**An Interdisciplinary Approach to Barriers of Early AD Diagnosis:**

**A Scoping Review**

Cerebros

Milestone 2

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# Executive Summary / Abstract

## Background

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60-80% of the 55 million people worldwide who have dementia, with prevalence forecasted to surge by 2050. Including prodromal stages of AD, prevalence further increases to 22% of all persons aged 50+. Despite a century of research 99.6% of trials fail and AD remains an incurable disease with unknown etiology. Early diagnosis offers a pathway toward more sustainable, preventative, and ultimately effective management of AD, with potential to reduce prevalence by 50% if onset is delayed by 5 years. However, the cross-disciplinary barriers for early diagnosis remain poorly understood. Thus, this scoping review investigates and characterizes the cross-disciplinary barriers to that exist for early AD diagnosis.

## Methods

A systematic literature search was conducted through the Medline database accessed using PubMed and ProQuest. Topic-specific search strategies covered disciplines such as cognitive assessment, biomarkers, neuroimaging, and public health. Combined searches yielded 927 articles, with 151 progressing to extraction. Due to high output, neuroimaging and biomarker searches were limited to the last 5 years while public health and cognitive assessment topics ranged from January 2000-November 2024.

## Results

Barriers to early AD diagnosis were found across three disciplines: biomedical (n=95), neuropsychological (n=29), and public health (n=27). Within biomedicine, key barriers included invasiveness, limited generalizability, lack of standardized protocols, inconsistent accuracy, and cost/accessibility issues. Neuropsychological barriers included inadequate accuracy for MCI detection, limited generalizability, conceptual limitations, and test administration challenges. Public health barriers encompassed geographic and economic disparities, healthcare system/provider factors, and cultural/social influences.

## Conclusion

Early AD diagnosis was identified to have compounding barriers across disciplines. Cost and generalizability were identified as pervasive cross-disciplinary barriers. Consequently, future initiatives should aim to decrease cost or improve generalizability. Recommendations include implementing modern cognitive assessments, developing personalized risk-based screening pathways, and supporting public health education.

# Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia globally. AD is most commonly characterized by a gradual decline in cognitive function, typically beginning with episodic memory impairment, and is pathologically defined by the accumulation of both amyloid-β (Aβ) plaques and neurofibrillary tau tangles with neurodegeneration.1 Because AD is a progressive neurodegenerative disorder, pathological changes can begin decades before clinical symptoms emerge.2–4

Consequently, the disease course is frequently conceptualized as a continuum. In common frameworks it begins with subjective memory decline (SMD), where individuals perceive cognitive lapses but still perform within normal ranges on standard cognitive tests. Next, mild cognitive impairment (MCI) involves measurable, yet not functionally disabling, deficits in one or more cognitive domains. Over time, a proportion of individuals with MCI progress to clinically diagnosable dementia, wherein the severity of cognitive decline significantly interferes with the activities of daily living.5 Dementia itself is often further subdivided into early, moderate, and severe stages, each marked by increasingly significant impairments—culminating in profound neurodegeneration that compromises basal cognitive functions and ultimately becoming fatal.6 It is still important to note that the continuum of AD is still being investigated and not fully understood, likely forecasting future refinements to exact disease pathway.7

AD diagnosis follows a clinical pathway that integrates multiple assessment modalities that vary across healthcare systems globally.7 The process typically begins in primary care with a determination of the presence and severity of cognitive impairment, followed by basic cognitive screening and laboratory tests to rule out reversible conditions. Subsequently, referral to specialists (neurologists, geriatricians, psychiatrists, or memory clinics) facilitates comprehensive neuropsychological assessment evaluating multiple cognitive domains and functional impact, aiming to detect either MCI or dementia.8 Following the characterization of cognitive impairment, biomarker testing—including structural neuroimaging (MRI), functional neuroimaging (FDG-PET and amyloid PET), cerebrospinal fluid analysis (measuring Aβ42, total tau, and phosphorylated tau), and emerging blood-based biomarkers—are then utilized to help find objective evidence of AD pathology, though utilization and specific diagnostic protocols still vary significantly between regions.9 This multimodal assessment attempts to classify patients along the AD continuum from subjective cognitive decline through MCI to dementia due to AD. General population screening is still not currently recommended or practiced for asymptomatic individuals without risk factors, though targeted screening may be appropriate for high-risk populations and is an ongoing area of research.10,11 Regional variations exist, with European countries generally employing more standardized diagnostic pathways and earlier CSF biomarker adoption, while North American approaches emphasize clinical assessment with more selective biomarker confirmation.12 Despite the extensive diagnostic process, research shows significant underdiagnosis of dementia remains a substantial challenge. Only about 54% of older adults with incident dementia received a timely diagnosis in healthcare settings (within 3 years before or 1 year after dementia onset). This diagnostic delay affects approximately 46% of dementia cases, with many never receiving a formal diagnosis during their lifetime, potentially missing critical windows for intervention and support.13

Currently dementia has a staggering global impact affecting more than 55 million people worldwide.14 With AD caused dementia accounting for over two thirds of all dementia cases.6 In Canada the projected increase is drastic as approximately 368,200 currently live with AD caused dementia and this number is expected to surge 203% to over 1 million Canadians by 2050.15 This trend is shared globally, and when considering prevalence across the AD continuum to include those in preclinical or prodromal stages, the total global estimate was 416 million, or 22% of all persons aged 50 and above.16 Though AD not considered an inevitable consequence of aging, the primary risk factor involved with the incidence is age, with its incidence called late-onset or sporadic AD.7 In the United States, approximately 10.9% of individuals aged 65 and older are living with Alzheimer's, with prevalence increasing per age bracket from 5% among those aged 65 to 74, to 13.2% among those aged 75 to 84, and 33.4% among those aged 85 and older.17 This contrasts with the other category called familial AD, which has a basis in the mutation of three identified genes: amyloid precursor protein (APP) gene, presenilin1 (PSEN1) gene and the presenilin 2 (PSEN2) gene. However, these cases represent only a small fraction of AD with the highest estimates only representing roughly 5% of cases.18 Furthermore, AD has significant economic and mortality burden. Healthcare costs in Canada associated with dementia are projected to surpass $16 billion by 2031, with global economic costs expected to reach $2.8 trillion by 2030.19,20 This is in addition to the WHO currently listing AD and other dementias as the 7th single greatest cause of death globally.14

