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Evidence-Based Therapeutic Strategies for Degenerative Neurocognitive Decline in Early Alzheimer's Disease: A Systematic Review of Randomized Controlled Trials

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Abstract

The early stages of Alzheimer's disease (AD) consist of mild cognitive impairment (MCI) from AD and mild AD dementia. The early stages offer a crucial opportunity for intervention to reduce cognitive and functional decline. In the last decade, multiple disease-modifying and non-pharmacological interventions have been examined in randomized controlled trials (RCTs). Yet, the research is fragmented according to treatment mechanism and outcome measurement, and results are not consistent between interventions. This systematic review was conducted to summarize the evidence regarding the efficacy and safety of interventions to reduce cognitive and functional decline in early AD.

An electronic search of databases, including PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, Scopus, and Web of Science, was performed for RCTs published from January 2015 to September 2026 evaluating therapeutic approaches for decelerating neurocognitive decline in early AD. Adults with MCI caused by AD, prodromal AD, or mild AD dementia were included if studies described cognitive, functional, or global clinical outcomes. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement was used as a guideline in conducting the systematic review. Cochrane Risk of Bias 2 (RoB 2) tool was employed to assess risk of bias.

Of the 2,712 records identified, 1,479 were screened after duplicate and automation-based removals. Following full-text assessment of 104 reports, 88 were excluded, and 16 publications (reporting 21 individual RCTs) were included in the systematic review. Lecanemab and donanemab showed slower decline of clinical endpoints in phase 3 or phase 2 studies with amyloid-related imaging abnormalities-edema (ARIA-E) in 12.6% and 24.0% of participants treated, respectively. Aducanumab achieved positive results on the primary endpoint in one out of two trials, whereas gantenerumab, crenezumab, and solanezumab showed no efficacy in slowing decline, despite amyloid clearance in certain studies. Beta-secretase inhibitors (verubecestat and lanabecestat), an anti-tau antibody (semorinemab), intranasal insulin, and oral semaglutide (two studies, 3,808 participants) demonstrated no clinical efficacy. Blarcamesine and a multinutrient approach showed beneficial outcomes; however, the bias risk was high in both cases. Supervised aerobic exercise showed reduced neuropsychiatric symptoms without consistent improvement of cognition. The bias risk in studies was low in four, some concerns in nine, and high in three studies. Monoclonal antibodies against amyloid-beta demonstrate promising but mild delay in the progression of disease in early AD. Nonetheless, the application of this treatment method is fraught with numerous dangers, including imaging alterations and possible serious complications. Data regarding the efficacy of other pharmacologic and non-pharmacologic approaches is inconclusive due to the small sample size and subject attrition.

The future treatment of patients with early AD should be personalized and evidence-based. Biomarkers of amyloid-beta and tau pathology, including amyloid PET and tau PET, may facilitate patient stratification and assessment of treatment response. Large RCTs are necessary to establish the effectiveness and safety of pharmacological and non-pharmacological treatments.

Categories: Neurology, Pharmacology, Geriatrics
Keywords: anti-amyloid monoclonal antibodies, donanemab, lecanemab, mild cognitive impairment, physical therapy

Introduction And Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and one of the most common causes of dementia worldwide. It is characterized by progressive deterioration in memory, reasoning, communication, behavior, and the ability to perform everyday activities. AD contributes substantially to

disability, caregiver burden, healthcare utilization, and mortality among older adults. In 2024, approximately 6.9 million Americans aged 65 years and above were living with Alzheimer's dementia [1]. Globally, the number of individuals affected by dementia was estimated at 57 million in 2019 and is projected to increase to approximately 153 million by 2050 [2].

Early AD is an important stage for therapeutic intervention and, as considered in this review, encompasses mild cognitive impairment (MCI) due to AD and mild AD dementia. Individuals with MCI due to AD have noticeable difficulties with memory or other cognitive abilities but generally remain independent in daily activities. Those with mild AD dementia experience greater difficulties that begin to affect their everyday functioning [3,4]. MCI due to AD is also frequently described as prodromal AD in clinical research, although the terminology may vary across diagnostic and research frameworks. Advances in biomarker research have improved understanding of AD by enabling identification of underlying biological changes, including amyloid and tau pathology, during an individual's lifetime. The National Institute on Aging-Alzheimer's Association (NIA-AA) research framework emphasizes the biological basis of AD alongside its clinical manifestations [5]. This early symptomatic stage represents an important therapeutic window, as interventions initiated before substantial neuronal and synaptic damage may have greater potential to delay clinical deterioration.

The amyloid cascade hypothesis has substantially influenced the development of disease-modifying treatments for AD. According to this hypothesis, the accumulation of amyloid-β contributes to subsequent pathological processes associated with neuronal dysfunction and cognitive decline [6]. However, the development of effective treatments has been challenging, with several unsuccessful clinical trials highlighting the need to investigate alternative therapeutic targets [7]. Among newer approaches, anti-amyloid monoclonal antibodies, particularly lecanemab and donanemab, have demonstrated modest slowing of clinical decline in individuals with early AD. Lecanemab was evaluated in the phase 3 CLARITY AD randomized controlled trial (RCT), which demonstrated a statistically significant reduction in clinical decline compared with placebo over 18 months [8]. Donanemab also demonstrated a slowing of clinical decline in the phase 3 TRAILBLAZER-ALZ 2 trial [9]. However, other agents, including gantenerumab and solanezumab, have demonstrated inconsistent or inconclusive clinical benefits despite efforts to reduce amyloid pathology [10,11]. Beta-secretase (BACE) inhibition, investigated through agents such as verubecestat, has also failed to demonstrate meaningful clinical benefit [12]. Anti-amyloid therapies also raise safety concerns because of amyloid-related imaging abnormalities (ARIA), which are changes detected on brain magnetic resonance imaging (MRI) scans. These may include swelling or fluid accumulation in the brain (ARIA-E) and small areas of bleeding (ARIA-H). These adverse effects highlight the importance of appropriate patient selection, MRI monitoring, and careful assessment of treatment-related risks [13,14].

In addition to disease-modifying pharmacological treatments, other therapeutic approaches have been explored to address cognitive and functional decline in AD. These include interventions targeting lifestyle and modifiable risk factors, as well as nutritional and physical activity-based approaches [15]. Evaluating treatment effectiveness in AD requires the assessment of both cognitive and functional outcomes. Treatment effectiveness in AD is evaluated using standardized tools that measure different aspects of disease progression, including cognition, overall disease severity, and the ability to perform daily activities. Commonly used clinical measures include the Clinical Dementia Rating (CDR), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), Mini-Mental State Examination (MMSE), and Integrated Alzheimer's Disease Rating Scale (iADRS) [16-19]. Additional instruments, including the Alzheimer's Disease Composite Score (ADCOMS), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), Neuropsychological Test Battery (NTB), and Symbol Digit Modalities Test (SDMT), provide further assessment of clinical progression, everyday functioning, and specific cognitive domains [20-23]. The interpretation of these measures alongside biomarker responses and treatment-related adverse events is essential for determining whether biological changes translate into meaningful clinical benefits. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [24], and the methodological quality of the included RCTs was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [25].

In addition to anti-amyloid treatments, researchers have investigated several other pharmacological and non-pharmacological approaches to manage early AD. These include additional amyloid-targeting agents and pharmacological interventions directed at alternative disease mechanisms [26-29]. Other pharmacological strategies include the BACE inhibitor lanabecestat, anti-tau immunotherapy with semorinemab, intranasal insulin, and blarcamesine; however, findings from these trials have been variable and warrant cautious interpretation [30-33]. Metabolic approaches, including oral semaglutide, have also been investigated [34]. In addition to pharmacological interventions, nutritional strategies, such as the multinutrient formulation evaluated in the LipiDiDiet trial, and supervised physical exercise have been explored as potential approaches to support cognitive and functional outcomes in individuals with early AD [35,36].

Despite advances in therapeutic research, the effectiveness of treatments for early AD remains uncertain. Clinical trials differ in their treatment approaches, participant characteristics, outcome measures, and follow-up periods. Furthermore, some interventions have demonstrated biological effects without corresponding improvements in clinical outcomes, whereas others have reported modest slowing of clinical

decline accompanied by important safety concerns [8-10]. These differences make it difficult to draw consistent conclusions across therapeutic categories. An integrated synthesis of randomized evidence evaluating pharmacological, nutritional, metabolic, and exercise-based approaches, while considering cognitive, functional, biomarker, and safety outcomes, is therefore needed to provide a broader understanding of their clinical effectiveness and limitations.

