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Early Detection of Alzheimer's Disease Using Scalable and Non-Invasive Approaches: A Systematic Review

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ADMINISTRATIVE INFORMATION

Support - NA.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 November 2025 and was last updated on 26 November 2025.

INTRODUCTION

Review question / Objective Review question: What scalable and non-invasive approaches are effective for the early detection, diagnosis, or prediction of mild cognitive impairment (MCI) or early-stage Alzheimer's disease in adults, based on empirical evidence of diagnostic accuracy, feasibility, and scalability?

SPIDER Framework:

Sample (S):
Adults diagnosed with mild cognitive impairment (MCI) or early-stage Alzheimer's disease. Studies with relevant control groups (e.g., cognitively healthy individuals) are also eligible if used for comparison.

Phenomenon of Interest (P):
Evaluation of early detection, diagnosis, or prediction of cognitive decline or Alzheimer's disease.

Design (D):
Empirical studies using longitudinal, cross-sectional, case-control, experimental, or clinical trial designs that assess scalable, non-invasive, or digital methods.

Evaluation (E):
Diagnostic accuracy metrics (e.g., sensitivity, specificity, AUC, predictive value); feasibility and scalability outcomes (e.g., cost, automation, potential for remote or mobile delivery); and efficacy of the approach in detecting MCI or early Alzheimer's.

Research type (R):
Quantitative, observational, or machine learning–based studies.

Definition of scalable:
For this review, a method is considered scalable if it is minimally invasive, low-cost, and does not require intensive resources for deployment or use. Scalable methods include those that are suitable for broad, population-level implementation, can be

automated or remotely delivered, and are feasible in routine clinical or research settings without specialised infrastructure. For this review, a method is considered scalable if it is minimally invasive, low-cost, and not resource-intensive, making it suitable for broad implementation across clinical or population settings.

Objective:
To systematically identify and synthesise empirical studies evaluating scalable and non-invasive or digital approaches for the early detection or prediction of MCI or early-stage Alzheimer's disease in adults, emphasising evidence on diagnostic accuracy, feasibility, and scalability.

Rationale Early identification of Alzheimer's disease (AD) and mild cognitive impairment (MCI) is crucial for enabling timely intervention, optimised care planning, and improved patient outcomes. However, most conventional diagnostic approaches, including PET imaging and lumbar puncture which are either highly invasive, costly, or require substantial resources, limiting their suitability for large-scale or population-level implementation.

This systematic review addresses a critical gap by focusing on scalable and non-invasive methods for early detection and diagnosis. Here, scalable is defined as approaches that are minimally invasive, low cost, and not resource-intensive, making them practical for broad use in diverse healthcare settings.

Given the increasing global burden of dementia and the essential need for accessible early diagnostic tools, synthesising evidence on the diagnostic accuracy, feasibility, and scalability of such methods can inform clinical practice, policy, and future research directions.

By systematically evaluating scalable and non-invasive detection approaches, the review aims to support the development and implementation of practical solutions for timely Alzheimer's diagnosis, benefiting patients, clinicians, and health systems worldwide.

Condition being studied Mild cognitive impairment (MCI) and early-stage Alzheimer's disease (AD).

Mild cognitive impairment is a clinical condition characterised by noticeable problems with memory or other cognitive abilities that go beyond normal age-related changes but do not significantly impair daily life or independence. MCI can be an early symptom of Alzheimer's disease, especially when changes are progressive and accompanied by biomarker or clinical evidence of AD pathology. Early-stage Alzheimer's disease refers to the initial phase of Alzheimer's dementia, where cognitive decline is present, but individuals remain largely independent in daily functioning.

This review focuses on studies targeting adults diagnosed with MCI or early-stage Alzheimer's disease, using established clinical, cognitive, or biomarker criteria for diagnosis, and aims to identify effective, scalable, and non-invasive early detection approaches.

METHODS

Search strategy A comprehensive literature search will be conducted using the following electronic databases: MEDLINE, Embase, Web of Science, and Cochrane Library, from database inception to present. The search will combine keywords and controlled vocabulary (e.g., MeSH terms) relating to (1) Alzheimer's disease or mild cognitive impairment, (2) early detection, diagnosis, or prediction, and (3) scalable, non-invasive, or digital methods.