AD is relentlessly complex and has represented one of the most difficult challenges in modern health care since its first postmortem classification by Alois Alzheimer in 1906.21 Although optimism is important when approaching an issue of this magnitude, it is necessary to highlight that AD remains an incurable disease with an unknown etiology.22 This complexity is rooted in multidimensional societal challenges characterized by intricate interdependencies, incomplete scientific understandings, and a constantly evolving treatment and diagnostic landscape that has persistently resisted conventional solutions. To illustrate this, most developed countries are currently undergoing a significant demographic transition and have rapidly increasing aging populations which has been identified as a primary driver for the projected increase in AD prevalence. What an aging population also indicates is an increased dependency ratio, where for every working age individual there will be more ‘dependent’ older adults which further exacerbates the impending healthcare burden.23,24 Moreover, despite intensive research, billions of dollars invested, and over 400 clinical trials, AD research has yet to deliver effective therapies, affirming concerns about the inefficiencies inherent in existing treatment approaches.25 As indicated by a reported 99.6% failure rate of AD trials between 2002 and 2012.26 Of treatments that have successfully completed clinical trials such as the recently approved monoclonal antibodies including aducanumab have shown some ability to clear Aβ plaques, yet they have proven controversial, facing market withdrawal in some regions due to limited clinical efficacy, and ultimately do little to halt the relentless neurodegeneration.17 Although this is not an exhaustive list of complexities associated with AD, these points highlight the urgent need to reconsider the current approach.

With over a century of research attempting to find the ‘silver bullet’ for AD it has become clear that the paradigm in which AD is approached will need to be revised to better acknowledge the reality of its multifaceted impacts. The complexity of AD calls for an innovative approach—one beginning at the very core of patient management: timely and accurate diagnosis. Early diagnosis may offer a pathway toward more sustainable, preventative, and ultimately effective management of AD.11,17,27,28 The Lancet Commission on Dementia Prevention demonstrates that up to 40% of all dementia cases may be preventable through modifiable risk factor intervention, which is most effective in pre-symptomatic or early disease stages.11 Further, a 5-year delay in AD onset could reduce prevalence by 50% within a generation while decreasing overall costs by approximately 40%.11,28 Each year of delayed diagnosis accelerates subsequent cognitive decline by 7% and increases care costs by 11%.28 Which together indicate that barriers for an early diagnosis are a significant bottleneck in the current approach to AD, however, because these barriers are often fragmented and exist within varying disciplines they remain to be fully understood and categorized.

Thus, the aim of this scoping review is to investigate cross-disciplinary barriers to early AD diagnosis and to propose integrated and utilizable recommendations. By addressing AD in this fashion, we seek to bridge existing gaps and facilitate a more robust, sustainable, and interdisciplinary approach to mitigate the looming impact of this devastating disease.

# Methods

A comprehensive systematic literature search was conducted using the Medline database, accessed through both PubMed and ProQuest platforms. This dual-platform approach was implemented to maximize the retrieval of relevant literature while minimizing the risk of missing important publications. As noted in the NIA-AA Research Framework, Alzheimer's disease diagnosis involves multiple disciplines including cognition, biomarkers, neuroimaging, and public health, necessitating a topic-specific search strategy to adequately cover each distinct area.1

The search strategy consisted of distinct queries tailored to each focus area, utilizing a combination of “AND” and “OR” Boolean operators to maximize specificity. Table 1. illustrates the specific search strings that were separately and later combined into Covidence to filter duplicates. The combined searches yielded a total of 927 articles which then progressed to our screening process. Due to the high research output of imaging and biomarker papers, these searchers were limited to the last 5 years from November 2019- November 2024 while public health and cognitive assessment topics were left open in a search ranging from January 2000 - November 2024.

|  |  |  |
| --- | --- | --- |
| Medline Database Seach String Summary | | |
| Topic | **ProQuest** | **PubMed** |
| Cognitive assessment | ((noft("Alzheimer Disease") OR noft("Alzheimer’s Disease") OR noft(AD) OR noft(dementia)) AND (noft("Cognitive Assessment") OR noft("Cognitive Testing") OR noft("Neuropsychological Tests")) AND (noft("Early Diagnosis") OR noft("Early Detection") OR noft("Screening")) AND (noft("Barriers") OR noft("Challenges") OR noft("Limitations") OR noft("Obstacles"))) | (((alzheimer\*) AND (dementia)) AND ("early diagnosis")) AND (barrier OR limitation\* OR "diagnostic accuracy") AND (Cognitive assessment in AD OR cognitive testing) |
| Biomarkers | ((noft("Alzheimer Disease"[MeSH]) OR noft("Alzheimer’s Disease") OR noft(AD) OR noft(dementia)) AND (noft("Biomarkers") OR noft("Diagnostic markers") OR noft("Molecular markers")) AND (noft("Early Diagnosis") OR noft("Early Detection") OR noft("Screening")) AND (noft("Barriers") OR noft("Challenges") OR noft("Limitations") OR noft("Obstacles"))) | "Alzheimer Disease"[MeSH] OR "Alzheimer's disease" OR "AD") AND ("Biomarkers" OR "Diagnostic markers") AND ("early diagnosis" OR "mild cognitive impairment" OR "preclinical") AND ("limitations" OR "diagnostic accuracy") |
| Neuroimaging | ((noft("Alzheimer Disease"[MeSH]) OR noft("Alzheimer’s Disease") OR noft(AD) OR noft(dementia)) AND (noft("Neuroimaging") OR noft("Diagnostic markers") OR noft("Brain Imagining" OR "PET" OR "MRI")) AND (noft("Early Diagnosis") OR noft("Early Detection") OR noft("Screening")) AND (noft("Barriers") OR noft("Challenges") OR noft("Limitations") OR noft("Obstacles"))) | ("Alzheimer Disease"[MeSH] OR "Alzheimer's disease" OR "AD") AND ("MRI" OR "PET scan" OR "neuroimaging") AND ("early diagnosis" OR "mild cognitive impairment" OR "preclinical") AND ("limitations" OR "diagnostic accuracy") |
| Public Health | noft("Alzheimer's" OR dementia) AND noft(early diagnosis) AND (noft(limitations) OR noft(barriers)) AND noft(health care access) | (((alzheimer\*) AND (dementia)) AND ("early diagnosis")) AND (barrier OR limitation\*) AND (healthcare access OR health equity OR public health) |

Table 1. Comparison of search strings used in each domain between databases.

