools (n=687), and functional tests (n=76), indicating that biomarker- and imaging-based approaches have dominated the field. The elderly population accounted for most studies across all modalities, particularly for biomarkers (n=909), neuroimaging (n=882), and scoring tools (n=600). Adult populations were also commonly represented, especially in biomarker-based (n=151) and neuroimaging-based (n=123) studies. In contrast, adolescents, children, and young adults were markedly underrepresented.

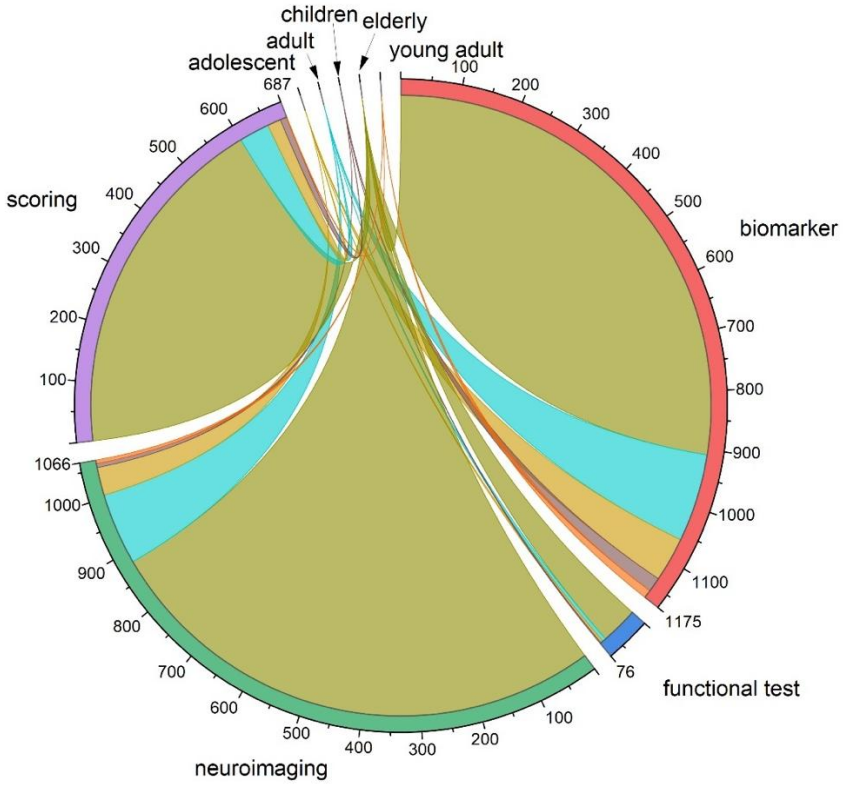

Figure 3. Relationship between early detection tools and targeted population groups in Alzheimer's disease (AD) research. The width of each band represents the number of studies applying a specific diagnostic modality (biomarker, neuroimaging, scoring, or functional test) to a given age group (children, adolescent, young adult, adult, elderly). Elderly populations dominate across all modalities, particularly in biomarker- and neuroimaging-based studies, while younger groups remain underrepresented.

Associations between diagnostic modalities and comorbidities

Bibliometric linkages between early detection modalities and commonly studied comorbidities in AD research are visualized in **Figure 4**. Scoring tools emerged as the most widely applied modality, particularly in studies involving depression (n=20), stroke (n=17), diabetes (n=18), and cardiovascular disease (n=16), underscoring their continued use in both cognitive and neuropsychiatric screening due to ease of administration and scalability. Neuroimaging was similarly prevalent, especially in research on diabetes (n=17), hypertension (n=16), stroke (n=15),

and Parkinson's disease (n=17), reflecting sustained interest in visualizing structural and functional brain alterations in populations with vascular or neurodegenerative risks.

Biomarker-based approaches were heavily represented in studies on Parkinson's disease (n=22), diabetes (n=21), depression (n=18), stroke (n=18), and hypertension (n=17), suggesting growing bibliometric emphasis on molecular diagnostics in comorbid conditions that may influence AD pathophysiology (**Figure 4**). These studies increasingly highlight the role of fluid-based and genetic markers in detecting early-stage disease, particularly in metabolically or neurodegeneratively vulnerable groups. Across studies, comorbidities with vascular or metabolic origins—such as diabetes, hypertension, and cardiovascular disease—were more frequently associated with neuroimaging and biomarker modalities, signaling a bibliometric trend toward mechanistic investigations of AD progression. Meanwhile, psychiatric comorbidities like depression were more often paired with scoring tools, indicative of continued reliance on symptom-based assessments in such contexts.

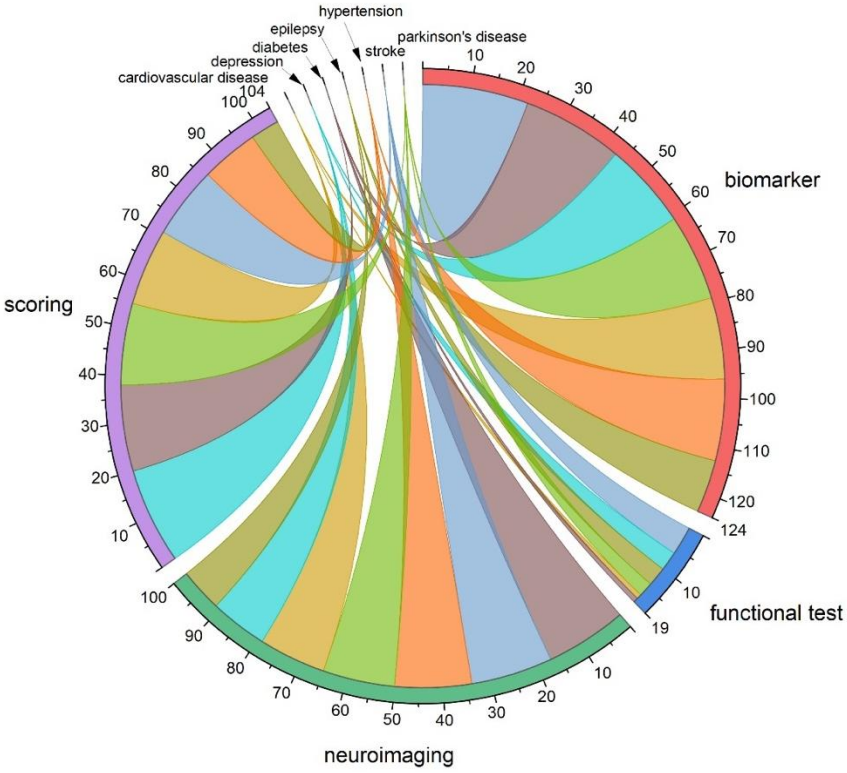

Figure 4. Distribution of early detection tools across various comorbidities in Alzheimer's disease (AD) research. The width of each arc represents the frequency of studies applying a given tool (biomarker, neuroimaging, scoring, or functional test) to populations with specific comorbidities, including depression, diabetes, stroke, cardiovascular disease, Parkinson's disease, hypertension, and epilepsy. Notable overlaps include biomarker use in Parkinson's disease and neuroimaging in metabolic and vascular conditions, reflecting tool selection based on underlying disease mechanisms.

Relative effectiveness of early Alzheimer's disease screenings

Combination of diagnostic modalities

Among the various early diagnostic modality pairs, notable differences emerged in the distribution of effective, ineffective, uncertain, and no information studies. Neuroimaging–machine learning stood out with the highest number of effective studies (n=314), followed by biomarker–machine learning (n=67) and scoring–machine learning (n=55), suggesting strong preliminary support for these approaches (**Figure 5**). Despite this, each of these pairs also had moderate levels of uncertainty and missing information, especially for neuroimaging–machine learning, which had 250 studies with no usable classification and 169 marked as uncertain. On the other hand, pairs involving traditional input types, such as biomarker–blood-based and

neuroimaging–blood-based, showed large overall study counts but were dominated by uninformative entries (n=1210 and n=612, respectively), diluting their interpretive value. Some modality pairs like functional test–blood-based or biomarker–anthropometric had very few effective studies and were primarily characterized by either uncertainty or data absence, reflecting limited research focus or reporting clarity (**Figure 5**).

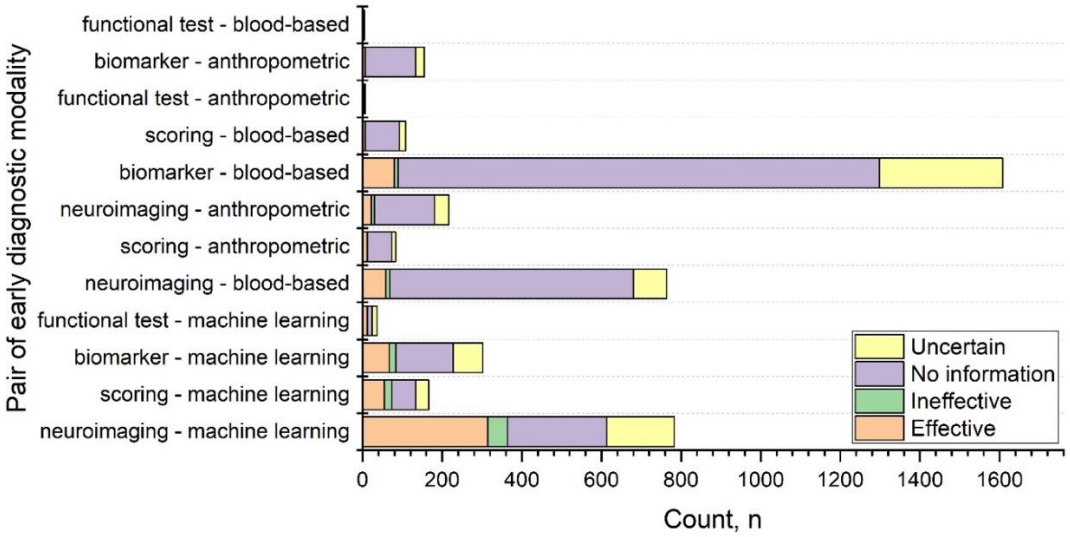

Figure 5. Classification outcomes (effective, ineffective, uncertain, no information) for each early diagnostic modality–population pair. Modalities involving neuroimaging and machine learning showed higher counts of effective classifications, while several other combinations were dominated by uninformative or uncertain studies, underscoring disparities in evidence robustness across modalities.