The period from January 2015 to September 2026 was considered to capture contemporary randomized evidence reflecting the evolving therapeutic landscape of early AD. During this period, clinical research expanded beyond conventional symptomatic management to investigate disease-modifying approaches, including anti-amyloid therapies, as well as alternative pharmacological and non-pharmacological interventions. The emergence of these treatment strategies, together with variation in their reported clinical benefits and safety profiles, provides a rationale for an updated assessment of the available evidence. Such an assessment may help clarify the current evidence regarding the effectiveness and limitations of these diverse therapeutic approaches.

The present systematic review aimed to identify and synthesize RCTs published between January 2015 and September 2026 that evaluated pharmacological and non-pharmacological therapeutic strategies for slowing neurocognitive decline in early AD. Specifically, the review examined their effects on cognitive, functional, and global clinical outcomes, biomarker responses, and treatment-related adverse events. By integrating evidence across different therapeutic categories and evaluating the methodological quality of the included trials, this review seeks to provide a clinically relevant overview of current treatment evidence and identify areas requiring further investigation. The conceptual framework illustrating the therapeutic approaches, evidence gaps, and objectives of the present review is presented in Figure *1*.

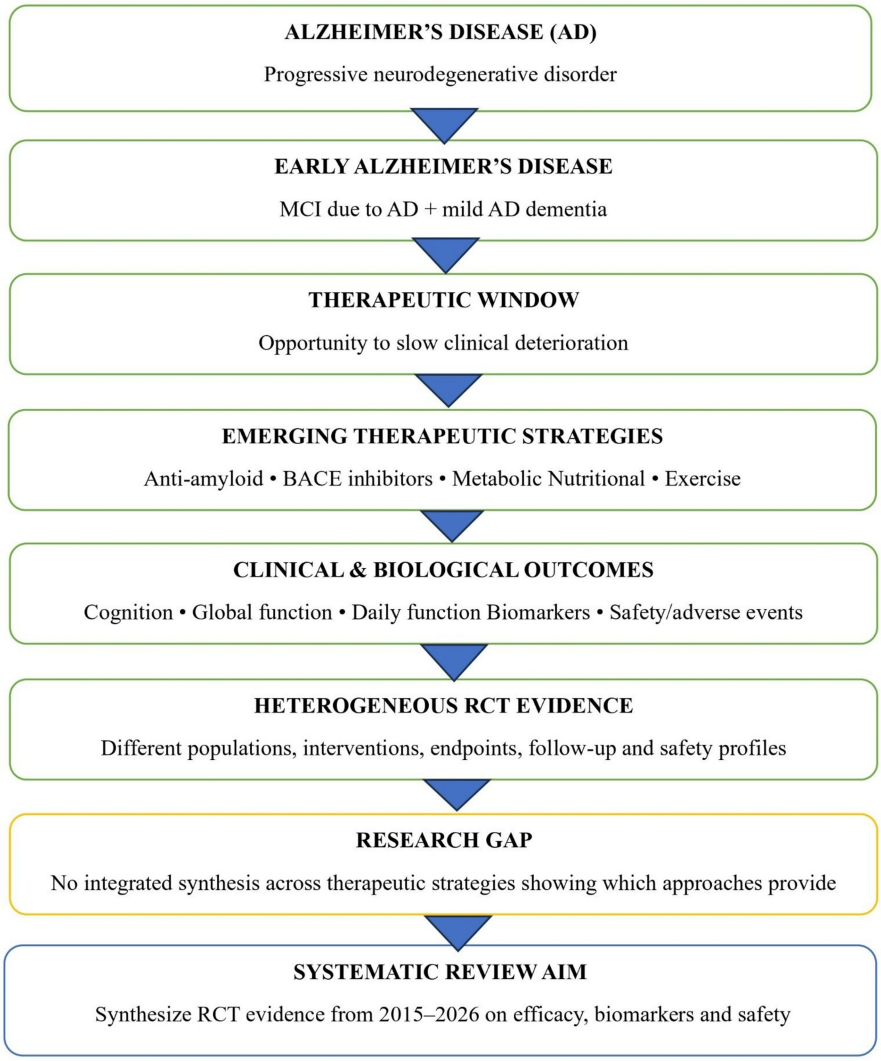


FIGURE 1: Conceptual flowchart of therapeutic strategies and evidence evaluation in early Alzheimer's disease

BACE: beta-secretase; MCI: mild cognitive impairment; RCT: randomized controlled trial.

The image was created by Prachi M. Kamble using Microsoft PowerPoint (Microsoft Corporation, Redmond, WA, USA).

The review was conducted following the PRISMA 2020 guidelines, with study selection, data extraction, and assessment of methodological quality performed using predefined eligibility criteria and the Cochrane RoB 2 tool, as detailed in the following sections.

Review

Method

Study Design

This systematic review was conducted and reported in accordance with the PRISMA 2020 guidelines [24]. The review protocol was not prospectively registered in an international systematic review registry.

Eligibility Criteria

Studies were eligible if they were peer-reviewed, full-text, English-language RCTs published between January 1, 2015, and September 30, 2026, involving at least 100 randomized adults with early-stage AD. Early AD was defined as MCI due to AD, including populations described as prodromal AD where

appropriate, or mild AD dementia. MCI due to AD involved measurable cognitive impairment with generally preserved independence in daily activities, whereas mild AD dementia involved greater cognitive impairment affecting daily functioning. Eligible populations could be clinically diagnosed, with or without biomarker confirmation. The minimum sample-size threshold was used as a pragmatic criterion to focus on larger trials and exclude small exploratory studies; it was based on the total number randomized, not the number completing treatment, and was not considered a measure of methodological quality or statistical power. Eligible trials compared an intervention with placebo, sham, usual care, or another active comparator and reported at least one cognitive, functional, or global clinical outcome. Studies involving participants at different stages of AD were included only when data for individuals with early-stage AD were reported separately. Studies without separately extractable data for the early-stage population were excluded, as shown in Table *1*.

Criteria	Inclusion criteria	Exclusion criteria
Study design	Randomized controlled trials (parallel-group, phase 2b/3, adaptive, factorial) with at least 100 randomized participants	Non-randomized studies, post hoc or secondary analyses, open-label extensions without randomization, trial protocols, reviews, meta-analyses, conference abstracts without full text
Population	Adults with MCI due to AD (prodromal AD) or mild AD dementia, established using clinical criteria, with or without biomarker confirmation	Preclinical or asymptomatic AD, MCI of unspecified etiology, non-AD dementias, and moderate-to-severe AD without separately reported early-stage data
Intervention	Any pharmacological, biological, nutritional, neuro-modulatory interventions, or lifestyle intervention aimed at slowing cognitive or functional decline	Prevention-only interventions, interventions solely for neuropsychiatric symptoms, studies with biomarker-only primary endpoints
Comparison	Placebo, sham, usual care, or active comparator	Single-arm studies; no comparator
Outcomes	At least one clinical outcome: CDR-SB, ADAS-Cog, iADRS, ADCOMS, MMSE, neuropsychological composite, functional scale; safety and adverse events	No clinical cognitive, functional, or global outcome reported
Language and period	Full-text, peer-reviewed, English-language publications, January 1, 2015 to September 30, 2026	Non-English publications; publications outside the period

TABLE 1: Eligibility criteria for study selection

AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCOMS: Alzheimer's Disease Composite Score; CDR-SB: Clinical Dementia Rating Sum of Boxes; iADRS: integrated Alzheimer's Disease Rating Scale; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination.

Information Sources

A systematic literature search was conducted using five electronic databases: PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science. The searches covered publications from January 1, 2015, to September 30, 2026. In addition to the electronic database searches, the reference lists of included trials and relevant systematic reviews were manually examined to identify additional potentially eligible publications. Trial registries and gray literature sources were not searched separately, as the review was restricted to peer-reviewed RCTs.

Search Strategy

The search strategy was developed to identify RCTs evaluating therapeutic interventions in adults with early-stage AD. It combined controlled terminology, including Medical Subject Headings (MeSH) and Emtree terms where available, with relevant free-text keywords related to AD, its early clinical stages, therapeutic interventions, and randomized study designs. Boolean operators (AND and OR) were used to combine the search terms.

The search strategy was adapted separately for each database to account for differences in indexing systems, search fields, and search interfaces. The date on which each database was searched and the publication date limits applied are also reported to facilitate reproducibility.

To cover different therapeutic approaches, intervention-related terms included pharmacological, biological, nutritional, and non-pharmacological interventions, such as monoclonal antibodies, BACE inhibitors, exercise, dietary supplements, and brain stimulation. The search strategy was adapted to the indexing system and search interface of each database. The complete database-specific search strings are presented in

Table 2.