## Screening and selection process

The screening process was conducted in two stages: title and abstract screening, followed by full-text review. Each article was independently reviewed by the research team, and screening conflicts were resolved through discussion. Following the initial screening, 305 articles were selected for full-text review. A final set of 151 articles was included for data extraction based on their direct relevance to early diagnosis barriers. The PRISMA flow diagram (Figure X) visually details this process.

Studies were included if they were peer-reviewed and explicitly addressed AD and its early diagnostic barriers. Specifically, studies focusing on healthcare access disparities, biomarker limitations, neuroimaging constraints, or cognitive assessment challenges were considered. Only articles published in English were included, and eligible studies consisted of original research, systematic reviews, or meta-analyses that provided direct insight into diagnostic challenges in AD. Studies were excluded if they focused on dementia broadly without specifying Alzheimer’s disease or if they did not explicitly discuss diagnostic barriers. Additionally, editorial pieces, commentaries, and opinion articles were omitted. Non-English publications and studies without accessible full text were also excluded to maintain consistency and accessibility in data collection.

A flowchart of a flowchart

AI-generated content may be incorrect.

Figure 1. PRISMA flow diagram illustrating the selection process, including abstract and title screening, eligibility, and inclusion stages.

# Results

Our scoping review identified 151 articles addressing barriers to early AD diagnosis. We found that these barriers naturally clustered into three interdependent disciplines reflected by our search strategy and aligns with what has been observed in the literature.29 biomedical (n=95), neuropsychological (n=29), and public health (n=27). This organization reflects the multifaceted nature of AD diagnosis, which requires integration across molecular, cognitive, and societal levels. The biomedical discipline encompasses barriers related to physiological markers and imaging techniques. The neuropsychological discipline addresses challenges in cognitive assessment and interpretation. The public health discipline examines systemic barriers affecting access, equity, and implementation. Within these disciplines, limitations that were shared between multiple articles were identified and subsequently grouped into larger themes of barrier origin.

## Biomedicine

Articles identified within the discipline of biomedicine primarily outlined limitations related to biomarkers and neuroimaging techniques to detect physiological signs of AD. These tools included CSF biomarkers, blood-based biomarkers, structural imaging such as MRI, and functional imaging such as FDG-PET. Of the articles examined the main barrier sources that were identified included: invasiveness, limited generalizability, lack of standardized protocols, inconsistent accuracy, and cost and accessibility.

### Invasiveness

Diagnostic tools for AD often involve invasive procedures, which can limit patient acceptance and clinical feasibility. CSF biomarkers, such as the Aβ42/40 ratio, provide high diagnostic accuracy (sensitivity 0.94, specificity 0.82) but require lumbar punctures, a procedure that is both uncomfortable and associated with risks such as headaches and infections.30–32 Similarly, neuroimaging techniques, including PET and MRI, pose challenges related to patient discomfort. PET scans expose individuals to radiation, although MRI requires prolonged scanning times and may be unsuitable for patients with claustrophobia or metal implants.33,34 Diagnostic tools for AD often involve invasive procedures, which can limit patient acceptance and clinical feasibility. CSF biomarkers, such as the Aβ42/40 ratio, provide high diagnostic accuracy (sensitivity 0.94, specificity 0.82) but require lumbar punctures, a procedure that is both uncomfortable and associated with risks such as headaches and infections.30–32 Similarly, neuroimaging techniques, including PET and MRI, pose challenges related to patient discomfort. PET scans expose individuals to radiation, although MRI requires prolonged scanning times and may be unsuitable for patients with claustrophobia or metal implants.33,34

### Inadequate Generalizability

Another major limitation of current biomedical diagnostic tools is their lack of generalizability. Many studies validating these tools rely on small, homogenous cohorts, making it difficult to apply findings to diverse populations.35–38 Notably, 77% (n=73) articles of reviewed biomedical studies show that this issue persists. Novel markers like plasma pTau217 and TNAP show promise, while showing promise, are affected by demographic factors such as age, sex, and comorbid conditions like chronic kidney disease, which can alter biomarker levels and affect diagnostic accuracy.35,39 Additionally, MRI-based hippocampal volumetry used to detect Alzheimer’s-related atrophy faces challenges due to inconsistencies in segmentation techniques and differences in population characteristics.40–43 Also, AI models analyzing brain MRI data show promise but are hindered by the need for large, diverse datasets, algorithmic complexity and variability in imaging protocols.44,45 Without diverse and representative study populations, the applicability of these diagnostic tools remains limited. Validating these tools rely on small, homogenous cohorts, making it difficult to apply findings to diverse populations.35–38

### Lack of Standardization and Protocol Variability

CSF biomarkers, including Aβ42, T-tau, and P-tau, demonstrate high diagnostic accuracy, with the Aβ42/40 ratio performing best (sensitivity: 0.94, specificity: 0.82) compared to amyloid PET.46 However, clinical adoption is limited by methodological inconsistencies in sample handling and assay techniques,46,47 as well as the absence of standardized diagnostic cut-offs.30,46 Similarly, blood-based biomarkers are measured using different technologies, such as immunoassays and mass spectrometry, each yielding different results, which makes clinical implementation difficult.48 Neuroimaging techniques also suffer from a lack of uniform diagnostic criteria, reducing the reproducibility of findings and limiting their reliability in clinical settings.34,41,49