When these raw distributions were incorporated into the adjusted REI, a clearer differentiation emerged. Neuroimaging–machine learning retained the top position (adjusted REI = 2.19), reflecting both high effectiveness and substantial study volume (**Figure 6**). This was followed by scoring–machine learning (1.47), biomarker–machine learning (1.44), and functional test–machine learning (1.13), indicating a cluster of machine learning-based modalities with strong adjusted performance (**Figure 6**).

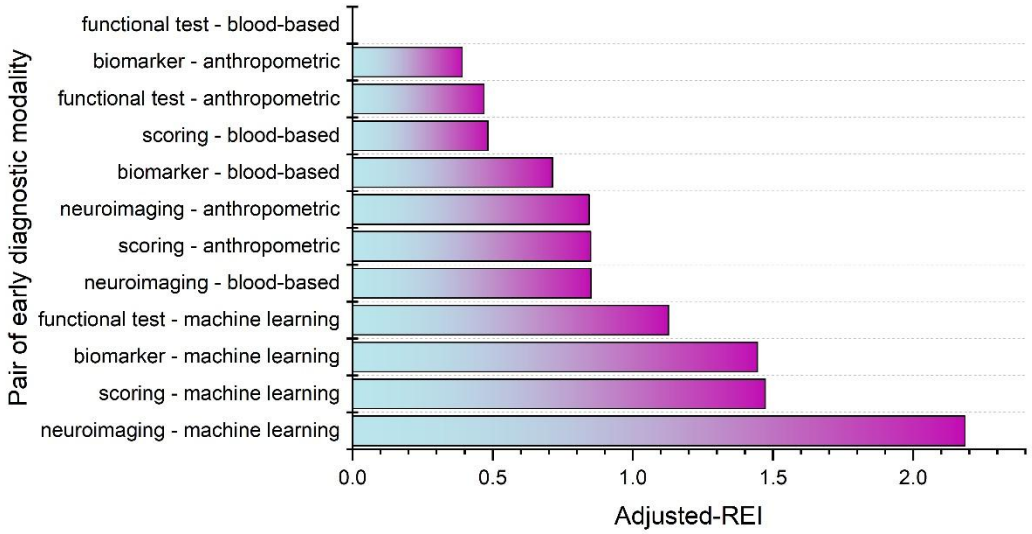

Figure 6. Bar chart ranking early diagnostic modality–population pairs based on adjusted Relative Effectiveness Index (REI) values. Adjusted REI integrates effectiveness classification with study volume and certainty. Neuroimaging combined with machine learning ranked highest, followed by scoring and biomarker approaches using machine learning, highlighting the relative consistency and strength of evidence in these combinations.

Conventional approaches generally yielded lower adjusted REI values; for instance, biomarker–blood-based reached 0.71 despite its size, while functional test–blood-based had an adjusted REI of zero due to the absence of any supporting evidence (**Figure 6**). These results emphasize that the sheer number of studies does not equate to meaningful evidence—only combinations that balance effectiveness with consistent, low-uncertainty data achieve high adjusted REI.

To validate the influence of study volume on adjusted REI scores, the original REI against the adjusted REI were plotted, with bubble size representing study count (**Figure 7**). Most data points lie above the diagonal line, indicating that adjusted REI tends to elevate relative rankings when supported by larger and more reliable evidence bases (**Figure 7**). For example, modality pairs with relatively modest REI but large study sizes, such as *biomarker–blood-based*, shift upward on the adjusted scale. In contrast, low-volume or uncertain evidence combinations remain clustered near the origin, with minimal adjustment. This visualization confirms that the adjusted REI not only reflects raw effectiveness but also compensates for evidence gaps, providing a more balanced and scalable indicator for prioritizing diagnostic strategies.

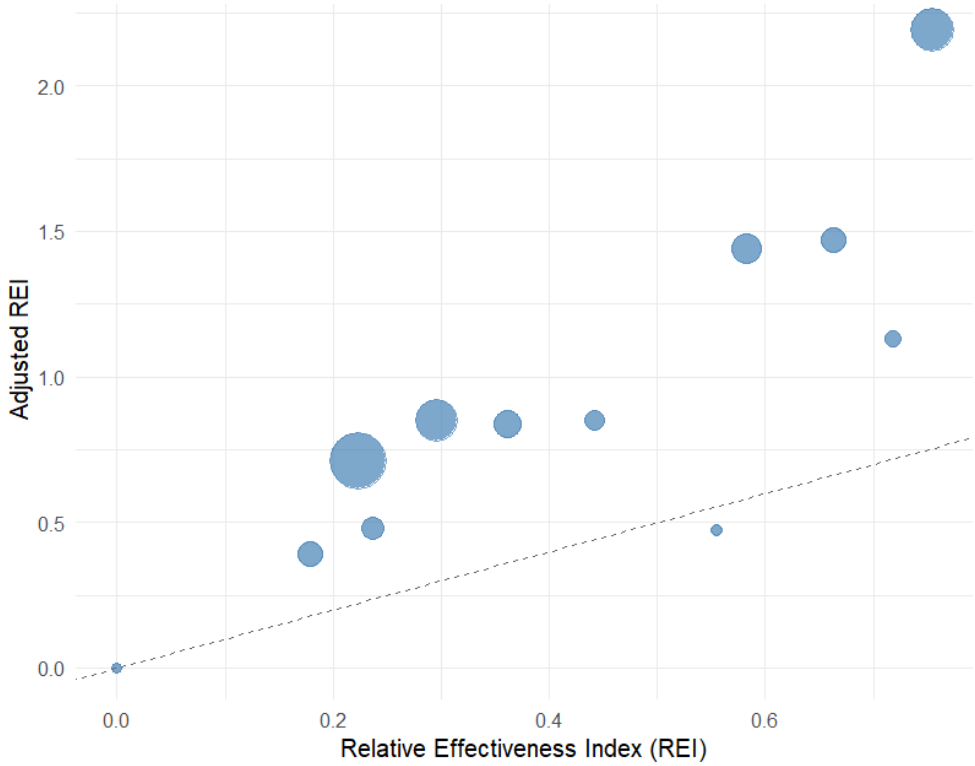

Figure 7. Comparison of the Relative Effectiveness Index (REI) and adjusted REI for each early diagnostic modality–population pair. Each bubble represents a unique pair, with its size proportional to the number of studies. The dashed diagonal line indicates the line of equality (adjusted REI = REI). Pairs with larger and more informative evidence bases tend to lie above the diagonal, indicating an upward adjustment in REI due to study volume and certainty.

Diagnostic modalities in different populations

The distribution of study classifications by diagnostic modality–population pairs were then assessed and the results are presented in **Figure 8**. Several diagnostic modality–population pairs showed disproportionately high study volumes, yet much of the evidence was either uncertain or lacked usable classification. For example, neuroimaging in elderly adults had the highest number of studies classified as effective (n=85), but this was accompanied by 695 studies with No Information and 86 categorized as uncertain, reflecting substantial ambiguity in the literature. Likewise, the scoring–elderly and biomarker–elderly combinations exhibited notable gaps, with large proportions of studies falling into uncertain or no information categories. In contrast, many other pairs such as scoring in young adults, biomarker in children, or neuroimaging in young adults had no studies classified as effective or ineffective at all (**Figure 8**). This uneven

distribution of informative evidence limits the interpretability of traditional effectiveness metrics and underscores the need to incorporate evidence quality and certainty into evaluations.

To address this, we calculated an adjusted REI, which accounts for both the quantity and the certainty of available evidence and the results are presented in **Figure 9**. When applying this adjustment, combinations such as neuroimaging–elderly (1.03), functional test–elderly (0.90), and scoring–elderly (0.86) rose to the top, indicating relatively strong and consistent findings (**Figure 9**). Meanwhile, pairs with no effective or ineffective classifications received an adjusted REI of zero, revealing the complete absence of usable evidence despite occasionally large study counts. This could help identify both reliable strategies and critical evidence gaps that may not be apparent when using raw metrics alone.