Database	Search date	Search strategy	Filters/limits
PubMed/MEDLINE	September 12, 2026	("Alzheimer Disease"[MeSH] OR "Alzheimer's disease"[tiab] OR "mild cognitive impairment"[tiab] OR prodromal[tiab] OR "early Alzheimer*"[tiab]) AND ("Therapeutics"[MeSH] OR "monoclonal antibod*" OR lecanemab OR donanemab OR aducanumab OR gantenerumab OR "BACE inhibitor*" OR exercise OR supplement* OR "brain stimulation") AND ("randomized controlled trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab])	English; Humans; 2015-2026
Embase	September 17, 2026	('alzheimer disease'/exp OR 'mild cognitive impairment'/exp OR 'early alzheimer*':ti,ab) AND ('drug therapy'/exp OR 'monoclonal antibody'/exp OR 'exercise'/exp OR 'dietary supplement'/exp OR lecanemab OR donanemab) AND ('randomized controlled trial'/exp OR random*:ti,ab OR placebo:ti,ab)	English; Articles; 2015-2026
Cochrane CENTRAL	September 21, 2026	#1 MeSH descriptor: [Alzheimer Disease] explode all trees; #2 (early Alzheimer* OR prodromal OR "mild cognitive impairment" OR "mild dementia"):ti,ab,kw; #3 #1 OR #2; #4 (treatment OR therapy OR "monoclonal antibod*" OR exercise OR supplement*):ti,ab,kw; #5 #3 AND #4	Trials; 2015-2026
Scopus	September 25, 2026	TITLE-ABS-KEY ((Alzheimer* AND (early OR prodromal OR "mild cognitive impairment" OR "mild dementia")) AND (treatment OR therapy OR "monoclonal antibod*" OR exercise OR supplement*) AND ("randomized controlled trial" OR randomi* OR placebo))	English; Article; 2015-2026
Web of Science	September 28, 2026	TS = ((Alzheimer* NEAR/3 (early OR prodromal OR mild)) AND (therap* OR treatment OR "monoclonal antibod*" OR exercise OR supplement*) AND (randomi* OR placebo))	English; Article; 2015-2026

TABLE 2: Database-specific electronic search strategies

CENTRAL: Cochrane Central Register of Controlled Trials; MeSH: Medical Subject Headings; ti,ab,kw: title, abstract, keywords; tiab: title/abstract; TITLE-ABS-KEY: title, abstract, and keywords; TS: topic search.

To improve the consistency of statistical reporting across the included studies, the primary endpoints, assessment time points, between-group treatment effects, 95% confidence intervals, and p-values were organized in a standardized format (Table 3). The table presents the 16 included publications, with results from individual RCTs reported separately wherever a publication described more than one trial. Clinical meaningfulness thresholds were included where available and supported by the relevant source.

Study	Primary endpoint and assessment time	Between-group treatment effect	95% CI	p-value	MCID/clinical meaningfulness
Van Dyck CH et al. (2023) [8]	CDR-SB, 18 months	−0.45 points	NR	NR	NR
Sims JR et al. (2023) [9]	iADRS, 76 weeks	Low/medium-tau population: 3.25 points*; combined population: 2.92 points*	NR	NR	NR
Bateman RJ et al. (2023) [10]	CDR-SB, 116 weeks	Trial 1: −0.30 points*; Trial 2: −0.19 points*	NR	Trial 1: 0.10; trial 2: 0.30	NR
Honig LS et al. (2018) [11]	ADAS-Cog14, 80 weeks	NR	NR	NR	NR
Egan et al. (2019) [12]	CDR-SB, 104 weeks	NR	NR	NR	NR
Mintun MA					

et al. (2021) [26]	iADRS, 76 weeks	3.20 points	0.12 to 6.27	0.04	NR
Swanson CJ et al. (2021) [27]	ADCOMS, 12 months	Primary endpoint not met; numerical treatment estimate to be verified	NR	NR	NR
Ostrowitzki S et al. (2022) [28]	CDR-SB, planned 105 weeks	Trial 1 and Trial 2: no significant clinical benefit reported; trials stopped early	NR	NR	NR
Budd Haeberlein S et al. (2022) [29]	CDR-SB, 78 weeks	EMERGE: −0.39 points; ENGAGE: +0.03 points	NR	EMERGE: 0.012; ENGAGE: 0.833	NR
Wessels AM et al. (2020) [30]	Primary cognitive/functional endpoints; 104 weeks (AMARANTH) and 78 weeks (DAYBREAK-ALZ)	Both trials stopped early for futility; numerical estimates to be verified	NR	NR	NR
Teng E et al. (2022) [31]	CDR-SB, 73 weeks	NR	NR	NR	NR
Craft S et al. (2020) [32]	Primary cognitive/functional endpoints, 12 months	No significant benefit in primary analyses	NR	NR	NR
Macfarlane S et al. (2025) [33]	ADAS-Cog13 and ADCS-ADL (co-primary), 48 weeks	Numerical between-group estimates to be verified	NR	NR	NR
Cummings JL et al. (2026) [34]	CDR-SB, week 104	EVOKE: −0.08 points; EVOKE+: +0.10 points	EVOKE: −0.35 to 0.20; EVOKE+: −0.17 to 0.38	NR	NR
Soininen H et al. (2021) [35]	NTB 5-item composite, 24 months (primary endpoint); 36-month follow-up	Primary endpoint not met at 24 months; later follow-up findings reported	NR	NR	NR
Hoffmann K et al. (2016) [36]	Primary endpoint and treatment estimate to be verified, 16 weeks	SDMT improvement of 4.2 points (95% CI: 0.5 to 7.9) reported in protocol-adherent participants; verify whether this was the primary endpoint	0.5 to 7.9 (SDMT)	NR	NR

TABLE 3: Standardized reporting of primary clinical outcomes and treatment effects across the 16 included publications

ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS: Alzheimer's Disease Composite Score; ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living; CDR-SB: Clinical Dementia Rating-Sum of Boxes; CI: confidence interval; iADRS: Integrated Alzheimer's Disease Rating Scale; MCID: minimal clinically important difference; NR: not reported in the current extracted data; NTB: neuropsychological test battery; SDMT: Symbol Digit Modalities Test.

The availability and reporting of statistical estimates varied across the included publications. While some studies reported between-group treatment differences with confidence intervals and p-values, others primarily presented changes from baseline or qualitative findings. Therefore, the reported results were interpreted according to the original trial analyses. Differences in outcome measurement scales, intervention protocols, participant characteristics, and follow-up durations also limited direct comparisons between studies. Statistical significance was consequently considered alongside the magnitude and direction of treatment effects and their potential clinical relevance.

Selection Process

All retrieved records were imported into reference management software, and duplicate records were removed before the screening process. Two independent reviewers conducted the initial screening of titles

and abstracts based on the predefined eligibility criteria. Subsequently, the full texts of potentially relevant reports were independently assessed by both reviewers to determine their eligibility. Any disagreements were resolved through discussion and consensus.

For studies reporting multiple publications or follow-up results from the same randomized trial, the reports were examined to identify the primary trial findings and relevant clinical outcome data. Duplicate reports from the same trial were not considered independent studies during the synthesis. Publications available within the predefined search period, ending on September 30, 2026, were considered for inclusion according to the established eligibility criteria.

References used for background information, outcome measure descriptions, and methodological guidance were not considered part of the therapeutic efficacy evidence. The therapeutic findings presented in this review were derived exclusively from the RCTs that fulfilled the predefined inclusion and exclusion criteria.

Data Collection Process

Data were extracted independently by two reviewers using a predefined data extraction form. The extracted information included the first author, year of publication, study name, study design, sample size, participant characteristics, intervention and comparator details, outcome measures, follow-up duration, main findings, and relevant adverse events. When a single publication reported findings from more than one RCT, the relevant information, including trial-specific sample sizes, interventions, comparators, outcome measures, follow-up periods, and clinical findings, was extracted separately for each individual trial wherever available. Each publication was counted once in the total number of included publications, while the individual trials reported within these publications were considered separately during the synthesis of trial characteristics and findings. Thus, the review included 16 publications reporting 21 individual RCTs. Any discrepancies in the extracted information were resolved through discussion and consensus between the reviewers.

Data Items

The data items included study characteristics, participant characteristics, intervention details, comparator information, and clinical outcomes. The primary data of interest were cognitive, functional, and global clinical outcomes reported in the included trials. Cognitive outcomes included measures such as the CDR-Sum of Boxes (CDR-SB), ADAS-Cog, iADRS, ADCOMS, and MMSE. Functional and global outcomes, neuropsychological measures, relevant biomarkers, and safety outcomes, including adverse events, were also considered. The duration of treatment and follow-up was recorded for each study.