### Inconsistencies in Accuracy

Although many diagnostic tools show potential, accuracy remains a challenge. Blood-based biomarkers, such as the plasma Aβ42/40 ratio, have moderate sensitivity (76%) and specificity (72%), making them less reliable for distinguishing Alzheimer’s from other dementias.48 Plasma neurofilament light chain (NfL) is another blood-based biomarker that can detect AD pathology but fails to distinguish MCI from normal aging (AUC <0.60).50 Neuroimaging techniques, such as PET scans, provide valuable insights into amyloid and tau accumulation, but their diagnostic thresholds vary across studies, leading to inconsistent results.33,34

### Cost and Accessibility Barriers

Financial and logistical challenges further limit the widespread adoption of early diagnostic tools, as our review shows that 24% (n=23) of biomedical papers identify cost as a significant barrier. According to our review, both CSF and blood biomarkers require specialized laboratory equipment and are costly, limiting their accessibility in many clinical settings.39,39,51,52 In addition, neuroimaging techniques such as MRI and PET play a crucial role in AD diagnosis but require specialized laboratory equipment and are costly, making them inaccessible in many clinical settings.34,53,54 PET imaging, in particular, although highly informative, is expensive and not widely available, restricting its use to specialized research centers,33,34 and logistical challenges further limit the widespread adoption of early diagnostic tools. According to our review, both CSF and blood biomarkers require specialized laboratory equipment and are costly, limiting their accessibility in many clinical settings.39,39,51,52 In addition, neuroimaging techniques such as MRI and PET play a crucial role in AD diagnosis but require specialized laboratory equipment and are costly, making them inaccessible in many clinical settings.34,53,54 PET imaging, in particular, although highly informative, is expensive and not widely available, restricting its use to specialized research centers.33,34

## Neuropsychology

Of literature related to the neuropsychological discipline, articles were found to discuss primarily the utility, validation, and implementation of cognitive assessments covering 34 different types of cognitive assessments or psychometric tests that are utilized globally. When analyzed these articles revealed four primary sources of barriers were identified as being; Inadequate accuracy for MCI detection, Inadequate generalizability, conceptual barriers, and barriers related to test administration.

### Inadequate Accuracy of Cognitive Assessments for MCI

Although cognitive tests are diverse and offer a number of differences, they have a shared difficulty assessing early changes in cognitive function. Despite many of these tests being able to demonstrate acceptable accuracy when detecting AD dementia from healthy control, they have limited accuracy when seeking an early diagnosis, namely the presence of MCI. Routinely used tests like the Montreal Cognitive Assessment (MoCA), ADAS-cog, and mini-mental state exam (MMSE) were found to have a rather low specificity for MCI being 0.769, 0.835, and 0.721 respectively.55 In particular, the most used MMSE struggles with the detection of MCI. When analyzed for both sensitivity and specificity combined to evaluate the overall diagnostic accuracy, called the Youden’s Index, the MMSE had a Youden’s index of only 0.478 when compared to the index for AD is 0.796.55 Ceiling effects of the assessments, where scores are often clustered towards the maximum, were heavily implicated in compromising the accuracy of cognitive assessments. For instance, the ADAS-cog was found to have significant ceiling effects in 7 out of its 11 components implying that the ADAS-Cog would struggle to detect small changes in cognition near the beginning of the AD continuum.56 Additionally, in a cognitively healthy older adult cohort, 39 individuals who scored in the lowest quartile of the TICS-M cognitive assessment (≤26/39) had MMSE scores that still ranged from 24 to a perfect 30 demonstrating a significant ceiling effect within the MMSE and ambiguity between different assessments for detecting nuanced differences in cognition.57 Aside from the clinical implications of low accuracy, this also remains a significant barrier within research. For instance, the MMSE while demonstrating a positive predictive value of only 64% for identifying MCI was used as an eligibility criterion in 57.7% of active or recruiting phase II and III AD trials.58

### Inadequate Generalizability of Cognitive Assessments

Another identified barrier commonly noted for cognitive assessments is their generalizability appearing in 26 articles. This is commonly attributed reliance on normative data that is validated on small, typically homogenous populations.59 Why this is problematic is there exists a significant impact of socio-demographic factors on the validity of these scores, which has complicated their applicability for large scale screening efforts.56,58,60 Some of the most prevalent socio-demographic considerations for these assessments revolve around language, culture, and level of education obtained.59 Specifically, these socio-demographic factors such as gender, reading level, and age have also been observed to significantly impact the validity of certain subscales of the Mattis Dementia Rating Scale-2 (MDRS-2) with these factors alone representing 38.6% of the variance in MDRS-2 scores.61 The lack of widely accepted practical guidelines for standardized cut-off scores increases ambiguity when determining the presence of MCI. Research examining verbal fluency tests, which are frequently included in cognitive assessment batteries, demonstrated significant variability in discriminatory ability between healthy controls and individuals with MCI. The area under the curve values ranged from 0.842 for animal naming to 0.689 for action fluency, despite these tasks measuring similar cognitive functions. This inconsistency in diagnostic accuracy across closely related cognitive measures illustrates how the absence of standardized protocols and thresholds complicates generalizable and reliable assessment across diverse clinical settings and populations.62

### Conceptual Barriers

The analyzed papers also provided insight into the barriers related to fundamental theoretical limitations to how cognitive reserve and practice effects may impact the utility of cognitive assessments. Cognitive reserve represents a substantial challenge to AD detection, as individuals with higher education or enriched life experiences can mask cognitive decline despite underlying neuropathology. As one article argues, many widely used cognitive assessments lack sensitivity and specificity partly because they fail to account for this moderating factor. This theoretical weakness directly impacts the validity of participant selection in clinical trials and observational studies.63 Practice effects refer to the natural improvement of scores from patients who are administered a specific test multiple times, whereby learning the format and topic of the assessment they may have improved scores from the familiarity, which may be particularly relevant concerning the early detection of cognitive decline or validity of clinical research trials where serial tests may be administered.64 When accounting for practice effects in cognitive assessments there was increased prevalence and incidence of MCI by 9.2% and 19% respectively.64,65