Sample search terms will include:
("Alzheimer disease" OR "mild cognitive impairment" OR MCI) AND ("early detection" OR "early diagnosis" OR "prediction" OR "screening") AND ("non-invasive" OR "scalable" OR "digital" OR "biomarker" OR "blood test" OR "retinal" OR "remote" OR "mobile health" OR "machine learning")*

Boolean operators (AND, OR) and database-specific controlled terms will be refined for each database.
No publication year restrictions will be applied.

Participant or population The population under study comprises adults diagnosed with mild cognitive impairment (MCI) or early-stage Alzheimer's disease (AD). Eligible studies may also include control groups, such as cognitively healthy adults, for comparative analyses.

MCI refers to measurable cognitive decline that does not significantly impair daily living but is greater than expected for age and education level. Early-stage Alzheimer's disease is characterized by mild but progressive deterioration of memory and other cognitive functions, with individuals generally retaining independence in most daily activities.

Intervention The interventions of interest are scalable and non-invasive, or digital methods for the early detection, diagnosis, or prediction of mild cognitive impairment (MCI) or early-stage Alzheimer's disease in adults. For this review, scalable interventions are defined as approaches that are minimally invasive, low-cost, and not resource-intensive, making them suitable for broad population-level or clinical implementation.

Comparator Eligible comparators include cognitively healthy adults (healthy controls) and, where relevant, participants with more advanced Alzheimer's disease or dementia. Healthy controls are individuals with preserved general cognitive function and no evidence of significant cognitive impairment.

Comparators also may include standard diagnostic methods or routine clinical assessment as reference standards for evaluating the diagnostic accuracy of scalable, non-invasive methods. Studies that compare scalable approaches directly to more invasive or costly benchmarks (e.g., PET imaging, CSF markers), when used as reference standards, are also eligible.

Study designs to be included Eligible study designs are empirical and include longitudinal, cross-sectional, case-control, clinical trials, experimental, and machine learning–based studies. Studies must evaluate scalable, non-invasive, or digital methods for early detection, diagnosis, or prediction of mild cognitive impairment (MCI) or early Alzheimer's disease, reporting diagnostic accuracy or predictive outcomes. Non-empirical studies, animal/in vitro research, and studies lacking relevant outcomes are excluded.

Eligibility criteria
Additional inclusion criteria:

Only studies published in English or with reliable English translations will be considered.

Full-text availability is required to enable thorough appraisal and data extraction.

Studies must present original, empirical data on diagnostic, predictive, or feasibility outcomes relevant to scalable, non-invasive approaches for early Alzheimer's or MCI.

Additional exclusion criteria:

Animal or in vitro studies, and non-empirical publications (editorials, reviews without new data, letters, case reports) are excluded.

Studies using only highly invasive or costly diagnostic methods (e.g., PET-only, lumbar puncture without a less-invasive alternative) will be excluded.

Reports lacking sufficient outcome data or relevance to diagnostic or predictive aims are ineligible.

Conference abstracts or unpublished studies will be excluded unless sufficient methodological and outcome information is available.

Information sources We will conduct systematic searches of the following electronic databases: MEDLINE, Embase, Web of Science, and Cochrane Library from inception to the date of search.

Main outcome(s) The primary outcomes are diagnostic accuracy and feasibility of scalable, non-invasive, or digital methods for early detection of MCI or early-stage Alzheimer's disease in adults. Diagnostic accuracy will be evaluated using sensitivity, specificity, area under the curve (AUC), and predictive values at the reported test threshold.

Feasibility and scalability outcomes include cost, automation, and potential for remote or mobile delivery. Where available, outcomes will be synthesised at the time point(s) specified in each study (e.g., baseline or during follow-up).

Data management All search results will be imported into a reference management software (such as EndNote or Zotero) for de-duplication. Citations will then be uploaded into systematic review management software (e.g., Covidence) for screening and selection. Two reviewers will independently screen titles, abstracts, and full texts; discrepancies will be resolved through discussion or a third reviewer. Data from included studies will be extracted using standardized forms, with pilot testing to refine extraction fields. Data will be stored securely, with clear documentation of inclusion decisions, extraction, and any data transformations, ensuring a transparent audit trail and facilitating future updates.