Risk-of-Bias Assessment

The risk of bias for included RCTs was assessed independently by two reviewers using the Cochrane RoB 2 instrument [25]. Any discrepancies that arose were settled through discussion to reach a consensus. The RoB 2 tool assesses five components (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result), giving an overall risk of low, some concerns, or high in each case. In antibody trials where ARIA could potentially unblind participants and assessors, this was taken into account in the measurement of the outcome and deviations from intended interventions sections.

Data Synthesis

Owing to considerable clinical and methodological heterogeneity among the included RCTs, quantitative meta-analysis was not performed. This decision was based on differences in intervention types, individual therapeutic agents, dosage regimens, participant characteristics, disease stages, comparator groups, primary outcome measures, and follow-up durations.

Although anti-amyloid monoclonal antibodies represented the largest intervention category, a separate class-specific quantitative meta-analysis was not undertaken. The included trials differed in the specific antibodies evaluated, treatment protocols, participant characteristics, outcome assessment methods, and follow-up time points. These differences limited the comparability of treatment-effect estimates required for reliable pooling. Similarly, network meta-analysis was not pursued because the comparability and transitivity of treatment comparisons across the available evidence could not be adequately established.

Formal statistical heterogeneity measures, including Cochran's Q, I^2, and τ^2, were not calculated because quantitative pooling was not undertaken. Instead, heterogeneity was assessed qualitatively by examining differences in study characteristics, interventions, populations, outcome measures, and follow-up periods. Accordingly, a narrative synthesis was conducted, with studies grouped according to intervention type: (i) anti-amyloid monoclonal antibodies; (ii) BACE inhibitors; (iii) anti-tau immunotherapy; (iv) repurposed metabolic and other pharmacological agents; (v) nutritional interventions; and (vi) exercise.

Within each intervention category, findings were summarized by examining the direction and magnitude of reported treatment effects on cognitive, functional, and global clinical outcomes, together with relevant safety findings. Cognitive, functional, and global outcomes were considered separately according to the assessment instruments used in individual trials. Treatment effects were described using reported between-group differences or changes from baseline. Relevant statistical estimates, including 95% confidence intervals and p-values, were reported wherever available in the original trial publications. Differences in outcome measures were addressed by interpreting findings within their respective assessment scales rather than directly comparing numerical changes across different instruments.

Results from intervention and comparator groups were considered at the reported assessment time points, taking differences in outcome measures and follow-up durations into account. Findings were interpreted within the context of each individual trial rather than through direct comparisons across interventions using different assessment methods or follow-up periods. Where multiple publications reported findings from the same trial, the information was integrated to avoid duplicate reporting. Risk-of-bias judgments were also considered when interpreting the consistency and limitations of the findings. No pooled effect estimates or statistical comparisons between intervention categories were calculated.

Result

Study Selection

A total of 2,712 records were identified through database searches, including PubMed/MEDLINE (n = 612), Embase (n = 748), CENTRAL (n = 391), Scopus (n = 524), and Web of Science (n = 437). Before screening, 1,046 duplicate records and 187 records reported as automatically removed were excluded. Following these exclusions, 1,479 records were screened, of which 1,372 were excluded. Two independent reviewers conducted the initial screening of titles and abstracts based on the predefined eligibility criteria. Subsequently, the full texts of potentially relevant reports were independently assessed by both reviewers to determine their eligibility. Any disagreements between the reviewers were resolved through discussion and consensus.

A total of 107 reports were sought for retrieval, and three could not be retrieved. The remaining 104 full-text reports were assessed for eligibility. Of these, 88 were excluded for the following reasons: ineligible population (n = 27), not a primary RCT report, including secondary or post hoc analyses, non-randomized extensions, or protocols (n = 29), ineligible intervention or comparator (n = 12), absence of an eligible clinical outcome (n = 9), duplicate publication of an included trial (n = 7), and conference abstract without full text (n = 4). Of the 104 reports assessed for eligibility, 88 were excluded for the reasons detailed above. Finally, 16 publications (reporting 21 individual RCTs) were included in the systematic review. The study selection process is presented in the PRISMA 2020 flow diagram (Figure *2*).

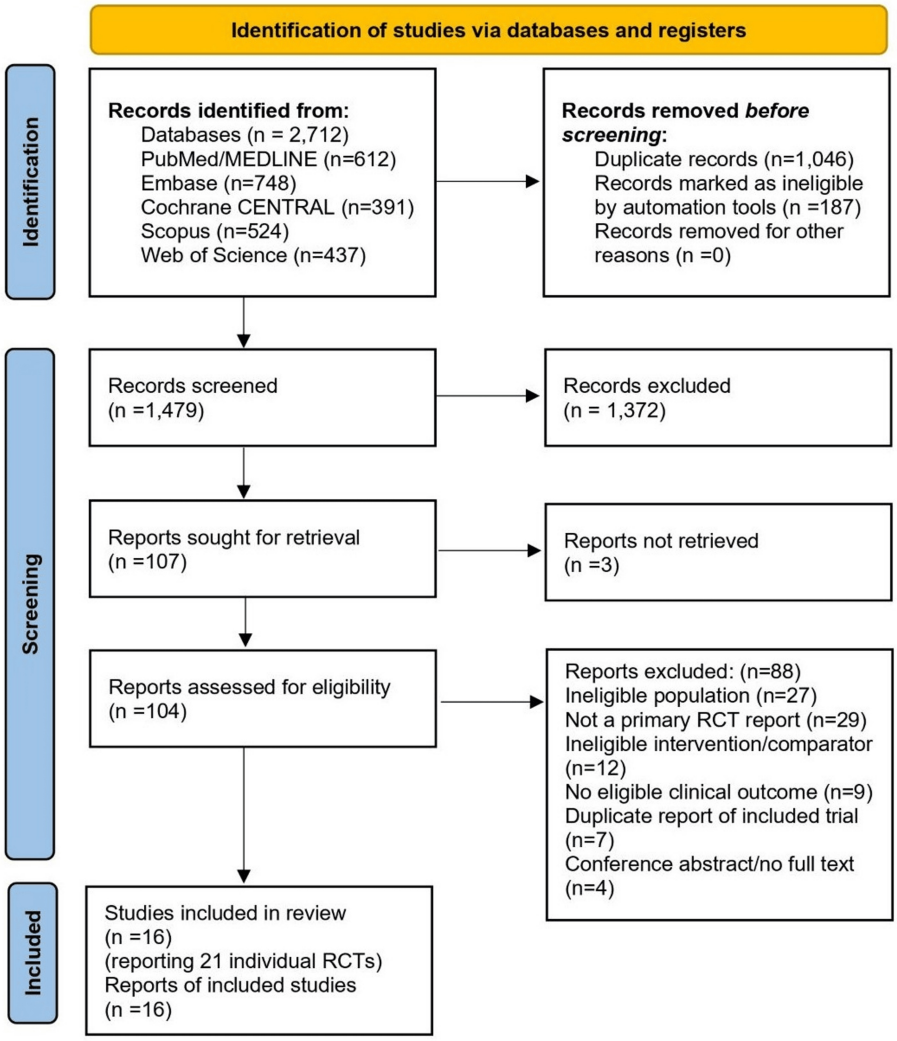


FIGURE 2: PRISMA 2020 flow diagram of study selection

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: randomized controlled trial.

Image credit: Authors; adapted from the PRISMA 2020 flow diagram template.

Characteristics of Included Studies

The 16 included publications reported findings from 21 individual RCTs investigating a range of therapeutic approaches, including anti-amyloid monoclonal antibodies [8-11,26-29], BACE inhibitors [12,30], anti-tau antibodies [31], metabolic and other pharmacological interventions [32-34], nutritional interventions [35], and supervised aerobic exercise [36]. Multidomain lifestyle interventions were not represented in the included studies. Although such interventions may combine dietary modification, physical activity, cognitive training, and management of vascular risk factors, no eligible RCT evaluating a comprehensive multidomain program in the predefined early AD population was identified in the included publications. Similarly, no eligible cognitive training trial met the inclusion criteria. Therefore, the effectiveness of these approaches could not be evaluated in the present review. The reported sample sizes ranged from 200 to 3,808 participants per publication. The treatment and follow-up durations ranged from 16 weeks to 3 years. Clinical outcomes included measures of cognition, function, and global disease progression, with the CDR-SB and integrated iADRS among the commonly reported primary outcomes. Detailed characteristics of the included publications and trials are presented in Table *4*.