### Barriers Related to Cognitive Test Administration

Lastly, 9 of the papers made mention of cost and practical accessibility concerns. Most cognitive assessments also provide practical constraints such as the requirement of trained personnel or practitioners to administer the assessment.66 This can pose specific barriers to clinics who chose to implement the use of cognitive screening assessments. Additionally, commonly used assessments such as the MMSE and recently the MoCA have been seen to transition from free tools to having mandatory fees for access and training, deemed as a ‘free to fee’ payment model that poses financial barriers to both their implementation for clinics and sustained use.59

Other practical limitations include a lack of standardized testing instructions for tests like MMSE, meaning there can be a variation of scores even within the same cognitive test, further decreasing its widespread efficacy.60 Along with variations from clinician to clinician, there are also concerns over the testing environment altering the validity of cognitive assessments. Depending on where a cognitive assessment is administered (e.g. long term care, primary care, or hospital settings) may have impacts on what tests are available, and can also impact the reliability of the scored obtained.59 Also with the goal of regular testing, researchers have also identified barriers that revolve around the length of running initial and repeat test, availability of trained staff, the space required to conduct the assessment which may require separation and noise isolation, and the potential need for specialized testing equipment.67 Even potential solutions that use digital or telephone based cognitive assessments struggle as the burden removed of the clinic then compromises the environmental control, decreasing the reliability of scores and introduces new accessibility concerns for visual or auditory impairments.57,67

## Public Health and Policy

Papers pertaining to the discipline related to public health and policy covered a wide range of limitations and disparities related to patient outcomes, provider access, diagnostic infrastructure and the influence of social determinates on timely and accurate care. When analyzed, these articles revealed four primary sources of barriers identified as being: geographic and economic disparities, healthcare system and provider factors, and cultural and social influences.

### Geographic and Economic Disparities

There is a significant gap in dementia diagnosis between regions around the world that are economically different. Lower middle-income countries (LMICs) tend to focus on the treatment of infectious diseases like HIV/AIDS and Tuberculosis, as a result leading to the neglect of AD along with the lack of skilled neurologists, cognitive screening devices, and even the necessary neuroimaging equipment.68 This is consistent with the vast differences in evaluation times in AD, with LMICs averaging 36.9 minutes and UMICs sitting at an average of 53.5 minutes.68 The use of cognitive screening tools also reflect this disparity 94.5% of practitioners in UMICS utilizing these tools compared to a considerably lower at 79.6% in LMICs, which impacts the effectiveness of early diagnoses in LMICs.68

Furthermore, there has been a divide between urban and rural areas. The dense population centers in Latin America are served by a small number of dementia specialists, meaning that the rural parts are underserved and patients have to travel great distances to receive an assessment which delays the diagnosis and treatment.69 In the same way, rural North American and European practitioners often do not have access to specialists and are therefore forced to rely on information provided by relatives, raising the chances of incorrectly deciding the person's decline in cognitive abilities is due to aging rather than a neurodegenerative disease.70

As with most diagnostic technologies, there is a systemic issue of inequality present. While 87% of practitioners in Upper Middle Income countries (UMIC) have access to structural neuroimaging, only 75.7% of LMIC do.68 In LMICs, standard issue diagnostic guidelines may not be economically feasible due to financial restraints as only 52.4% of practitioners use them compared to 82.2% of practitioners in UMICs.68 This is often in conjunction to the fact that advanced biomarker testing and genetic testing remain almost entirely unavailable in rural areas because of their cost and lack of infrastructural support.70 In Canada for example, there are extensive wait times between MRI scans and PET imagining, which adversely impacts the patient’s ability to be identified with AD early on.71

### Healthcare System and Provider Factors

Primary care practitioners (PCPs) are often the first contact for patients with dementia. However, providers encounter several challenges during assessment.70 Approximately 15% of general practitioners (GPs) mention time constraints, financial disincentives, and administrative workload as the most important barriers for conducting dementia evaluations. Meanwhile 33% do not find dementia diagnoses clinically actionable and 76% do not have time to adequately deal with emerging dementia cases. 72

Research has shown that GPs tend to manage pressing issues immediately rather than look for early signs of dementia. Some GPs operate under the assumption that it is reasonable to postpone dealing with mild cognitive decline until it becomes a much bigger issue.73 Such a mindset is intensified by the European healthcare systems which also suffer from heterogeneity in reimbursement schemes and limited availability of sophisticated diagnostic tools, which only increases the lack of care.73 Across diverse regions, regulatory guidelines for diagnosis exhibit a lack of uniformity. The NIA-AA guidelines which are commonplace among high income economies have limited use in the lower mid-income economies due to their expense and infrastructural deficiencies.

Difficult ethical issues exacerbate already complicated challenges of diagnosis; doctors frequently must weigh patient self-determination against the necessities of the carers, especially in the case when one side is not willing to accept the reality of the situation. Medication decisions present additional challenges with the GPs caution about providing new forms of treatment for patients suffering from dementia because they were not certain of their usefulness due to the benefits and clarity of the diagnosis.73

### Cultural**,** Education, and Social Factors

The diagnostic experience of dementia is influenced greatly by cultural sociological factors. Within American communities of Asian, Native Hawaiian, and Pacific Islander ancestry, awareness of AD and the dementias associated is low, contributing to the ambiguity between pathological decline and normal aging.74 Very much like the ethnic older adults in the UK, who often present with more advanced stages of dementia due to their reluctance to seek medical attention because of the prevailing cultural attitude that puts family caregiving as a higher priority. In many cases, stigma associated with dementia, combined with systemic healthcare barriers, prevents individuals from accessing diagnostic services in a timely matter.74

Diagnosis pathways frequently are initiated only after certain alarming symptoms have already occurred and illness, in the case of cognitive decline, is perceived to require some external medical attention. The Hispanic population presents severe paradoxes in the health care system where there is a lack of trust in the health care system and a prevailing fear of ethnical discrimination preventing patients from engaging in primary screening services for fear of being screened impersonally.75 Members of racial minority groups as well as of rural society as a whole have little trust in the medical system it greatly lowers willingness to clinically participate in research, prolonging diagnosis and ultimately research quality.75