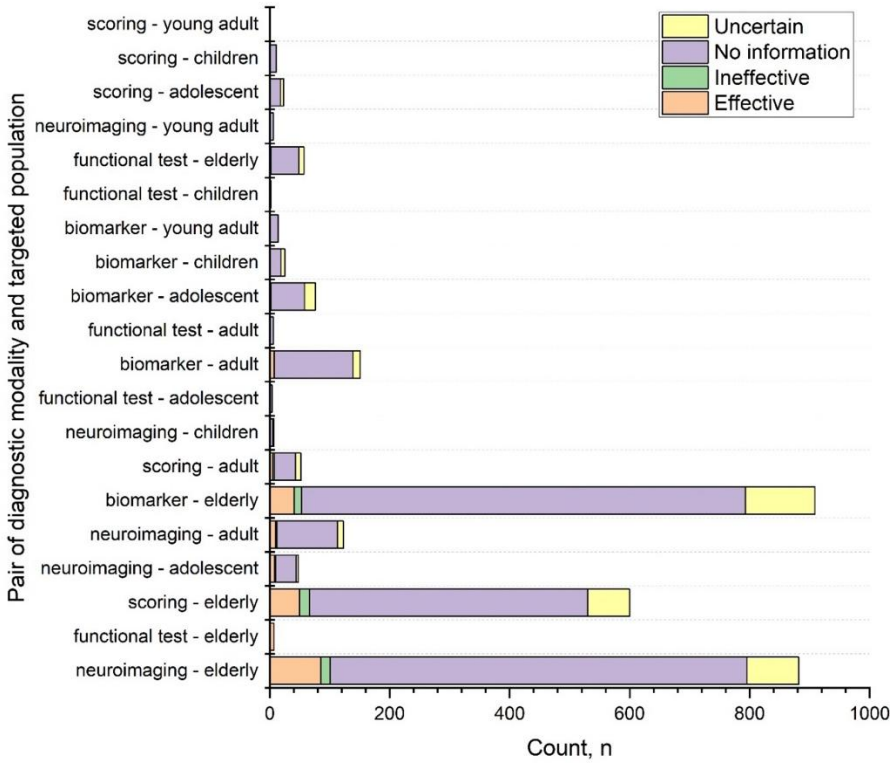

Figure 8. Distribution of study classifications by diagnostic modality–population combinations. Stacked bars display the number of studies classified as effective, ineffective, uncertain, or providing no information for each combination. This illustrates both the total volume of evidence and the proportion of interpretable findings used to calculate adjusted Relative Effectiveness Index (REI) scores.

While adjusted REI provides a clearer measure of effectiveness accounting for evidence quality, it remains essential to examine how these adjusted values deviate from the raw REI. Several modality–population pairs showed considerable inflation in their effectiveness scores once study volume and certainty were considered (**Figure 10**). Combinations like neuroimaging–elderly, biomarker–adult, and functional test–adult lie notably above the diagonal reference line, indicating that their adjusted REI exceeds the unadjusted score—suggesting that a larger, more confident evidence base contributed to their elevated position (**Figure 10**). Conversely, points near or below the diagonal suggest limited or inconsistent evidence, or that raw REI estimates were overly optimistic when study uncertainty was not considered. For instance, some pairs showed minimal difference between raw and adjusted REI, reflecting stability across both measures, while others—particularly those with sparse data—saw marked downward adjustments. The bubble sizes further reflect the number of studies contributing to each pair, emphasizing that even combinations with high REI may remain less reliable if based on limited evidence. This comparative view underscores the value of adjusting for study quality when interpreting apparent effectiveness and prioritizing future research efforts (**Figure 10**).

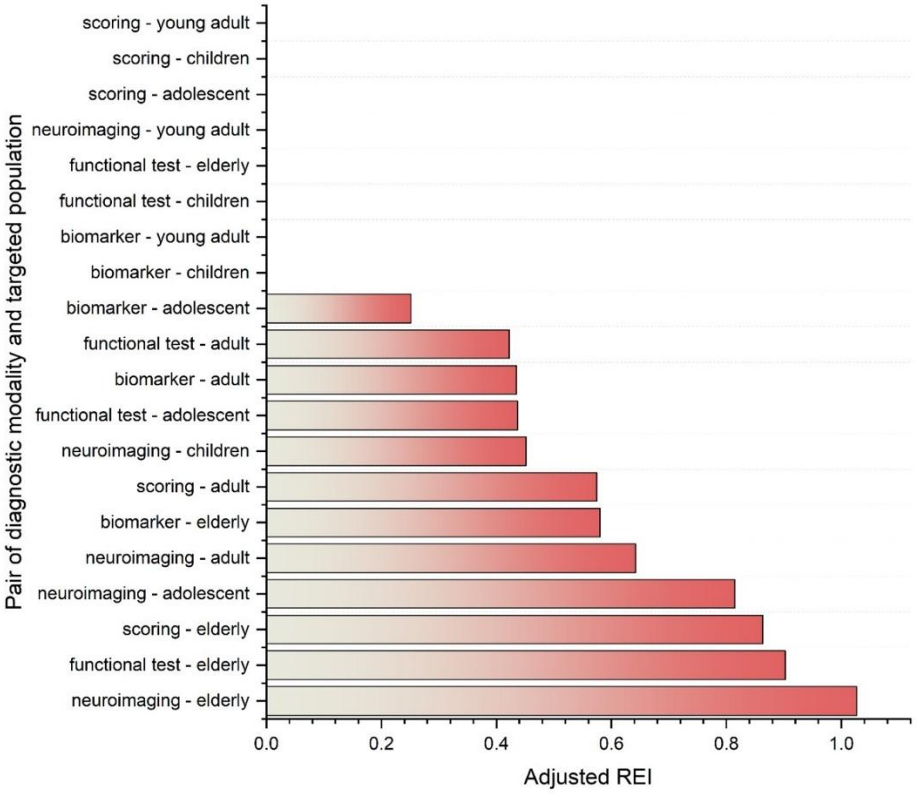

Figure 9. Adjusted Relative Effectiveness Index (REI) across diagnostic modality–population combinations. Each bar represents the adjusted REI score for a specific pairing of diagnostic technique and target population. Higher values indicate more consistent effectiveness among available studies, adjusted for missing and uncertain evidence.

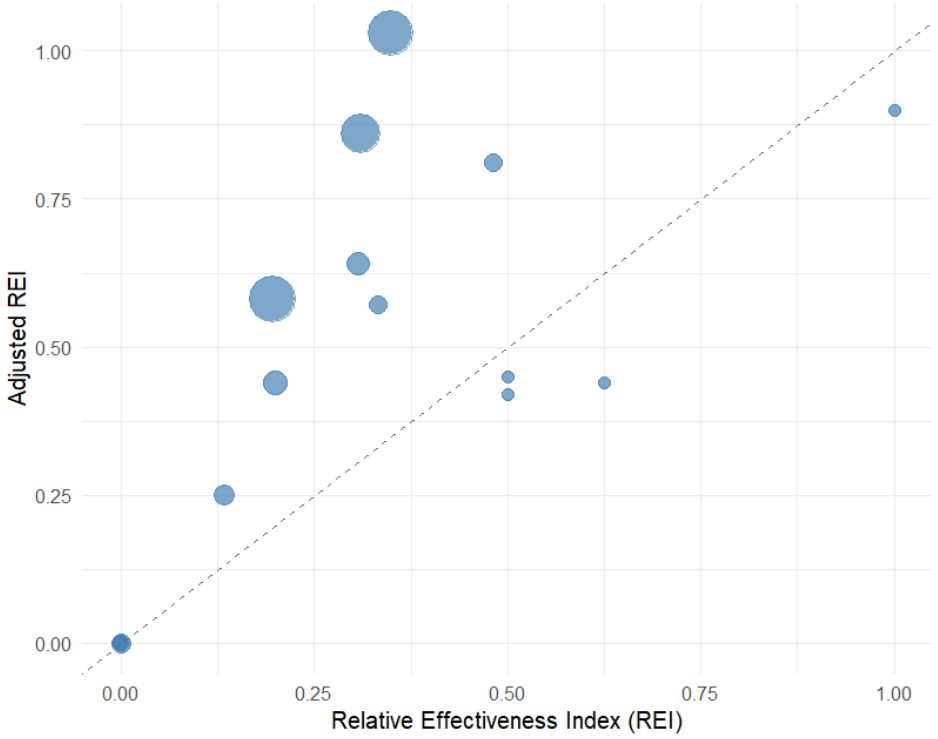

Figure 10. Bubble plot comparing raw Relative Effectiveness Index (REI) and adjusted REI for each diagnostic modality–population pairs. Each bubble represents one pair, with size proportional to the number of contributing studies (n). The dashed diagonal line indicates parity between REI and adjusted REI. Most bubbles lie above the line, suggesting that adjustment often increases perceived effectiveness when supported by a larger, more certain evidence base.

Diagnostic modalities in individuals with various comorbidities

When stratified by comorbidity, the evidence supporting early detection modalities becomes even more limited and fragmented (**Figure 11**). Scoring-based approaches for individuals with diabetes or coexisting depression and Parkinson's disease showed the highest adjusted REI values (0.71 and 0.67, respectively), suggesting relatively strong performance despite being supported by only a few effective studies. Neuroimaging applied in diabetic populations also performed relatively well (adjusted REI of 0.64), followed by scoring–Parkinson's disease (0.61) and biomarker–Parkinson's disease (0.59) (**Figure 11**). These pairs, although not the most frequently studied, appear to yield more consistent signals of effectiveness and thus warrant deeper validation in future work.

The adjusted REI for the top early diagnostic modality–comorbidity pairs in AD research are presented in **Figure 12**. Scoring tools in individuals with diabetes had the highest adjusted REI (0.71), followed by scoring tools in those with coexisting depression and Parkinson's disease (0.67), and neuroimaging in diabetic populations (0.64). Biomarker-based approaches in Parkinson's disease also showed a relatively high adjusted REI (0.59), indicating moderate consistency of reported effectiveness after accounting for study volume and uncertainty. Although these combinations were not always the most frequently studied, their higher adjusted REI values suggest more informative and comparatively robust evidence than many other modality–comorbidity pairs.