Study	Design and sample size	Population	Intervention vs comparator	Outcome measures and follow-up	Main findings

Van Dyck CH et al. (2023) [8]	Double-blind phase 3 RCT n = 1,795 (898 vs 897)	Early AD (MCI or mild dementia), amyloid-positive	Lecanemab 10 mg/kg IV every 2 weeks vs placebo	CDR-SB (primary), ADAS-Cog14, ADCOMS, ADCS-MCI-ADL; 18 months	CDR-SB change 1.21 vs 1.66 (difference -0.45; 27% slowing); ARIA-E 12.6% vs 1.7%; infusion reactions 26.4% vs 7.4%
Sims JR et al. (2023) [9]	Double-blind phase 3 RCT n = 1,736 (860 vs 876)	Early symptomatic AD; amyloid with low/medium or high tau on PET	Donanemab IV every 4 weeks (up to 72 weeks) vs placebo	iADRS (primary), CDR-SB; 76 weeks	iADRS change -6.02 vs -9.27 (low/medium tau) and -10.19 vs -13.11 (combined); ARIA-E 24.0% vs 2.1%
Bateman RJ et al. (2023) [10]	Two double-blind phase 3 RCTs n = 985 and 980	MCI or mild dementia due to AD, amyloid-positive	Gantenerumab SC (titrated to 510 mg every 2 weeks) vs placebo	CDR-SB (primary), amyloid PET; 116 weeks	CDR-SB change 3.35 vs 3.65 (p = 0.10) and 2.82 vs 3.01 (p = 0.30); amyloid reduction of 66.44 and 56.46 centiloids without clinical benefit
Honig LS et al. (2018) [11]	Double-blind phase 3 RCT n = 2,129 (1,057 vs 1,072)	Mild AD dementia (MMSE 20-26), amyloid-positive	Solanezumab 400 mg IV every 4 weeks (76 weeks) vs placebo	ADAS-Cog14 (primary), MMSE, ADCS-ADL, CDR-SB; 80 weeks	No significant effect on cognitive decline; MMSE change -3.17 vs -3.66
Egan et al. (2019) [12]	Double-blind phase 3 RCT n = 1,454 (485/484/485)	Prodromal AD, amyloid-positive	Verubecestat 12 mg or 40 mg/day vs placebo	CDR-SB (primary); 104 weeks	Stopped for futility; no improvement in CDR-SB; some measures suggested worse cognition/function with verubecestat; more adverse events
Mintun MA et al. (2021) [26]	Double-blind phase 2 RCT n = 257 (131 vs 126)	Early symptomatic AD; tau and amyloid on PET (MMSE 20-28)	Donanemab (700 mg x3 then 1,400 mg IV every 4 weeks, up to 72 weeks) vs placebo	iADRS (primary); 76 weeks	iADRS change -6.86 vs -10.06 (difference 3.20, 95% CI 0.12 to 6.27, p = 0.04); secondary outcomes mixed; ARIA-E occurred
Swanson CJ et al. (2021) [27]	Double-blind, Bayesian adaptive phase 2b RCT n = 854 treated (609 vs 245)	MCI due to AD or mild AD dementia	Lecanemab, 5 dose regimens (2.5-10 mg/kg) vs placebo	ADCOMS at 12 months (primary); CDR-SB, ADAS-Cog14, amyloid PET; 18 months	12-month primary endpoint not met; consistent amyloid reduction and trends supporting phase 3
Ostrowitzki S et al. (2022) [28]	Two double-blind phase 3 RCTs n = 813 and 806	Prodromal to mild AD, amyloid-confirmed	Crenezumab 60 mg/kg IV every 4 weeks vs placebo	CDR-SB (primary), ADAS-Cog, MMSE, ADCS-ADL; planned 105 weeks	Stopped early after interim analysis; no reduction in clinical decline or change in disease biomarkers; well tolerated
Budd Haeberlein S et al. (2022) [29]	Two double-blind phase 3 RCTs n = 1,638 and 1,647	MCI due to AD or mild AD dementia, amyloid-positive	Aducanumab low or high dose IV every 4 weeks (76 weeks) vs placebo	CDR-SB (primary), MMSE, ADAS-Cog13, ADCS-ADL-MCI; 78 weeks	EMERGE high dose: CDR-SB difference -0.39 (22% slowing, p = .012); ENGAGE: +0.03 (p = .833)
Wessels AM et al. (2020) [30]	Two double-blind RCTs (phase 2/3; phase 3) n = 2,218 and 1,722	Early AD (MCI due to AD) and mild AD dementia	Lanabecestat 20 mg or 50 mg/day vs placebo	Cognitive and functional scales, MRI biomarkers; 104 weeks (AMARANTH), 78 weeks (DAYBREAK-ALZ)	Both stopped early for futility; no slowing of cognitive or functional decline; well tolerated; greater hippocampal volume loss in AMARANTH
Teng E et al. (2022) [31]	Double-blind phase 2 RCT n = 457	Prodromal to mild AD (MMSE 20-30), amyloid-positive	Semorinemab 1,500, 4,500 or 8,100 mg IV vs placebo	CDR-SB (primary), tau PET, safety; 73 weeks	Similar CDR-SB increase across all arms (2.36-2.41 vs 2.19 with placebo); no slowing of tau accumulation; acceptable safety
Craft S et	Double-blind phase 2/3 RCT n	Amnestic MCI	Intranasal insulin 40	Cognition, function	No cognitive or functional benefit in

al. (2020) [32]	= 289 randomized (240 in primary ITT)	or AD dementia (age 55-85)	IU/day vs placebo (12 months + 6-month open-label)	(ADCS-ADL-MCI), CDR-SB, CSF/MRI biomarkers; 12 months	primary analyses; mid-trial device change complicated interpretation
Macfarlane S et al. (2025) [33]	Double-blind phase 2b/3 RCT n = 508 randomized (338 vs 170); ITT n = 462	Early AD (MCI or mild dementia)	Blarcamesine 30 mg or 50 mg orally daily vs placebo	ADAS-Cog13 and ADCS-ADL (co-primary), CDR-SB; 48 weeks	Authors reported slowed clinical progression in the ITT population; 73.2% completed; serious adverse events 16.7% vs 10.1%
Cummings JL et al. (2026) [34]	Two double-blind phase 3 RCTs n = 3,808 (1,855 and 1,953)	MCI or mild dementia due to AD, amyloid-confirmed	Oral semaglutide up to 14 mg daily (up to 156 weeks) vs placebo	CDR-SB at week 104 (primary); biomarkers, safety	No benefit: CDR-SB difference -0.08 (95% CI -0.35 to 0.20) in evoke and 0.10 (-0.17 to 0.38) in evoke+; adverse events 91.2% vs 84.8%
Soininen H et al. (2021) [35]	Double-blind RCT n = 311 (162 completed 36 months)	Prodromal AD (IWG-1 criteria)	Fortasyn Connect multinutrient drink daily vs isocaloric placebo drink	NTB 5-item composite (primary), CDR-SB, brain/hippocampal atrophy; 36 months	Less decline in cognition and function and slower brain atrophy at 36 months; primary NTB not met at 24 months; heavy attrition and censoring
Hoffmann K et al. (2016) [36]	Single-blind multicenter RCT n = 200	Mild AD dementia, community-dwelling	Supervised moderate-to-high-intensity aerobic exercise (60 min, 3x/week) vs usual care	SDMT, neuropsychiatric symptoms, ADL; 16 weeks	Exercise reduced neuropsychiatric symptoms; SDMT improved (mean difference 4.2, 95% CI 0.5 to 7.9) only in protocol-adherent participants

TABLE 4: Overview of the 16 included publications

AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCOMS: Alzheimer's Disease Composite Score; ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living; ADL: activities of daily living; ARIA-E: amyloid-related imaging abnormalities with edema or effusion; CDR-SB: Clinical Dementia Rating Sum of Boxes; CI: confidence interval; ITT: intention to treat; IV: intravenous; IWG: International Working Group; iADRS: integrated Alzheimer's Disease Rating Scale; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; NTB: Neuropsychological Test Battery; PET: positron emission tomography; RCT: randomized controlled trial; SC: subcutaneous; SDMT: Symbol Digit Modalities Test.

To provide an overview of the therapeutic approaches evaluated in the included trials, the interventions and their principal findings are summarized in Table 5.