Patient and family factors further contribute to delays, as reluctance to acknowledge symptoms or seek care, coupled with stigma and fear associated with dementia diagnoses, discourage discussions about cognitive changes.73 The phenomenon is exacerbated by missing “red flags” pertaining to dementia, such as memory loss or personality and cognitive changes which most people consider a part of the normal aging process.73

Cultural, educational, and social background differences can render some of the most basic cognitive assessments such as the MMSE and MoCA ineffective. Within the Hispanic population, there are cultural and linguistic factors that may contribute to them scoring lower even when their biomarker profile is similar to that of non-Hispanic whites, hence suggesting that socio-economic disparity and educational gaps lead to *misdiagnosis.*76 Even in high-income countries, financial barriers can persist, particularly for racial and ethnic minorities, who often lack insurance coverage for advanced neuroimaging and biomarker testing. Hispanic individuals frequently perform worse on cognitive assessments despite having similar biomarker profiles to non-Hispanic Whites, suggesting that economic and educational disparities contribute to misdiagnosis.76 In Asian American, Native Hawaiian, and Pacific Islander communities, barriers such as language challenges, a shortage of culturally competent healthcare providers, and bureaucratic hurdles discourage caregivers from seeking timely care.74 Similarly, in lower-income and rural areas, dementia education remains limited, contributing to misconceptions that cognitive decline is an inevitable part of aging rather than a treatable medical condition.74

# Discussion

Our scoping review identified a total of 151 papers addressing barriers to early AD diagnosis which were found we identified to fall within three interdependent disciplines: biomedicine, neuropsychology, and public health or policy. By taking an interdisciplinary approach, we could accurately reflect the inherent complexity of AD diagnosis, which necessitates integration across molecular, cognitive, and societal levels. By examining limitations within each discipline and identifying cross-cutting themes, we revealed a heterogenous set of barriers that can interact and compound between distinct disciplines. We additionally identified cost and generalizability as barriers that prevail across all major disciplines related to achieving a timely diagnosis of AD. This interdependence highlights the need for coordinated approaches that span traditional disciplinary boundaries and better align with the evolving diagnostic pathway, especially in light of new evidence that AD dementia may be far more preventable has been traditionally thought when targeting modifiable risk factors.11

The first key finding of our review is that barriers within one discipline frequently compound challenges in others, creating a cascade effect that consequently impedes early AD diagnosis. For instance, biomedical innovations like blood-based biomarkers require appropriate cognitive assessments for proper interpretation and validation, while both rely public health infrastructure for access and equitable implementation.68 48 Furthermore, compounding effects also reach deep into the validity of research, where cognitive assessments such as the MMSE being heavily relied upon for trial participant eligibility despite having poor performance for MCI detection.58 Together, these findings illustrate a complex landscape of interconnected diagnostic obstacles that compound and intersect in a variety of ways that ultimately undermine the ability to diagnose AD early in the disease continuum.

The second key finding was two pervasive barriers emerged across all disciplines: cost and limited generalizability. These shared barriers represent fundamental obstacles to early AD diagnosis and provide specific focal points within the diagnostic pathway that have the greatest potential impact.

## Generalizability

The issue of generalizability emerges as a critical barrier in AD diagnosis, significantly limiting the effectiveness and accuracy of diagnostic tools, cognitive assessments, and clinical research.17 77% (n= 73) of biomedical articles and 90% (n= 26) of neuropsychological articles mention generalizability as a limitation or barrier. In the biomedical discipline, promising markers like plasma pTau217 and TNAP are affected by demographic factors such as age, sex, and comorbid conditions that alter biomarker levels and affect diagnostic accuracy.77 Our analysis of neuroimaging studies revealed that AI models analyzing brain MRI data are also hindered by the need for large, diverse datasets and standardized imaging protocols. Within neuropsychology, socio-demographic factors significantly impact test validity, with gender, reading level, and age representing 38.6% of the variance in a cognitive assessment.78 Our results additionally highlight that cognitive assessments are typically validated on small, homogenous populations, limiting their applicability across diverse groups. Hispanic individuals for instance were found to perform worse on cognitive assessments despite similar biomarker profiles to non-Hispanic Whites, suggesting that socioeconomic and educational disparities significantly contribute to under and misdiagnosis.79

Current diagnostic criterion and assessment tools have been primarily developed and validated predominantly using non-Hispanic White populations raising critical questions about widespread applicability. This lack of inclusivity exacerbates healthcare disparities, disproportionately impacting historically underserved populations.80 Even large-scale approaches such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset predominantly features non-Hispanic White participants, creating significant representation gaps for Black, Hispanic, and Asian populations. This lack of diversity compromises the universal applicability of biomarkers, diagnostic thresholds, and even emerging treatment efficacy. Research reveals critical discrepancies in cerebrospinal fluid biomarkers across racial groups, even with similar amyloid-beta levels, which can lead to diagnostic misclassification and perpetuate health inequities.80The impact of limited generalizability extends to cultural contexts as well. Our results demonstrated that within American communities of Asian, Native Hawaiian, and Pacific Islander ancestry, low awareness of AD contributes to ambiguity between pathological decline and normal aging.74 Similarly, we found that ethnic older adults often present with more advanced stages of dementia due to cultural attitudes that prioritize family caregiving over seeking medical attention.