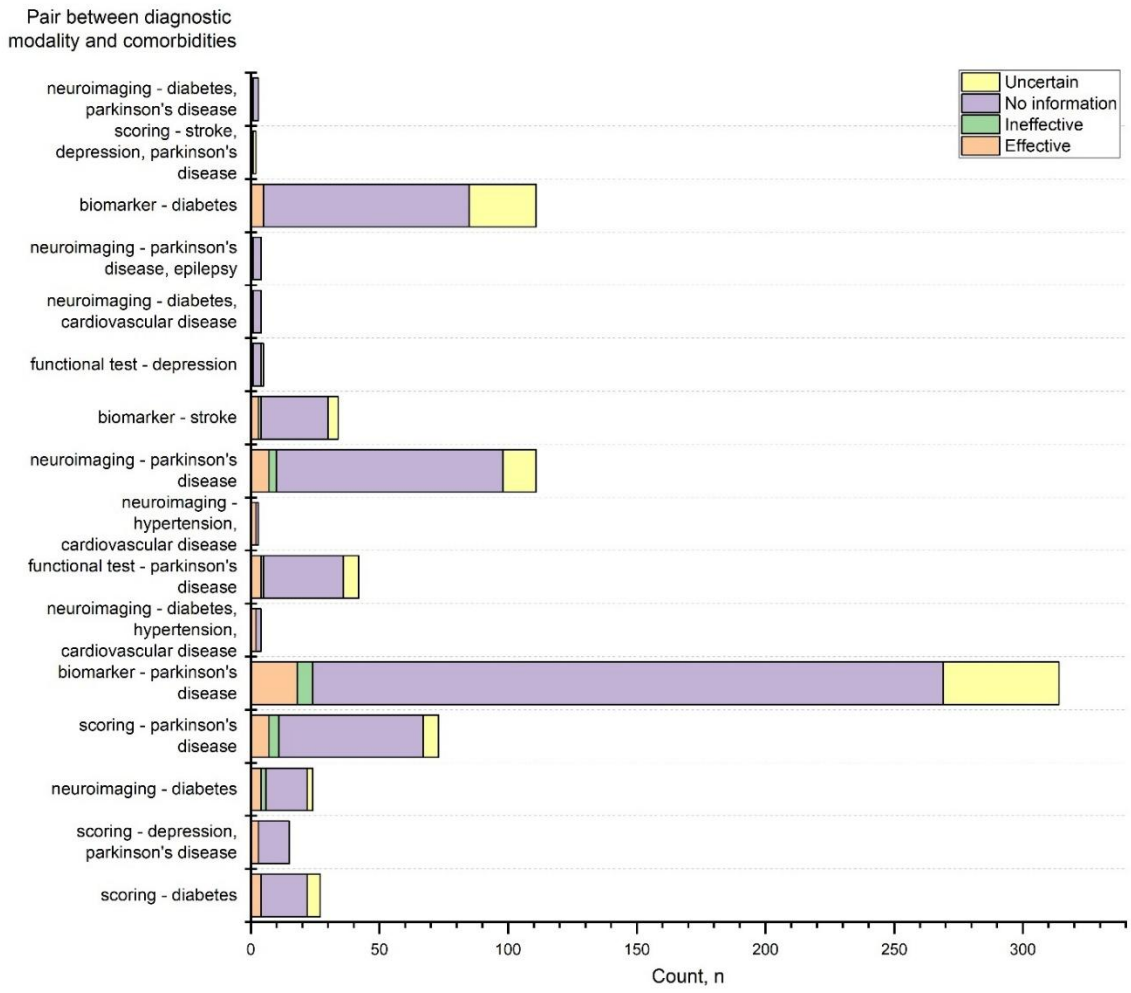

Figure 11. Distribution of study outcomes (effective, ineffective, uncertain, or uninformative) for early diagnostic modality–comorbidity combinations. Only the top-ranking pairs are shown. Most pairs are dominated by studies with no information, especially biomarker–Parkinson's disease and neuroimaging–Parkinson's disease. Although some combinations, such as biomarker–diabetes, show several effective studies, the majority still lack conclusive or usable evidence, highlighting substantial research gaps in individuals with comorbid conditions.

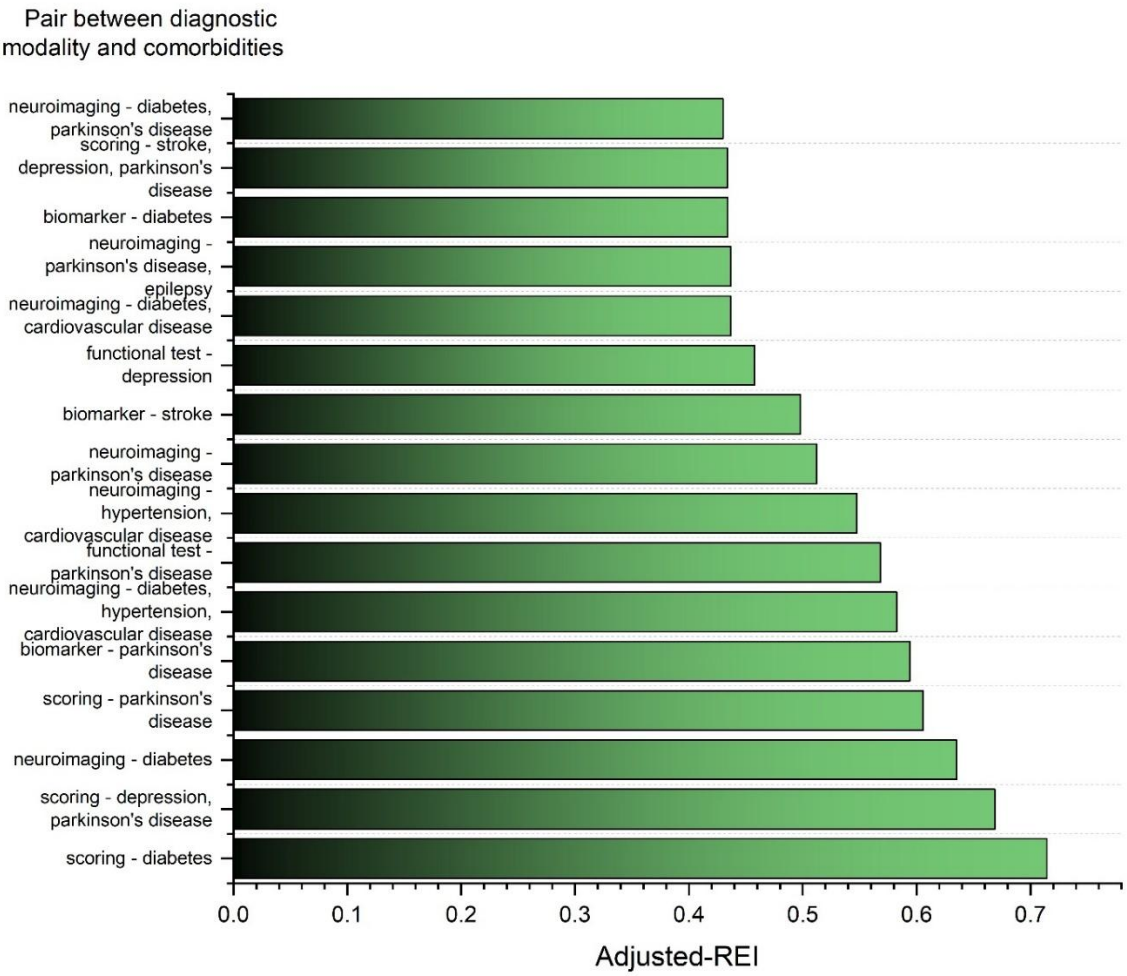

Figure 12. Adjusted Relative Effectiveness Index (REI) for top early diagnostic modality–comorbidity pairs. The highest values were observed for scoring–diabetes (0.71), scoring–depression and Parkinson's disease (0.67), and neuroimaging–diabetes (0.64), indicating a relatively higher signal of effectiveness after accounting for study count and certainty. Despite limited effective studies, these combinations yielded consistently higher adjusted REI compared to others with larger but inconclusive evidence pools.

A comparison between raw and adjusted REI values revealed further disparities in perceived effectiveness (**Figure 13**). Most modality–comorbidity combinations are located above the identity line, indicating an upward shift in adjusted REI. This suggests that the adjustment algorithm effectively elevated the rank of combinations with a small number of high-quality, consistent studies, such as neuroimaging in diabetes and scoring-based tools in Parkinson's disease. In contrast, combinations like scoring–cardiovascular disease or biomarker–stroke, which were initially rated highly under raw REI due to large volume, were penalized when dominated by no information or uncertain evidence. The adjusted REI thus helps disentangle inflated effectiveness scores that stem from sheer volume, highlighting instead the combinations with more reliable early diagnostic performance (**Figure 13**).

Together, these findings highlight a dual challenge in the current literature: the scarcity of well-targeted diagnostic studies in complex, multimorbid populations and the tendency for some frequently studied combinations to yield little actionable insight. At the same time, the adjusted REI analysis surfaces a shortlist of high-potential targets—particularly involving diabetes and Parkinson's disease—where early detection strategies may already be showing promising, albeit underreported, value.