Intervention category	Interventions represented in the review	Overall findings	Key considerations
Anti-amyloid therapies [8-11,26-29]	Lecanemab, donanemab, gantenerumab, solanezumab, crenezumab, and aducanumab	Findings were mixed. Some trials reported benefits on clinical measures of cognitive and functional decline, whereas others did not demonstrate significant benefit on their primary clinical outcomes.	Results varied across agents and trials. Amyloid-related imaging abnormalities and other treatment-related adverse events are important safety considerations.
BACE inhibitors [12,30]	Verubecestat and lanabecestat	Trials did not establish a meaningful clinical benefit in early or prodromal Alzheimer's disease.	Treatment efficacy was limited, and adverse effects contributed to concerns about this therapeutic approach.
Other pharmacological approaches [31-34]	Semorinemab, intranasal insulin, blarcamesine, and oral semaglutide	Findings were variable across agents, with evidence ranging from no clear clinical benefit to potentially favorable results requiring cautious interpretation.	Differences in drug mechanisms, study populations, outcome measures and trial duration limit direct comparisons.
Nutritional intervention [35]	Fortasyn Connect (LipiDiDiet)	The nutritional intervention showed some favorable findings on selected cognitive and functional measures, although results were not consistently significant across the assessed outcomes.	Evidence is limited to a small number of trials and should be interpreted in the context of the study population and outcome measures.
Exercise-based intervention [36]	Aerobic exercise (ADEX trial)	Exercise-based intervention evidence was limited, with no consistent evidence of a significant benefit on the primary cognitive outcome.	The limited number of eligible trials prevents firm conclusions about the effectiveness of exercise in early Alzheimer's disease.
Anti-tau therapy [31]	Semorinemab	No significant clinical benefit was established.	Evidence is currently limited to the included trial.

TABLE 5: Summary of intervention categories and main findings in included randomized controlled trials

AD: Alzheimer's disease; BACE: beta-site amyloid precursor protein-cleaving enzyme; RCT: randomized controlled trial.

Overall, the included evidence was predominantly focused on pharmacological interventions, particularly anti-amyloid therapies. Evidence for nutritional and exercise-based interventions was comparatively limited, restricting conclusions regarding their effectiveness in early AD.

Risk of Bias

The risk of bias was independently assessed by two reviewers using the RoB 2 tool in five domains. Across the 16 assessed publications, four were classified as having an overall low risk of bias, nine as having some concerns, and three as having a high risk of bias. Although several included trials were large, multi-center phase 3 RCTs, trial size and phase alone do not determine risk of bias. RoB 2 assessments considered all five methodological domains. Some concerns arose from potential unblinding, missing outcome data, or outcome measurement limitations, while high-risk judgments mainly reflected substantial attrition or selective reporting. Thus, classifications were based on methodological limitations rather than trial size or phase. These counts refer to publications rather than the total number of individual randomized trials reported within them. Most included trials reported adequate randomization procedures; however, the randomization domain was assessed separately for each trial result using the RoB 2 criteria. The most common reasons for having concerns include missing outcome data (early stopping for futility in the BACE inhibitor and crenezumab trials, high attrition, or exclusions from the analysis population), potential unblinding due to ARIA or adverse effects in the antibody studies, and the selection of a particular finding when the primary objectives were not achieved. Detailed evaluations for each study are summarized in Table *6*.

Study	Randomization process	Deviations from interventions	Missing outcome data	Measurement of outcome	Selection of reported result	Overall risk of bias	Rationale

Van Dyck et al. (2023) [8]	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns	Although randomization and outcome data handling were adequate, potential functional unblinding related to treatment-associated adverse events, including ARIA, may have influenced outcome assessment.
Sims et al. (2023) [9]	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns	Randomization and missing data management were adequate; however, potential functional unblinding due to treatment-related adverse events may have affected outcome measurement.
Bateman et al. (2023) [10]	Low risk	Low risk	Some concerns	Some concerns	Low risk	Some concerns	Incomplete information and early termination-related limitations raised concerns regarding missing outcome data and outcome measurement.
Honig et al. (2018) [11]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	The study reported adequate randomization, intervention procedures, outcome data, and prespecified outcome assessment.
Egan et al. (2019) [12]	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns	Early termination and incomplete follow-up information raised concerns regarding the completeness of outcome data.
Mintun et al. (2021) [26]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	The study demonstrated adequate methodological procedures and outcome reporting.
Swanson et al. (2021) [27]	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns	Some concerns remained regarding the selection and reporting of outcome results; this requires confirmation against the prespecified analysis plan.
Ostrowitzki et al. (2022) [28]	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns	Early discontinuation and incomplete follow-up information raised concerns regarding missing outcome data.
Budd Haeberlein et al. (2022) [29]	Low risk	Some concerns	Low risk	Low risk	High risk	High risk	Differences in findings between the EMERGE and ENGAGE trials and concerns about outcome reporting raised concerns regarding selective reporting.
Wessels et al. (2020) [30]	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns	Early termination and limited follow-up information raised concerns regarding missing outcome data.
Teng et al. (2022) [31]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	The study demonstrated adequate randomization, intervention procedures, outcome measurement, and reporting.
Craft et al. (2020) [32]	Low risk	Some concerns	Some concerns	Low risk	Some concerns	Some concerns	Changes in the intervention device and incomplete information regarding follow-up and outcome reporting raised some concerns.
Macfarlane et al. (2025) [33]	Low risk	Low risk	High risk	Low risk	Some concerns	High risk	Substantial attrition and incomplete outcome data raised serious concerns regarding missing data and the reliability of the reported results.
Cummings et al. (2026) [34]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	The study demonstrated adequate methodological procedures and outcome reporting.
Soininen et al. (2021) [35]	Low risk	Low risk	High risk	Low risk	Some concerns	High risk	Attrition and censoring raised concerns regarding missing outcome data and the potential influence on the reported findings.
Hoffmann et al. (2016) [36]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns	The single-blind design may have allowed deviations from the intended intervention, resulting in some concerns in this domain.

TABLE 6: Risk-of-bias assessment of included randomized controlled trials using the Cochrane RoB 2 tool

ARIA: amyloid-related imaging abnormalities; RoB 2: risk of bias 2.

Influence of Risk of Bias on the Interpretation of Findings

The risk-of-bias assessments were considered when interpreting the treatment effects reported across the included RCTs. Findings from studies with a low risk of bias were given greater confidence, whereas results from studies with some concerns or a high risk of bias were interpreted cautiously. Potential methodological limitations, including concerns related to the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting, may have influenced the reliability of the reported treatment effects. Therefore, statistically significant findings were not considered sufficient on their own to establish treatment effectiveness. The consistency of findings across studies, the magnitude of reported effects, and the methodological quality of the supporting evidence were also considered. Consequently, conclusions regarding interventions supported by studies with methodological concerns were framed cautiously.

Effects of Interventions

The included studies evaluated heterogeneous interventions, outcomes, and follow-up periods; therefore, quantitative meta-analysis was not performed. The findings are presented narratively according to intervention category.

Overall Interpretation of Intervention Effects

Among the intervention categories evaluated, anti-amyloid monoclonal antibodies demonstrated the most consistent evidence of slowing clinical decline, particularly with lecanemab and donanemab. However, the magnitude of the observed benefits was modest, and treatment-related safety concerns, particularly ARIA, remain important considerations. Other intervention classes, including BACE inhibitors and anti-tau therapies, did not demonstrate consistent clinical benefits. Findings from metabolic, nutritional, and exercise-based interventions were variable and required cautious interpretation. The following sections discuss the overall findings within each intervention class and the differences observed among individual therapeutic agents.

Anti-amyloid Therapies

Among the anti-amyloid monoclonal antibodies, lecanemab demonstrated a statistically significant reduction in clinical decline compared with placebo in the phase 3 CLARITY AD trial. At 18 months, the between-group difference in CDR-SB change was −0.45 points (95% CI, −0.67 to −0.23; $p < 0.001$), corresponding to a reported 27% reduction in clinical decline. However, the absolute treatment effect was modest and indicated slower clinical deterioration rather than improvement in cognitive function. The earlier phase 2b study did not meet its 12-month primary endpoint, although favorable findings were reported in some secondary analyses [8,27].

Safety Outcomes of Anti-amyloid Therapies

Safety outcomes were examined separately for lecanemab and donanemab to compare the incidence of adverse events between treatment and placebo groups. The assessment included overall adverse events, serious adverse events, ARIA-E, ARIA-H, treatment discontinuations due to adverse events, and deaths. Event counts and percentages were considered using the reported safety population denominators for each trial. The comparative findings are presented in Table 7.