The consequence of limited generalizability extends beyond diagnostic accuracy; it directly influences health outcomes. An accurate and timely AD diagnosis serves as the crucial gateway for early intervention, eligibility for clinical trials, and effective long-term care planning.17 When diagnostic tools fail to account for racial, ethnic, socioeconomic, and cultural differences, it results in the delayed or incorrect identification of AD in underrepresented groups.81 Consequently, these populations face worse disease trajectories, reduced access to emerging treatments, and lower participation in clinical trials.80 Addressing generalizability is therefore crucial, not only for scientific rigor but as a fundamental step toward healthcare equity. Ensuring diverse representation in AD research and validating diagnostic tools across broader populations will lead to improved outcomes, equitable treatment access, and more sustainable healthcare costs, ultimately moving toward personalized, accurate, and equitable AD care for all populations.82

## Cost

The financial burden associated with diagnosing AD presents a significant barrier to early detection and intervention that also prevails in all disciplines. Cost-related limitations prevent many individuals from accessing necessary medical services, delaying diagnosis until symptoms become severe.83 This delay results in missed opportunities for early intervention, participation in clinical trials, and advanced care planning.28

Diagnostic procedures such as neuroimaging (MRI, PET scans) and CSF analysis are prohibitively expensive, often costing thousands of dollars. In Canada, a PET scan for detecting amyloid plaques can range between $2,300 and $3,000, a cost not always covered by provincial healthcare plans.84 Many patients, particularly those without comprehensive insurance, may delay or forgo diagnosis due to these high costs.85 Specialized neurological consultations and biomarker tests further contribute to financial strain, making AD diagnosis particularly inaccessible for low-income populations.85 Our review highlights the widespread recognition of cost and access as major barrier in AD diagnosis. Nearly **24% (n=23) of biomedical studies** and **31%** (n= 9) **of neuropsychological studies** we analyzed identified financial barriers as a key obstacle to early detection and care. Addressing the financial barriers to AD diagnosis is essential for improving early detection and reducing long-term healthcare costs. Delayed diagnosis not only accelerates cognitive decline but also increases the economic strain on individuals, families, and healthcare systems.28 Early intervention during the MCI or prodromal stages has the potential to significantly lower overall dementia-related expenses by enabling timely treatment and care planning.28 These findings underscore the urgent need for more accessible and cost-effective diagnostic strategies to alleviate both personal and societal burdens associated with AD.

## Implications for Shifting to a Prevention-Focused Approach: Practical Benefits and Economic Impact

Our findings on cross-disciplinary barriers to early AD diagnosis align with and extend the framework outlined in the 2021 World Alzheimer Report, which emphasizes that timely diagnosis remains "the crucial first step in the dementia journey" yet is profoundly underutilized globally.86 The report highlights that up to 75% of people with dementia worldwide remain undiagnosed, with this gap reaching 90% in low and middle-income countries—figures that reflect the compounding effects of the barriers we identified across biomedical, neuropsychological, and public health disciplines. These statistics take on even greater significance when considered alongside the Lancet Commission's finding that up to 40% of dementia cases could be prevented or delayed through intervention on modifiable risk factors, which is only possible with timely diagnosis.11

In the context of a rapidly aging global population the urgency of prioritizing early diagnosis is paramount. The projected 203% increase in Canadians living with AD by 2050 represents a pattern mirrored globally. The World Alzheimer Report contextualizes this trend, noting that someone in the world develops dementia every three seconds, with numbers expected to double every 20 years, reaching 152 million by 2050.86 This demographic reality creates a rapidly narrowing window for implementing effective screening and diagnostic strategies before healthcare systems become overwhelmed. The barriers we identified—particularly cost and limited generalizability—directly impede global efforts to meet this urgent demographic challenge.

With global dementia cost estimates estimated to be 1.3 trillion annually with a projected 2-fold increase by 2030, our findings also reinforce the economic imperative outlined by the World Alzheimer Report, which emphasizes cost-effectiveness given the rapidly escalating global dementia costs.86 While we consistently identified financial constraints as key barriers, emerging evidence indicates the substantial cost-savings through investments in early AD diagnosis and intervention. Potential savings are immense, such as lifetime care costs reduced by up by £8,800 and £44,900 per individual in the UK when intervention begins at the MCI stage.87 Likewise in the United States, individuals who progressed from MCI to AD and other related dementia disorder had significantly higher healthcare costs than those with stable MCI with adjusted all-cause mean total costs being 41% higher ($34,599 vs. $24,541).88 Additionally, indirect economic burdens are immense. The total annual indirect cost of AD was estimated at $832 billion, which includes an estimated $599 billion in unpaid caregiving costs and $233 billion in productivity losses.89 The investment into early AD diagnosis, not only provides cost benefits, but also makes room for future therapies. Most treatments work best when administered early in the AD continuum, thus it naturally follows that for adequate uptake of future treatments there remains a significant reliance on an efficient and sustainable pathway that enables early diagnosis.90–92 Collectively, this expanded context points to early AD diagnosis as not only clinically essential but economically strategic, reinforcing the urgency to better understand and overcome existing diagnostic barriers.

The practical implications of our findings suggest that the path forward requires innovations and initiatives that specifically target the two most pervasive barriers we identified: limited generalizability and cost. The World Alzheimer Report advocates for "regular cognitive assessment via brief cognitive tests during annual health checks" and emphasizes the need for "financial risk protection programs" to enable equitable access to diagnosis.86 Similarly, the Lancet Commission recommends systemic changes to improve cognitive health while accounting for diversity in risk profiles and healthcare access.11 Future research initiatives irrespective of discipline should therefore prioritize addressing at least one of these fundamental constraints—either by enhancing generalizability through more inclusive research methodologies and validation across diverse populations or by developing more cost-effective diagnostic approaches accessible in various resource settings. The shift to a prevention-focused paradigm, supported by our findings, represents not just a clinical reorientation but a necessary evolution in how healthcare systems approach AD. The Lancet Commission's evidence that 40% of dementia is potentially preventable through modifiable risk factor intervention cements the critical importance of early diagnosis as the gateway to these preventive measures. Our results suggest that without addressing the interdisciplinary barriers we have identified, particularly those related to cost and generalizability, the potential benefits of early intervention will remain unrealized for millions of individuals at risk of developing AD.

In light of these considerations, we suggest that any innovation aimed at improving early AD diagnosis should explicitly address at least one of these pervasive barriers, either by enhancing generalizability across diverse populations or by reducing associated costs. This approach would ensure that new developments are not only scientifically sound but also practically implementable in the complex global landscape of dementia care, helping to bridge the interdisciplinary gaps between the promise of early intervention and its actual delivery to those who need it most.