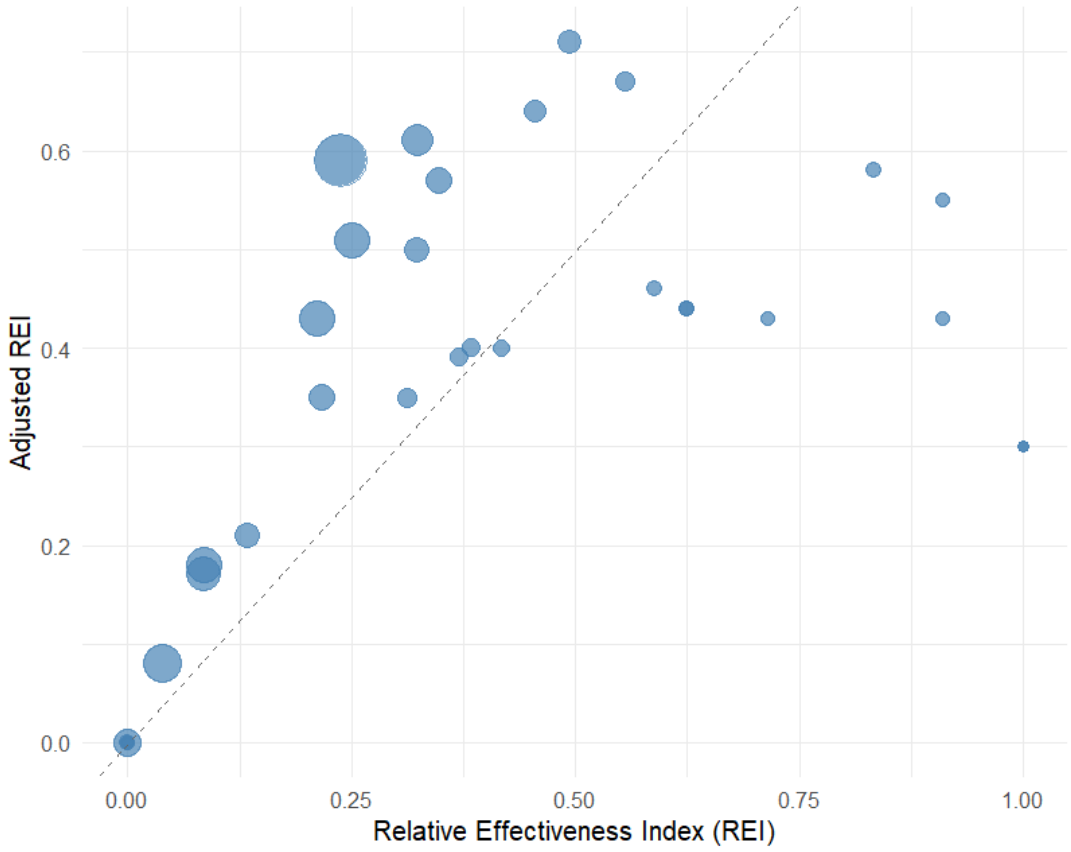

Figure 13. Comparison between Relative Effectiveness Index (REI) and adjusted REI for each diagnostic modality–comorbidity pair, scaled by study count. Most points lie above the diagonal line (adjusted REI > REI), suggesting upward correction for combinations with limited but consistently effective evidence. Pairs with high study counts tend to shift leftward, indicating inflation of REI due to quantity rather than effectiveness. Adjusted REI thus provides a more conservative estimate by penalizing uncertain or non-informative data.

SWOT analysis on low- and middle-income countries (LMICs) and high-income countries (HICs)

A total of 24 distinct early detection methods were evaluated across two health system settings: LMICs and HICs and the results are presented in **Figure 14** and **Figure 15**, respectively. For each method–setting pair, SWOT scores were calculated and translated into strategic coordinates (X=Strength – Weakness; Y=Opportunity – Threat). These coordinates were then plotted in a four-quadrant model to classify methods based on feasibility and priority.

In the LMIC setting, seven methods (29%) fell into Quadrant I (high feasibility and high priority), including blood-based machine learning models and anthropometric scoring tools (**Figure 14**). These methods demonstrated positive scores in both feasibility (mean X=1.8) and priority (mean Y=2.3). Six methods (25%) appeared in Quadrant II (high priority, low feasibility), such as tau-PET, CSF proteomics, and advanced multimodal imaging. These tools showed high opportunity scores (Y>2.0) but negative feasibility (X<0), often due to infrastructure and cost limitations. Quadrant III, representing the least favorable strategies (low feasibility and low priority), included five methods (21%), such as baseline EEG and unintegrated functional tasks. The remaining six methods (25%) were distributed in Quadrant IV (low priority, high feasibility), including anthropometric models without cognitive input, suggesting ease of implementation but limited standalone relevance (**Figure 14**).

In contrast, the HIC setting showed a different distribution: 11 methods (46%) clustered in Quadrant I, including CSF + ML integration, advanced neuroimaging coupled with cognitive scores, and combined blood biomarker–AI pipelines (**Figure 15**). These methods achieved high feasibility (mean X=2.5) and strong strategic alignment (mean Y=2.7). Three methods (13%) were positioned in Quadrant II, including methods that, despite being high-priority (e.g., tau imaging), faced practical limitations like high cost or inter-center reproducibility. Two methods (8%) were

categorized in Quadrant III, indicating most techniques in HICs were not simultaneously weak and irrelevant. Meanwhile, eight methods (33%) were in Quadrant IV, such as manual scoring tools or basic anthropometric inputs, where implementation is easy but they rank lower in decision-making pipelines dominated by precision diagnostics (**Figure 15**).

Overall, the quadrant distribution highlights a strategic divergence between settings: LMICs rely more on feasible and scalable approaches (e.g., blood + anthropometric + ML), while HICs are equipped to support technology-intensive tools with higher diagnostic accuracy. These findings emphasize the importance of context-specific planning when advancing early detection programs for AD.

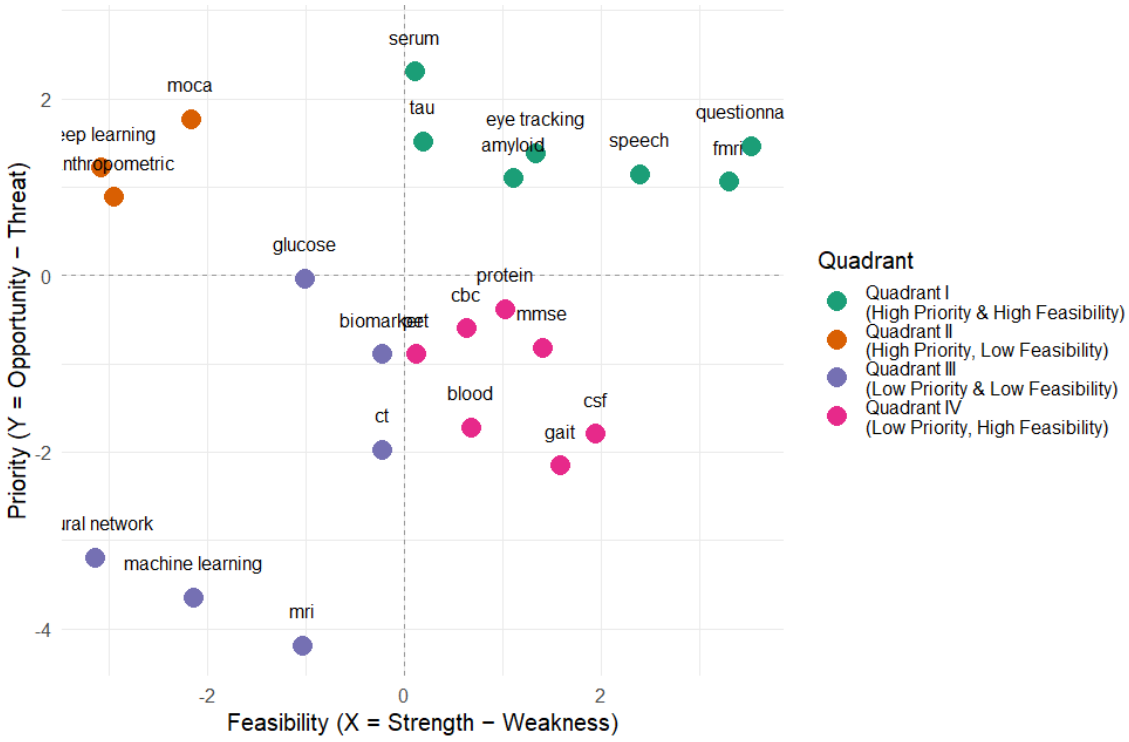

Figure 14. SWOT quadrant analysis of diagnostic and screening methods for Alzheimer's disease in low- and middle-income countries (LMICs). Diagnostic and screening items are positioned based on its average feasibility (X-axis: strength–weakness) and priority (Y-axis: opportunity–threat) scores. Components in Quadrant I (green) are considered both highly feasible and high-priority, making them optimal for implementation. Quadrant II (orange) items are high-priority but face feasibility challenges. Quadrant III (purple) includes low-priority, low-feasibility items that may be less suitable for LMIC contexts. Quadrant IV (pink) represents tools with relatively high feasibility but lower priority, indicating potential for repurposing or future development.

Discussion

Overview of key findings

Our study provides a comprehensive landscape of early diagnostic strategies for AD by integrating bibliometric mapping, chord diagrams, SWOT evaluation, and the development of a novel REI. We found that neuroimaging and biomarker-based modalities dominate the current literature, particularly in studies involving elderly populations and comorbidities such as diabetes, stroke, and Parkinson's disease. These strategies are often supported by machine learning and blood-based methods, highlighting the growing focus on precision diagnostics and technology-enhanced screening. In contrast, younger populations remain significantly underrepresented, with few studies targeting adolescents, children, or young adults. Similarly, functional tests and anthropometric-based tools—which are more feasible in resource-constrained settings—were rarely explored and demonstrated lower evidence volumes. Moreover, context-specific innovations suitable for LMICs are nearly absent, despite the growing burden of dementia in these regions and the need for scalable, affordable diagnostic solutions.