Trial/intervention	Any adverse events	Serious adverse events	ARIA-E	ARIA-H	Discontinuation due to adverse events	Deaths
Lecanemab [8]	88.9% vs 81.9%	14.0% vs 11.3%	12.6% vs 1.7%	17.3% vs 9.0%	6.9% vs 2.9%	0.7% vs 0.8%
Donanemab [9]	89.0% vs 82.2%	17.4% vs 15.8%	24.0% vs 1.9%	31.4% vs 13.6%*	13.1% vs 4.3%	1.9% vs 1.1%

TABLE 7: Safety outcomes of lecanemab and donanemab compared with placebo

ARIA-E: amyloid-related imaging abnormalities with edema or effusion; ARIA-H: amyloid-related imaging abnormalities with hemosiderin deposition.

The safety findings showed higher incidences of adverse events, serious adverse events, ARIA-E, ARIA-H, and treatment discontinuations in the anti-amyloid treatment groups compared with placebo. ARIA-E occurred in 12.6% of participants receiving lecanemab and 24.0% receiving donanemab, compared with 1.7% and 1.9% in their respective placebo groups. Similarly, ARIA-H occurred in 17.3% and 31.4% of the respective treatment groups. Serious adverse events and treatment discontinuations were also more frequent with both interventions. However, deaths were relatively uncommon in both treatment and placebo groups. These findings highlight the importance of considering treatment-related safety risks alongside the reported clinical benefits.

Donanemab also demonstrated statistically significant benefits in the phase 3 TRAILBLAZER-ALZ 2 trial. At 76 weeks, the between-group differences in iADRS change were 3.25 points (95% CI, 1.88 to 4.62; $p < 0.001$) in participants with low or medium tau pathology and 2.92 points (95% CI, 1.51 to 4.33; $p < 0.001$) in the combined population. Corresponding differences in CDR-SB change were −0.67 and −0.70 points, respectively (both $p < 0.001$). Although these findings indicated statistically significant slowing of clinical decline, the absolute differences were relatively modest. The earlier phase 2 trial also reported a favorable iADRS result, although its secondary clinical findings were mixed [9,26].

Aducanumab showed inconsistent findings across its two phase 3 trials: EMERGE demonstrated a statistically significant benefit on CDR-SB, whereas ENGAGE did not [29]. Similarly, gantenerumab reduced amyloid plaque burden but did not significantly slow clinical decline in either GRADUATE trial [10]. Crenezumab and solanezumab also failed to demonstrate significant benefits on their respective primary clinical outcomes [11,28]. The principal findings of the individual anti-amyloid trials are summarized in Table *4*.

BACE Inhibitors

Neither verubecestat nor lanabecestat demonstrated clinical benefit in early AD. In the verubecestat APECS trial, the higher dose was associated with significantly greater CDR-SB worsening compared with placebo, suggesting a possible worsening of clinical outcomes [12]. Similarly, the AMARANTH and DAYBREAK-ALZ trials of lanabecestat were discontinued early because of futility, with no consistent evidence of slowing cognitive or functional decline [30]. The findings are summarized in Table *4*.

Anti-tau Therapies

Semorinemab, an anti-tau monoclonal antibody, did not demonstrate a significant clinical benefit in patients with prodromal to mild AD. CDR-SB worsening was similar across the treatment and placebo groups, indicating no meaningful reduction in clinical decline. Although the intervention demonstrated an acceptable safety and tolerability profile, its efficacy in slowing disease progression was not established [31].

Metabolic and Other Pharmacological Interventions

Oral semaglutide did not demonstrate a significant effect on clinical progression in either of the two phase 3 evoke trials, with no significant between-group differences in CDR-SB change at week 104 [34]. Intranasal insulin also failed to demonstrate significant cognitive or functional benefits in the primary intention-to-treat analysis of the SNIFF study. Interpretation of this trial was complicated by a change in the delivery device during the study [32].

In contrast, the phase 2b/3 study of blarcamesine reported statistically significant differences in selected cognitive outcomes, including ADAS-Cog13 and CDR-SB. However, the functional co-primary outcome, ADCS-ADL, did not demonstrate a statistically significant between-group difference. These findings should be interpreted cautiously in view of participant attrition and the higher incidence of serious adverse events

in the treatment group [33]. Further details of these interventions are presented in Table 4.

Nutritional Interventions

The LipiDiDiet trial evaluated Fortasyn Connect, a multinutrient formulation, in patients with prodromal AD. At 36 months, the intervention demonstrated a significant difference in the five-item NTB composite score compared with placebo (between-group difference, 0.212; 95% CI, 0.044 to 0.380; p = 0.014), corresponding to a reported 60% reduction in cognitive decline. A reduction in CDR-SB decline was also reported (p = 0.014). However, the primary NTB composite outcome was not significantly different at the 24-month assessment. Furthermore, only 162 of the 311 randomized participants completed the 36-month study, and the limited number with eligible 36-month efficacy data should be considered when interpreting these findings [35].

Exercise

The ADEX trial investigated supervised moderate-to-high-intensity aerobic exercise in patients with mild AD dementia. In the intention-to-treat analysis, no significant differences were observed between the intervention and control groups in the primary cognitive outcome, SDMT, or in activities of daily living. However, the intervention was associated with a significant reduction in neuropsychiatric symptoms (mean difference, −3.5; 95% CI, −5.8 to −1.3; p = 0.002). An improvement in SDMT performance was observed only among participants who adhered to the exercise program (mean difference, 4.2; 95% CI, 0.5 to 7.9; p = 0.028), suggesting a possible association between adherence and cognitive outcomes [36].

The interpretation of treatment effects should consider both their absolute magnitude and relative effects, wherever reported, rather than relying solely on statistical significance. Although some interventions demonstrated statistically significant differences compared with placebo, the magnitude of these differences should also be considered in relation to their potential clinical relevance. In particular, statistically significant slowing of cognitive or functional decline does not necessarily indicate a substantial improvement in patients' daily functioning. Therefore, treatment effects should be interpreted in the context of the outcome measure used, disease stage, duration of follow-up, and established clinical meaningfulness thresholds, where available.

Discussion

Anti-amyloid Monoclonal Antibodies: Class Effect, Individual Agents, and Clinical Meaningfulness

The findings of this review indicate that anti-amyloid monoclonal antibodies demonstrated the most consistent evidence of slowing clinical decline among the therapeutic approaches evaluated in early AD. However, the observed benefits varied across individual agents. Lecanemab and donanemab demonstrated statistically significant reductions in clinical decline compared with placebo, whereas gantenerumab, crenezumab, and solanezumab did not establish significant benefits on their primary clinical outcomes. Aducanumab also demonstrated inconsistent findings across its two phase 3 trials [8-11,26-29]. These findings indicate that the clinical effects of anti-amyloid therapies should be interpreted at the individual agent level rather than assuming a uniform class effect.

Although lecanemab and donanemab demonstrated statistically significant treatment effects, the absolute differences in clinical outcome scores were relatively modest. Their benefits primarily involved slowing clinical deterioration rather than reversing existing cognitive or functional impairment. Therefore, statistical significance should not automatically be interpreted as evidence of a substantial or clearly perceptible improvement in everyday functioning. Furthermore, thresholds established for clinically meaningful change in individual patients should not be directly equated with between-group mean differences reported in clinical trials. The practical significance of these treatment effects for patients and caregivers consequently requires careful consideration.

The contrasting findings among individual anti-amyloid agents also suggest that reducing amyloid plaque burden does not consistently translate into clinical benefit. Differences in treatment characteristics, degree of amyloid removal, disease stage, baseline tau pathology, and trial design may partly explain the variation in outcomes. Moreover, AD involves multiple pathological processes, including tau accumulation, neuroinflammation, synaptic dysfunction, and neuronal loss, which may continue despite amyloid reduction. Consequently, amyloid removal alone may not be sufficient to reverse established neuronal damage or produce substantial improvements in cognitive function.

Safety Considerations: ARIA Risk and Treatment-Related Adverse Events

ARIA represents an important safety concern associated with anti-amyloid monoclonal antibody treatment. The findings of this review indicate that both lecanemab and donanemab were associated with higher incidences of ARIA-E and ARIA-H compared with placebo. The incidence of these abnormalities varied between individual agents, with donanemab showing higher reported rates in its respective phase 3 trial.

Other treatment-related adverse events, including infusion-related reactions and treatment discontinuations, also contributed to the overall safety burden [8,9].

These findings highlight the importance of evaluating anti-amyloid therapies through a benefit-risk approach rather than considering clinical efficacy alone. Patient selection, assessment of relevant risk factors, APOE ε4 status where appropriate, and baseline and follow-up MRI monitoring are important considerations. Patients and caregivers should also be informed about the potential benefits, treatment-related risks, and monitoring requirements before initiating therapy [13,14].