Quality assessment / Risk of bias analysis Risk of bias and methodological quality of included studies will be independently assessed by two

reviewers using tools appropriate for each study design.

For randomised controlled trials, the Cochrane Risk of Bias (RoB 2) tool will be used.

For observational, diagnostic accuracy, and machine learning studies, validated instruments such as QUADAS-2 (for diagnostic studies) and the JBI critical appraisal checklists will be applied.

Any disagreements will be resolved by consensus or a third reviewer. The results of quality appraisal will be documented and incorporated into data synthesis and interpretation. Overall confidence in the findings will be summarised using tools such as GRADE, where appropriate, to assess the certainty of evidence for main outcomes.

Strategy of data synthesis Data from included studies will first be summarised in structured tables capturing study characteristics, populations, interventions, comparators, and main outcomes. Given anticipated clinical and methodological heterogeneity, a narrative synthesis will be performed to systematically describe and compare findings across studies, highlighting patterns in diagnostic accuracy, feasibility, and scalability. Where appropriate and where sufficient homogeneity exists in study design, populations, and outcomes (e.g., for studies using the same index test and reporting sensitivity/specificity), a quantitative synthesis or meta-analysis may be conducted using random-effects models, pooling diagnostic accuracy measures such as sensitivity, specificity, and AUC. Heterogeneity will be assessed, and subgroup or sensitivity analyses will be considered as needed.

The synthesis will clearly report cases where meta-analysis is not feasible. All results will be presented in text, tables, and figures according to PRISMA guidelines. Evidence certainty will be assessed for key outcomes.

Subgroup analysis Where sufficient data are available, subgroup analyses will be conducted to explore potential sources of heterogeneity in diagnostic accuracy and feasibility outcomes. Planned subgroups may include:

Participant characteristics: age groups, sex, education level, or clinical risk factors

Type or modality of scalable method: e.g., blood-based biomarkers, digital cognitive tests, sensor-based tools

Setting: clinical vs. community-based populations, geographic location, or healthcare resource context

Subgroup analyses will be pre-specified in the protocol, and any additional subgroups identified during data extraction will be clearly identified as post hoc. For each analysis, we will:

Report if a statistically significant subgroup effect is detected, using the p-value for the test of subgroup differences.

Assess the plausibility and clinical relevance of any observed interactions.

Consider the distribution and number of studies/participants within each subgroup, and interpret with caution if subgroups are small or unevenly distributed.

Account for heterogeneity and uncertainty when interpreting results, following established guidance.

Results will be presented in tables or forest plots, and interpreted in light of the key criteria for valid subgroup analysis: statistical significance, sample size, biological plausibility, and clinical importance.

Sensitivity analysis Sensitivity analysis will be performed to assess the robustness of review findings against key methodological decisions and assumptions. Analyses may include excluding studies at high risk of bias, varying inclusion criteria, or testing the impact of different analytical models. If meta-analysis is feasible, sensitivity will be examined by systematically removing studies with high bias, outlying results, or differing methodologies to determine whether overall findings remain consistent. This approach will help evaluate the certainty and validity of pooled estimates, ensuring conclusions are not unduly influenced by specific studies or analysis choices.

Language restriction This review will include studies published in English or with a reliable English translation.

Country(ies) involved United Kingdom.

Keywords Alzheimer's Disease; MCI; early detection; non-invasive; scalable; biomarker; remote assessment; mobile health; cognitive decline; feasibility; diagnostic accuracy; sensitivity; specificity.

Dissemination plans Findings from this systematic review will be disseminated through publication in a peer-reviewed journal and presentations at relevant national and international conferences. Summaries will be shared with academic, clinical, and policy audiences via academic seminars, conference posters, and oral presentations. To maximise reach and impact, lay summaries and infographics will be prepared for wider audiences, including patient or caregiver groups and relevant advocacy organisations. Where appropriate, key findings will also be communicated through institutional websites and professional social media platforms. Requests for more detailed results will be addressed as feasible, and the full protocol and review will adhere to PRISMA reporting standards to support replicability and transparency.

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