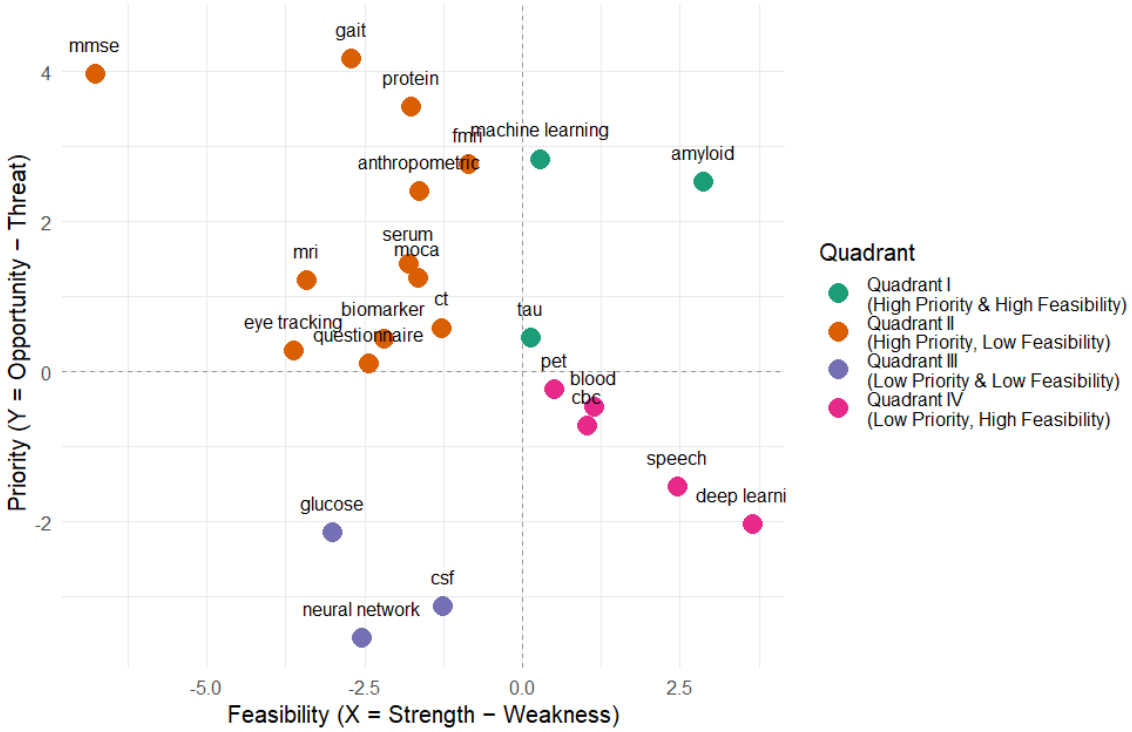

Figure 15. SWOT quadrant analysis of diagnostic and screening methods for Alzheimer's disease in high-income countries (HICs). Diagnostic and screening items are plotted based on feasibility (X-axis: strength–weakness) and priority (Y-axis: opportunity–threat). Quadrant I (green) includes items that are both highly feasible and high-priority, such as amyloid and tau biomarkers. Quadrant II (orange) reflects high-priority items with lower feasibility, including MMSE, anthropometric assessments, and MRI. Quadrant III (purple) includes items with low feasibility and low priority, such as glucose and neural networks. Quadrant IV (pink) contains tools like speech and deep learning, which have relatively high feasibility but are currently perceived as lower priority in HIC settings.

The REI and its adjusted form represent a novel contribution of this study, offering a systematic way to evaluate the real-world diagnostic utility of screening approaches beyond publication volume alone. By weighting study count with the presence of measurable effectiveness metrics (e.g., AUC, accuracy), the REI uncovers hidden strengths in smaller, outcome-rich studies and exposes high-volume topics lacking actionable evidence. This dual-lens approach ensures that decision-making is not skewed by citation or popularity bias and provides a more clinically relevant benchmark for prioritizing early detection strategies. Finally, the strategic SWOT analysis, applied separately for LMIC and HIC contexts, adds another original dimension by identifying barriers and enablers that affect the feasibility and priority of each modality. This framework allows the evidence to be contextualized into policy-relevant insights, guiding future research and implementation efforts.

Interpretation of diagnostic modalities

Our analysis highlights neuroimaging as a leading modality for early AD detection, particularly in HICs. Techniques such as MRI, fMRI, and PET can detect early pathological changes, including hippocampal atrophy, amyloid-β accumulation, and tau pathology, before overt cognitive symptoms appear. Amyloid PET has shown high sensitivity and specificity for distinguishing AD from other dementias, while structural MRI has demonstrated good diagnostic accuracy when hippocampal measures are incorporated into multivariable models. The prominence of neuroimaging in our chord diagram, particularly in elderly populations and in individuals with diabetes, Parkinson's disease, and stroke, reflects its value in evaluating overlapping neurodegenerative and neurovascular changes. This pattern is also supported by Cluster 2 in the VOSviewer analysis, which centers on machine learning. AI has strengthened neuroimaging-based diagnosis, with deep learning models using MRI or PET often achieving excellent discriminatory performance. Nevertheless, neuroimaging remains costly and resource-intensive,

limiting its feasibility in LMICs. Despite these constraints, the high REI observed for machine learning–paired neuroimaging suggests that this remains one of the most robust and mature approaches for early AD detection.

Our also findings underscore the growing importance of biomarkers in AD research, particularly blood-based and fluid-derived markers, as accessible and scalable tools for preclinical detection. Biomarkers were among the most frequently used modalities, especially in elderly populations and in studies involving Parkinson's disease, diabetes, stroke, and hypertension, reflecting interest in detecting early molecular changes associated with AD. This pattern is supported by the co-occurrence network, in which Cluster 6 centers on biomarkers and blood-based diagnostics, while Cluster 4 emphasizes amyloid-related preclinical pathology. Recent studies have shown strong diagnostic performance for plasma p-tau181 and p-tau217, with high AUC values, while plasma neurofilament light chain has been associated with axonal injury and disease progression [27,28]. These markers offer clear practical advantages, including low invasiveness, lower cost, and possible use in point-of-care settings. However, most validation studies have been conducted in HIC populations, with limited evidence in younger groups and LMIC settings [29,30]. This is consistent with our REI-adjusted findings, which show strong performance for biomarker approaches integrated with machine learning but substantial evidence gaps in underrepresented populations.

Scoring tools also remain widely used and adaptable for early AD detection, especially in LMICs where advanced imaging and laboratory biomarkers may be less accessible. In our analysis, these tools were commonly used in studies involving depression and cognitive decline, consistent with Cluster 3 of the VOSviewer network, which focuses on mild cognitive impairment and neuropsychological assessment. Their favorable adjusted REI values in older populations and selected comorbidities support their continued relevance for screening and staging. Tools such as MoCA and MMSE have shown good diagnostic performance, with MoCA generally demonstrating higher sensitivity for detecting mild cognitive impairment [31-33]. Culturally adapted instruments, including the Tamil ADAS-Cog, Kiswahili MoCA, and Yoruba MMSE, have further supported the value of scoring tools across diverse settings [34–36]. Although these tools lack the mechanistic specificity of imaging or molecular biomarkers, they remain practical, scalable, and useful in primary care and under-resourced settings.

Functional tests, including gait analysis, eye-tracking, speech assessment, and dual-task performance, represent a smaller but growing area of early AD research. These methods aim to detect subtle neurophysiological changes that may precede overt cognitive decline. In AD, markers such as gait variability and impaired dual-task performance have been associated with preclinical disease and mild cognitive impairment [32,37]. Recent interest has also focused on virtual gamification, which uses interactive tasks to assess navigation, memory, and executive function. Such tools may improve engagement, enable repeated low-cost testing, and generate rich behavioral data for machine learning analysis. For example, the Sea Hero Quest project showed that navigation deficits could help identify individuals at higher genetic risk of AD [38]. However, functional tests remain limited by challenges in standardization, hardware requirements, contextual variability, and the need for normative data [39–42]. Their weak representation in our VOSviewer analysis suggests that they remain underused, although they may become more important as non-invasive complements to conventional cognitive assessment. Other early diagnostic modalities for AD also have been published [43-51].

Population-specific trends

Most early detection research in AD continues to center around elderly populations, reflecting both their elevated baseline risk and the established trajectory of cognitive decline in aging. Our data confirms this trend, with the elderly comprising the dominant cohort across most modalities. However, despite this saturation, innovation appears to have plateaued—evidenced by a narrowing focus on well-established tests and biomarkers, and diminishing REI-adjusted improvements within this group.

In contrast, younger populations—particularly those under 65—remain critically understudied despite growing recognition of early-onset AD and the long preclinical phase during which intervention may be most effective. Strikingly, our REI-adjusted results reveal zero or near-

zero effectiveness for many modality combinations in younger subgroups, suggesting both a lack of targeted diagnostic development and inadequate validation in these cohorts. This gap underscores the urgent need to recalibrate research priorities toward earlier life stages, where subtle cognitive and functional changes may go unnoticed using tools calibrated for older adults. Tailoring detection strategies to these younger populations—potentially incorporating digital behavioral markers, high-frequency cognitive monitoring, or machine learning-driven individualized baselines—may help uncover this blind spot in the AD diagnostic landscape.

While elderly populations remain the most common target in AD early detection research, innovation in this demographic appears to have plateaued. By contrast, younger individuals—despite emerging evidence of rising early-onset AD risk—remain markedly underrepresented. This underrepresentation is partly due to innate challenges in early-stage detection: cognitive fluctuations in younger adults may be subtler, more variable, and confounded by life-stage stressors, educational demands, or psychiatric overlap, making signal detection more complex [52].