Other Pharmacological Classes

Evidence from alternative pharmacological approaches was generally less consistent than that observed with selected anti-amyloid monoclonal antibodies. BACE inhibitors and anti-tau therapies have not established significant clinical benefits, while metabolic interventions have produced variable findings across individual agents. Although blarcamesine demonstrated favorable results on selected cognitive outcomes, the absence of a significant benefit on its functional co-primary outcome and concerns regarding participant attrition limit the certainty of these findings [12,30-34]. Overall, these findings suggest that alternative therapeutic mechanisms remain important areas of investigation, but their clinical effectiveness in early AD requires further confirmation through adequately powered RCTs.

Non-pharmacologic Treatments

The exercise intervention included in this review demonstrated a reduction in neuropsychiatric symptoms, although no significant cognitive benefit was observed in the overall intention-to-treat analysis. Improvement in cognitive performance was reported among participants with higher exercise adherence, suggesting that sustained participation may influence intervention outcomes [36].

Nutritional interventions also demonstrated potentially favorable findings on selected cognitive and functional outcomes. However, substantial participant attrition and inconsistencies across assessment time points limit the certainty of these findings [35]. Exercise and nutritional approaches may therefore be considered supportive components of broader patient care, but their independent effects on disease progression remain uncertain.

Furthermore, combining physical exercise and nutritional interventions may represent a potential multidomain approach to supporting cognitive and functional outcomes in early AD. However, no eligible multidomain lifestyle RCT was identified in this review. Therefore, the effectiveness of comprehensive lifestyle-based programs cannot be established from the available evidence.

General Considerations

Overall, the findings indicate that the evidence for slowing clinical progression in early AD varies across therapeutic approaches. Selected anti-amyloid monoclonal antibodies have demonstrated modest slowing of clinical decline, although their benefits must be considered alongside treatment-related safety risks. Other pharmacological and non-pharmacological interventions have not yet established sufficiently consistent evidence to support firm conclusions regarding their effects on disease progression. These findings highlight the need to distinguish promising treatment effects from established clinical benefits and to interpret the available evidence in the context of its methodological limitations.

Clinical Implications

The findings have important implications for treatment decisions in early AD. Anti-amyloid monoclonal antibody treatment may be considered for appropriately selected patients with confirmed amyloid pathology and eligible early-stage disease, in accordance with applicable treatment guidance. However, treatment decisions should account for the expected magnitude of clinical benefit, individual risk factors, and the possibility of treatment-related adverse events, particularly ARIA. Assessment of APOE ε4 status, where appropriate, and baseline and follow-up MRI monitoring may assist in evaluating and managing treatment-related risks [13,14].

APOE ε4 status is particularly relevant when considering anti-amyloid monoclonal antibody treatment because carriers have an increased risk of developing ARIA. However, APOE genotyping was not uniformly applied or reported across all included trials. Therefore, the findings of this review do not establish a consistent approach to genetic risk assessment across all treatment settings.

For other pharmacological interventions evaluated in this review, the available randomized evidence remains insufficient to establish their routine use as disease-modifying treatments in early AD. Exercise and nutritional interventions may be considered supportive components of broader patient care, although their effects on disease progression remain uncertain. Clinicians should communicate that the demonstrated

benefits of selected anti-amyloid treatments primarily involve slowing clinical decline rather than reversing existing impairment. Shared decision-making with patients and caregivers is therefore essential to establish realistic expectations regarding treatment benefits, risks, and monitoring requirements.

Strengths and Limitations

Among the strengths of this review are its focus on RCT evidence, a defined publication period covering major developments in early AD treatment, independent study selection and risk-of-bias assessment, and consideration of both pharmacological and non-pharmacological interventions. The inclusion of clinical, functional, biomarker, and safety outcomes also provides a broader perspective on the effects of the evaluated therapeutic approaches.

However, several limitations should be acknowledged. Considerable heterogeneity in interventions, participant characteristics, diagnostic criteria, outcome measures, and follow-up durations prevented quantitative meta-analysis and limited direct comparisons across studies. Differences in biomarker confirmation and baseline disease severity may also have contributed to variation in treatment effects. Although narrative synthesis was appropriate given this clinical and methodological heterogeneity, the absence of quantitative synthesis remains a limitation. In particular, a separate meta-analysis of anti-amyloid monoclonal antibodies was not conducted, despite this being the largest intervention category. Differences in individual antibodies, treatment regimens, participant characteristics, outcome measures, and assessment time points limited the comparability of treatment-effect estimates required for reliable pooling. Consequently, pooled treatment effects and statistical measures of between-study heterogeneity could not be estimated. Future systematic reviews with sufficiently comparable trial data may consider class-specific quantitative synthesis to provide more precise estimates of treatment effects.

Furthermore, restricting eligibility to English-language, peer-reviewed, full-text RCTs with at least 100 randomized participants may have introduced language and publication bias and excluded smaller pilot studies. Trial registries and gray literature were not searched separately, which may have limited the identification of ongoing, unpublished, or recently completed trials. Although reference lists of included studies and relevant systematic reviews were examined manually, the possibility of missing eligible evidence cannot be excluded.

The evidence base was also unevenly distributed across therapeutic categories, with a greater representation of pharmacological interventions than non-pharmacological approaches. In particular, the absence of eligible multidomain lifestyle and cognitive-training trials restricted the assessment of comprehensive non-pharmacological strategies in early AD. The limited number of adequately powered trials investigating exercise and nutritional interventions further reduces the certainty of conclusions regarding their clinical effectiveness. Therefore, the findings should not be interpreted as a comprehensive assessment of all potential therapeutic approaches.

Finally, most included trials were industry-sponsored and involved predominantly Caucasian participants from high-income countries, potentially limiting the generalizability of the findings to more diverse populations. Several publications reported findings from multiple trials or follow-up assessments, requiring careful consideration of the corresponding trial populations and reporting periods. The search was restricted to publications available up to September 30, 2026; therefore, evidence published after this date was not considered. Missing outcome data, early trial termination, and participant attrition in some included trials may also have influenced the reliability and precision of the reported treatment effects. Early termination may have limited the availability of long-term outcome data, while incomplete follow-up could have introduced attrition bias, particularly where withdrawal patterns differed between treatment groups. Although these factors were considered when interpreting the findings and evaluating risk of bias, their potential influence should be acknowledged when drawing conclusions about treatment effectiveness.

Additionally, an independent statistical review of the feasibility of class-specific quantitative synthesis and the completeness and consistency of effect size extraction was not undertaken. Although the statistical findings were interpreted using information reported in the original trial publications, independent statistical scrutiny could have provided further assessment of treatment-effect comparability, heterogeneity, missing data, early trial termination, and participant attrition. This should be considered when interpreting the methodological robustness of the present review. In addition, findings from studies with relatively small sample sizes or high risk of bias should be interpreted cautiously, as these methodological limitations may affect the reliability of the reported treatment effects.

Directions for Future Research

Future RCTs should use standardized diagnostic criteria, biomarker assessments, and clinically relevant outcome measures to improve comparability across studies. Consistent assessment of cognitive, global, and functional outcomes using validated instruments, such as the CDR-SB, iADRS, ADAS-Cog, and ADCS-ADL, may help clarify the clinical significance of treatment effects. Longer follow-up periods are also needed to establish the durability of treatment benefits and identify potential long-term safety concerns. Further

research should investigate combination treatment strategies targeting multiple pathological mechanisms, including amyloid, tau, and neuroprotective pathways. In addition, larger and adequately powered trials involving diverse populations are required to clarify the potential roles of exercise, nutritional, and multidomain interventions in early AD. Improved participant retention and appropriate methods for handling missing data will also be important to strengthen the reliability of future findings.

Conclusions

This systematic review of RCTs conducted between 2015 and 2026 suggests that lecanemab and donanemab may modestly slow clinical decline in individuals with early AD. However, their potential benefits must be carefully balanced against the risks of ARIA and other adverse events, treatment burden, and the need for regular MRI monitoring. Therefore, careful patient selection and individualized risk-benefit assessment are essential before initiating treatment. On the other hand, gantenerumab, crenezumab, solanezumab, BACE1 inhibitors, semorinemab, intranasal insulin, and oral semaglutide have not provided any evidence of clinical benefits in slowing down disease progression. Blarcamesine and multinutrient therapies are still unclear due to methodological issues, whereas non-pharmacological treatments have yet to show their benefits.

Decisions about the treatment of people with early AD need to be made individually based on the characteristics of their disease, results of appropriate biomarkers if available, benefits of treatment, possible risks of adverse events, and patient preferences. More high-quality and appropriately powered RCTs are required to confirm treatment effects, evaluate safety concerns, and understand the subgroup of patients that would benefit from certain therapy. Cognitive, functional, and global assessments should be performed together with biomarkers to demonstrate actual clinical benefits.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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