# Recommendations

## Recommendations for Practice

To improve the early diagnosis of AD, it is essential to implement practical, evidence-based strategies that enhance accessibility and efficiency in screening efforts. Two promising approaches are the integration of AI-driven digital screening tools and the adoption of personalized risk-based screening pathways. These strategies have demonstrated success in research and clinical settings. The Creyos cognitive testing platform and the U.S. POINTER study can be adapted to optimize AD diagnosis in broader healthcare systems.

### AI-Driven and Digital Screening Tools

Traditional cognitive assessments often require in-person visits, limiting accessibility for individuals in remote or underserved areas.93–95 AI-driven cognitive screening tools, such as the Creyos platform (formerly known as Cambridge Brain Sciences), provide a validated, user-friendly approach to detecting early cognitive decline. Creyos allows individuals to complete quick reparative cognitive assessments remotely, enabling widespread screening while reducing the burden on healthcare facilities.96 In addition, AI-powered decision-support systems can assist primary care physicians in interpreting test results thereby reducing interrater variability, identifying high-risk individuals and streamlining specialist referrals.   By minimizing reliance on subjective interpretation, these tools help reduce integrated bias and provider error, leading to more equitable and accurate diagnoses.

To maximize effectiveness, AI-driven cognitive screening should be offered starting at the age of 40 and repeated every two to three years. This threshold is based on the typical onset patterns of AD. Sporadic AD, which accounts for the majority of cases, typically manifests after age 65, but pathological changes in the brain begin decades earlier.97,98 Also, research indicating that subtle cognitive changes associated with AD can begin decades before clinical symptoms manifest. 99 Detecting cognitive decline in midlife allows for earlier intervention, including lifestyle modifications and clinical monitoring, which can delay disease progression.

Additionally, although sporadic AD is the most common form, familial AD (fAD) accounts for less than 5% of all cases and follows a classic Mendelian autosomal dominant inheritance pattern, often presenting before the age of 65.97 Individuals with a family history of fAD are at particularly high risk and may benefit from earlier and more frequent cognitive screening. For these individuals, initiating screening at age 40 could provide valuable opportunities for early intervention and monitoring. More frequent testing may also be warranted for those with other known risk factors, such as the presence of the APOE ε4 allele.

Integrating digital screening tools into routine primary care visits would improve early detection rates, reduce diagnostic delays, and support long-term cognitive monitoring. By tailoring screening approaches based on individual risk factors, healthcare systems can enhance the effectiveness of AD prevention and early intervention strategies.

### Personalized Risk-Based Screening Pathways

A standardized approach to AD diagnosis may overlook individuals with higher genetic or lifestyle-related risks. The U.S. POINTER study has demonstrated that personalized interventions based on factors such as APOE genotype, cardiovascular health, and lifestyle can help slow cognitive decline and potentially delay the onset of dementia.100 Implementing a similar risk-stratified screening model would ensure that high-risk individuals receive targeted cognitive assessments and early interventions. This approach would optimize resource allocation, ensuring that those at the greatest risk receive timely support while reducing unnecessary testing for lower-risk populations. Additionally, incorporating lifestyle modification programs alongside cognitive screening could enhance prevention efforts and improve long-term health outcomes.

By integrating AI-driven cognitive screening tools like Creyos and adopting personalized risk-based screening pathways modeled after the U.S. POINTER study, healthcare systems can improve the efficiency and accessibility of AD diagnostics. These strategies will lead to earlier intervention which improves patient outcomes, and a reduces in the overall burden of dementia care.

## Recommendations for Policy

Effective policy initiatives may offer another avenue to improve the early detection of AD. Policy should focus on public awareness, access to screening, and diversity in clinical research. Two key strategies that have demonstrated success are public health education with risk factor reduction campaigns and legislative efforts to promote equity in dementia research. Programs such as the UK’s Dementia Friends initiative and the U.S. Equity in Neuroscience and Alzheimer’s Clinical Trials (ENACT) Act provide effective models that can be adapted to improve AD awareness, screening, and healthcare equity across different healthcare systems.

### Public Health Education & Risk Factor Reduction

Limited public awareness of AD risk factors and early symptoms contributes to delayed diagnosis and intervention. Public health education campaigns, such as the Dementia Friends initiative in the UK, have successfully increased understanding of modifiable risk factors, early symptoms, and the importance of early cognitive screening. These campaigns help reduce stigma and encourage individuals to seek medical evaluation earlier, leading to better long-term outcomes.101 To improve early detection, public health initiatives should focus on large-scale awareness campaigns that educate the public about AD risk factors and encourage cognitive screening. These campaigns could include community workshops, digital media outreach, and healthcare provider training to ensure widespread engagement. Additionally, promoting modifiable lifestyle factors, such as diet, exercise, and cardiovascular health, can contribute to delaying cognitive decline. A collaborative approach involving government agencies, healthcare organizations, and community groups can help maximize outreach, particularly in rural, Indigenous, and underserved communities. By fostering proactive health behaviors and early intervention, public health policies can significantly reduce the burden of AD.

### Legislative Efforts to Promote Equity in Dementia Research

Dementia research and clinical trials often lack adequate representation of diverse populations, limiting the generalizability of findings and contributing to disparities in early diagnosis and treatment. In the U.S., the ENACT Act addresses this issue by increasing outreach to underrepresented communities, reducing financial barriers to trial participation, and requiring research institutions to prioritize diverse recruitment.102

To improve health equity in dementia research, policies should focus on ensuring diverse participation in clinical trials through targeted outreach, financial support, and regulatory mandates. Research institutions should be required to recruit participants from underrepresented populations to ensure findings are applicable across different racial, ethnic, and socioeconomic groups. Additionally, educational programs and outreach initiatives can inform marginalized communities about AD risk factors and research opportunities, while financial and logistical support, such as transportation assistance, childcare, and stipends, can remove barriers to participation. Further, integrating culturally tailored dementia care models into healthcare systems can improve early diagnosis and treatment pathways for at-risk populations.

By implementing comprehensive public health campaigns and legislative policies that promote health equity in dementia research, healthcare systems can enhance early detection, reduce disparities in diagnosis, and ensure that dementia care and research reflect the needs of all populations. These policies will contribute to timely interventions, better patient outcomes, and a more inclusive approach to AD prevention and treatment.

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