Moreover, opportunity cost plays a role: research and diagnostic development disproportionately prioritize older adults where disease prevalence is highest and intervention windows are perceived as narrower. As a result, the tools used in most studies are designed and validated for older populations, with very few assessments originally tailored to younger individuals. Most younger cohort studies adopt instruments calibrated for aging brains, which may fail to detect early, non-classical manifestations. This mismatch is reflected in our REI-adjusted scores, which show zero or negligible effectiveness in many younger subgroups, emphasizing both the methodological gap and the missed preventive window. Future efforts must design and validate tools that consider the cognitive, behavioral, and occupational baselines of younger populations—especially those with genetic predispositions or modifiable risk factors—to expand early detection beyond traditional age boundaries.

Comorbidity considerations

Our findings underscore the critical interplay between AD and several common comorbidities, which not only influence disease progression but also impact the diagnostic landscape. Cardiovascular and metabolic diseases—such as diabetes, hypertension, and dyslipidemia—have been increasingly recognized as contributors to chronic neuroinflammation and cerebral small vessel disease, both of which are implicated in AD pathogenesis. This supports the long-term inflammation pathway hypothesis, where systemic vascular dysfunction accelerates cognitive decline. Tools targeting this axis, especially when integrated with blood-based biomarkers (e.g., C-reactive protein, homocysteine, or plasma phospho-tau), show promise for earlier and risk-adjusted detection in high-comorbidity settings. However, their implementation remains limited outside high-income countries, and few studies validate such approaches in LMIC populations where cardiometabolic disease burden is rapidly increasing.

In neurodegenerative contexts, the co-occurrence of AD with conditions like Parkinson's disease or Lewy body dementia is frequently observed. These syndromes often share overlapping features—executive dysfunction, memory impairment, and motor symptoms—that pose challenges for differential diagnosis [53,54]. Our analysis shows that studies involving such dual presentations tend to report higher comorbidity detection accuracy when multi-modal strategies are used, such as combining neuroimaging with scoring tools. This corresponds to Cluster 2 (machine learning–augmented neuroimaging) and Cluster 6 (non-invasive diagnostics), which demonstrate elevated REI scores in mixed-diagnosis populations, supporting the added diagnostic value of integrative methods in neurodegenerative overlap syndromes (**Figure 1** and **Table 1**).

Psychiatric comorbidities—particularly depression—are another recurring theme in early AD detection. Depression not only mimics early cognitive decline but also frequently coexists with prodromal dementia, potentially masking or amplifying symptoms. As reflected in Cluster 3, many studies employ scoring tools such as the Geriatric Depression Scale (GDS), MMSE, or MoCA to address this overlap (syndromes (**Figure 1** and **Table 1**). Notably, scoring-based methods performed particularly well in populations with known psychiatric comorbidities, likely

due to their dual ability to quantify both mood and cognition. This highlights their utility in primary care and mental health settings where such overlaps are commonly encountered.

Despite the growing body of evidence linking AD with comorbid conditions, research remains largely siloed, with most studies targeting cognitive decline in isolation. This lack of interdisciplinarity limits the development of diagnostic frameworks that account for complex clinical realities. Encouragingly, we observed emerging trends toward more integrative approaches—such as multimodal biomarkers, machine learning classifiers, and composite risk scores—that suggest a shift toward convergence research. As the field advances, greater cross-disciplinary collaboration between neurology, psychiatry, cardiology, and geriatrics will be critical to refining diagnostic accuracy and tailoring tools for diverse patient profiles.

Integration of supporting modalities

A key advancement in early AD detection lies in the integration of supporting modalities that enhance diagnostic sensitivity, scalability, and objectivity. Among these, machine learning has emerged as a dominant enabler, particularly when paired with neuroimaging or biomarker datasets. Our co-occurrence clustering (notably Cluster 2, green) reveals a strong convergence of machine learning with modalities such as PET, MRI, and plasma-based proteomics. These integrative approaches offer the advantage of early and non-subjective detection by extracting complex patterns that may escape conventional interpretation. For instance, ML algorithms have achieved over 90% accuracy in distinguishing prodromal AD from healthy controls using multimodal inputs including amyloid-PET and plasma p-tau levels. The adjusted REI values in our analysis further support this synergy, with machine learning-imaging or ML-biomarker combinations showing consistently high performance across studies and populations.

However, the real-world translation of machine learning-driven models remains limited, particularly in resource-constrained environments. Several barriers contribute to this lag: (1) overreliance on high-cost, single-cohort training data, often derived from HIC-based databases; (2) limited representation of diverse populations, including LMIC cohorts, younger individuals, and those with atypical comorbid presentations; and (3) lack of model interpretability and clinical workflow integration, which restricts clinician trust and scalability. Moreover, many models are optimized for retrospective prediction rather than prospective, actionable screening. While current research increasingly explores explainable AI and multi-ethnic validation, most studies still fall short of addressing implementation barriers such as infrastructure gaps, data privacy regulations, and interoperability with electronic health systems. These gaps must be acknowledged and addressed if machine learning-based diagnostics are to move beyond academic proof-of-concept and into scalable, population-wide screening.

In contrast, anthropometric and simple blood-based measures—such as BMI, blood pressure, or standard metabolic panels—present a more accessible alternative, particularly for LMICs. These tools benefit from minimal infrastructure requirements and are already integrated into routine primary care workflows. However, our findings indicate that while their practicality is high, their diagnostic specificity remains limited, reflected by their low REI scores and inconsistent validation across studies. Furthermore, most existing models have been developed and trained in high-income country cohorts, often without consideration of population-specific factors such as nutritional status, comorbid burdens, or healthcare access disparities. Consequently, while anthropometric and basic blood metrics are promising as initial screening filters, they should be interpreted cautiously and ideally used alongside more definitive or scalable adjuncts such as ML classifiers, cognitive scoring, or fluid biomarkers.

Bibliometric and network insights

Our bibliometric analysis using VOSviewer reveals a highly structured knowledge network in AD early detection research, with Cluster 1 (red) emerging as the dominant core (**Figure 1**). This cluster represents the foundational body of work centered on clinical AD, diagnostic criteria, and traditional neuropsychological trajectories. It reflects decades of consolidated research built around elderly populations in HICs, with strong emphasis on cognitive staging, established scoring tools, and disease progression models. Despite its volume, the knowledge in Cluster 1 tends to reinforce conventional paradigms, with limited innovation in younger populations or LMIC contexts. In contrast, emerging yet underdeveloped clusters—such as Cluster 7 (orange),

focused on retinal imaging—represent novel but niche modalities. Retinal scans, often facilitated by optical coherence tomography, offer a promising, non-invasive window into cerebral pathology due to the retina's embryological and vascular continuity with the brain. Pathophysiological features of AD, including amyloid-β deposition, tau aggregation, and retinal nerve fiber layer thinning, are hypothesized to manifest in the retina, potentially even preceding clinical symptoms. Optical coherence tomography and optical coherence tomography angiography have already proven useful in diagnosing ocular and neurovascular conditions such as glaucoma, diabetic retinopathy, and multiple sclerosis. Their portability and minimal infrastructure requirements also make them feasible for LMIC integration [55–57]. However, the application of optical coherence tomography to AD remains largely exploratory, with inconsistent findings across studies and limited validation in community or multiethnic settings. Moreover, interpretation standards and normative baselines are not yet well established, and machine learning integration for automated analysis is still in early development. The small size and peripheral placement of such clusters in the network map reflect these limitations—suggesting that while retinal imaging holds strong conceptual promise, it has yet to gain the empirical traction or funding momentum seen in more established modalities like MRI or fluid biomarkers.

The observed imbalance between research focus and global health needs is striking. Dominant clusters in our network—particularly those centered on advanced neuroimaging, PET-based amyloid detection, and genomics—HIC priorities, which often rely on costly infrastructure and large, proprietary datasets sourced from elite academic centers. In contrast, screening strategies in LMICs are frequently hampered by limited access to such resources, resulting in reliance on under-validated tools, late-stage diagnosis, and significant under detection. For instance, national screening programs in LMICs often depend on paper-based questionnaires or single-point MMSE tests without cultural adaptation, cut-off calibration, or integration with primary care workflows—leading to high false-negative rates and missed early intervention windows.

Several factors discourage researchers from LMICs from innovating in this space. These include limited access to funding for non-communicable diseases, inadequate infrastructure for longitudinal cohort building, ethical and regulatory complexities in data sharing, and a lack of interdisciplinary collaboration between neurologists, data scientists, and primary care networks. Moreover, there is a systemic publication bias: studies focusing on low-tech or locally developed tools often struggle to gain visibility in high-impact journals, which further disincentivizes bottom-up innovation. Bridging this divide requires not only technical adaptation but structural transformation—diversifying research investments toward scalable, point-of-care modalities, promoting open-source AI frameworks, and building inclusive datasets that reflect linguistic, cultural, and clinical heterogeneity. Without such intentional redirection, the translation of global Alzheimer's research into equitable outcomes will remain constrained, deepening diagnostic disparities in already underserved populations.

SWOT-based strategic implications

From a strategic perspective, our SWOT analysis reveals distinct yet complementary roles of early detection methods across global health settings. In HICs, diagnostic innovation is driven by AI-enhanced platforms—particularly machine learning–augmented neuroimaging, CSF proteomics, and multi-modal biomarker integration—which cluster in the high-feasibility–high-priority quadrant. These tools not only deliver high accuracy in identifying prodromal and preclinical AD but also align with precision medicine goals. HICs are uniquely positioned to push the technological frontier, acting as incubators for complex innovations that may later diffuse to other contexts. This mirrors a Preston curve dynamic, where despite increasing national income and health expenditure, marginal gains in population-level AD detection plateau—signaling a need for breakthrough modalities rather than incremental improvements. Thus, strategic investment in high-risk, high-reward platforms such as deep learning pipelines, molecular imaging, and digital twin simulations remains justified and globally beneficial.

Conversely, in LMICs, strengths lie in scoring tools, blood-based models, and anthropometric inputs that are more adaptable to infrastructure constraints. These methods frequently fall into the high-feasibility–moderate-priority quadrant, particularly where task-

shifting and primary care engagement are central. Opportunities exist to enhance these tools using low-resource-compatible AI algorithms, mobile platforms, and culturally adapted assessment protocols [58,59]. However, weaknesses persist—chief among them being fragmented digital systems, lack of skilled workforce, and limited integration of cognitive health into chronic disease management programs. Threats include reliance on proprietary tools, absence of LMIC data in AI training pipelines, and continued underrepresentation in multicenter studies, raising ethical concerns about algorithmic bias and equity.

Quadrant interpretation also highlights emerging modalities, such as retinal imaging, digital behavior analytics, and gamified diagnostics, which cluster in low-feasibility–moderate-priority zones across both contexts. While still exploratory, these tools offer upward potential if investment, validation, and regulatory frameworks keep pace. Notably, some HICs are now piloting hybrid strategies—combining at-home digital assessments with cloud-based analytics—to reduce clinic dependence and improve scalability, innovations that may eventually inform LMIC adaptations. It is worth noting that while LMICs require scalable, context-aware methods that ensure access and equity, HICs must continue to pursue technological breakthroughs that shift the detection curve [60,61].

Policy and research recommendations

A comprehensive response to AD detection disparities should adopt a cascade of care framework, recognizing that early-stage interventions, accurate diagnosis, and system-level coordination require distinct but connected efforts across care levels. At the primary care level, scalable and low-cost screening tools—such as validated scoring instruments (e.g., MMSE, MoCA), anthropometric markers, and basic point-of-care blood assays—should serve as the first line of detection, especially in LMICs. These tools are suitable for broad application, require minimal infrastructure, and are critical for identifying at-risk individuals in community or outpatient settings. Tertiary care centers, in contrast, play a pivotal role in confirmatory diagnosis and advanced characterization, using neuroimaging, fluid biomarkers, and machine learning–augmented platforms. These facilities should act as regional hubs for diagnostic refinement, comorbidity mapping, and clinical trial recruitment, especially for atypical or early-onset cases.

A robust digital health infrastructure plays a pivotal role in connecting primary and tertiary care within the AD diagnostic and care continuum. At the primary level, digital tools such as mobile-based cognitive assessments and tele-neuropsychology platforms allow early, community-level screening—particularly valuable in remote or under-resourced areas. Once individuals at elevated risk are identified, integrated electronic health records facilitate seamless communication between care levels, enabling advanced referral systems that automatically flag cases for specialist review at tertiary centers. These systems can incorporate comorbidity data—such as cardiovascular and psychiatric history—allowing specialists to contextualize cognitive changes within broader clinical profiles. Furthermore, digital infrastructure supports longitudinal monitoring, ensuring that individuals who screen positive or borderline are not lost in follow-up. This continuity across the cascade of care—from initial risk identification in the community to comprehensive evaluation and intervention in tertiary centers—ensures that cognitive decline is addressed earlier and more systematically, especially in populations vulnerable to drop-offs due to logistical or systemic barriers.

Furthermore, data sharing across institutions and borders is crucial to break the siloed nature of AD research. Shared datasets allow for the validation of screening tools across diverse populations, facilitate meta-analytic insights, and support the development of AI models trained on representative samples—not just those from high-income, academic cohorts [62–64]. Initiatives should promote interoperable data systems, open-access diagnostic algorithms, and cross-national consortia, particularly those that include LMIC participation. Interdisciplinary collaboration must also be prioritized. AD research should move beyond neurology and geriatrics to include cardiology, psychiatry, endocrinology, and primary care—reflecting the true clinical complexity of early AD presentation. Co-designed research that includes these specialties is more likely to generate tools with real-world feasibility and translational value [65].

Finally, achieving equity in AD diagnostics means intentionally supporting: research representation from underrepresented regions and age groups, especially younger individuals at

risk of early-onset AD. Younger individuals, including those at risk of early-onset Alzheimer's, and populations in LMICs face critical unmet needs in early disease detection [66]. Excessive screen time, sedentary behavior, and unhealthy diets among younger people pose growing threats: a UK Biobank study (n > 415,000) showed that >3 h/day of TV viewing was associated with a 33% higher dementia risk (HR 1.33; 95%CI 1.25–1.42), while computer use appeared protective [67]. Additional research found that >4 h/day of screen time in young adults (18–30 years) predicted impairments in executive function and working memory, and excessive digital device use was linked to changes in brain gray and white matter [68]. Likewise, unhealthy midlife diets high in sugars and processed foods doubled dementia risk and correlated with elevated amyloid burden [69].

Culturally and linguistically adapted tools are essential for ensuring the relevance and accuracy of AD detection across diverse populations. Standard instruments like the MMSE, MoCA, or ADAS-Cog often rely on language comprehension, cultural familiarity, and literacy levels that do not translate uniformly across settings. For example, studies have shown that modifications such as substituting unfamiliar proverbs, figures, or symbols with locally recognized equivalents significantly improve test comprehension and reduce false positives—particularly in low-literacy or rural populations [69]. Translating and validating these tools is not merely a linguistic exercise but requires re-calibration against culturally appropriate norms and cognitive baselines, as demonstrated by region-specific adaptations in Taiwan, South India, and sub-Saharan Africa. Without such adjustments, many individuals' risk being misclassified due to cultural incongruence rather than true cognitive decline [70].

Equally critical is the development of structured training programs for primary care workers, who serve as the first point of contact in most health systems. These programs should go beyond test administration to include modules on recognizing early cognitive signs, understanding how comorbidities (like diabetes or depression) can alter presentation, and applying brief, validated screening tools with confidence. Evidence from countries such as Indonesia, Kenya, and Mexico suggests that even short training sessions—when supplemented with visual aids and digital platforms—can significantly enhance diagnostic accuracy and referral behavior. Importantly, such programs should be integrated into existing continuing medical education systems, with certification and supervisory feedback mechanisms to ensure quality and sustainability [71,72].

Trends in our study findings highlight an urgent opportunity: the need for epidemiological surveillance and targeted intervention trials among young, at-risk groups—especially given rising cognitive risks from modern lifestyles. For LMICs, where advanced diagnostic infrastructure is limited, neglecting early-onset and behavioral risk factors may delay recognition and intervention. Integrating digital health tools, lifestyle monitoring, and scalable scoring or blood-based biomarkers can bridge these gaps. Therefore, our study emphasizes a more inclusive diagnostic framework—one that expands beyond traditional elderly-focused models to encompass younger individuals with modifiable lifestyle risks and resource-constrained regions. Such a shift could enable earlier detection, personalized preventive strategies, and equitable health outcomes across diverse global populations.

Strengths and limitations

This study offers several notable strengths. To our knowledge, it is the first to integrate bibliometric mapping, REI modeling, and SWOT-based strategic appraisal into a single, cohesive framework for evaluating AD early detection strategies. This multidimensional approach enables both macro-level insights into research trends and micro-level assessments of diagnostic feasibility and population coverage. Furthermore, the analysis draws from a large, well-defined dataset, systematically filtered from Scopus-indexed literature spanning over a decade, ensuring both scope and relevance. The combination of quantitative metrics and qualitative synthesis provides a comprehensive view of diagnostic landscape gaps and opportunities.

However, certain limitations must be acknowledged. Our reliance on abstracts rather than full-text analysis may have restricted the depth of methodological evaluation and risked omitting nuanced details about study design, population characteristics, or tool validation protocols. Abstracts often underreport critical variables such as comorbidity stratification or data collection settings, which are essential for accurate REI calibration. This literature pool was limited to

studies indexed in Scopus, which may bias the dataset toward higher-resource countries and exclude valuable contributions from regional or non-indexed journals, particularly those originating in LMICs. This indexing bias may underrepresent grassroots innovations or context-specific tools that are highly relevant to LMIC settings but remain outside mainstream academic repositories.

Conclusions

Neuroimaging and biomarker-based methods are the most studied early diagnostic tools for AD, particularly in elderly populations and in the context of comorbidities like diabetes, stroke, and Parkinson's disease. However, many combinations—especially those involving younger populations, low-cost tools, or LMIC-relevant settings—were rarely studied or lacked usable effectiveness data. Our findings suggest that scoring tools, while less precise, remain valuable due to their accessibility and feasibility. The REI revealed mismatches between publication volume and actual diagnostic utility, emphasizing the need for better alignment of research focus with practical impact. SWOT analysis confirmed that while high-precision methods offer diagnostic advantages, they are often constrained by cost and infrastructure limitations, especially in LMICs. In contrast, simpler tools like scoring or anthropometric assessments may offer scalable solutions but require further validation. We strongly encourage future research to prioritize underrepresented populations and cost-effective diagnostic strategies that can support timely detection of AD globally.

Acknowledgments

None.

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

This study received no external funding.

Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study used artificial intelligence (AI) tool, ChatGPT, was employed for language refinement (improving grammar, sentence structure, and readability of the manuscript). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

How to cite

Arsyi K, Hartono GI, Fridayanti KD, *et al*. Global mapping of early diagnostic tools for Alzheimer's disease: Integrating bibliometric analysis, SWOT strategy, and a novel Relative Effectiveness Index. Narra Rev 2026; 2 (1): e17 - http://doi.org/10.52225/narrarev.v2i1.17.

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