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Depression in Alzheimer's Disease: Diagnostic Challenges, Risk Factors, and Evidence-Based Interventions

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ABSTRACT

Background: Depression is a common and clinically significant symptom in Alzheimer's Disease (AD), but assessment and management are complicated by cognitive decline and heterogeneity in measurement tools. To systematically evaluate the prevalence, risk factors, diagnostic challenges, symptom trajectories, and effectiveness of interventions for depression in Alzheimer's disease, highlighting evidence-based insights and methodological challenges across recent studies. Methods: A narrative review was conducted using studies published between 2021 and 2026. Relevant literature on Alzheimer's disease and depression was identified from major databases including PubMed, Scopus, Web of Science, and PsycINFO. Key search terms included Alzheimer's disease, depression, diagnosis, risk factors, and treatment. A total of 20 studies were included based on relevance and synthesized thematically to summarize the evidence. Results: Twenty studies were included, comprising observational cohorts, randomized controlled trials, and psychometric investigations on depression in Alzheimer's disease. Previous depression history was associated with depressive symptoms, although findings varied across populations. Longitudinal studies suggested that persistent depressive symptoms may be linked to cognitive decline and AD progression. Pharmacological treatments showed limited effects, while psychosocial, caregiver-supported, and neuromodulation approaches showed potential benefits in selected studies. Heterogeneity in assessment methods, populations, and outcomes limited direct comparisons. Conclusions: Pharmacological treatments for depression in Alzheimer's disease showed mixed effects, while non-pharmacological approaches may provide potential benefits in selected studies. Depression remains underrecognized in AD, highlighting the need for improved assessment strategies and individualized interventions to support clinical management and patient care.

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KEYWORDS
Alzheimer's Disease; Depression; Diagnostic Challenges; Risk Factors; Interventions

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia, characterized clinically by gradual deterioration in memory, cognition, executive function, and the ability to perform daily activities [1]. As the disease progresses, individuals with AD frequently develop neuropsychiatric symptoms in addition to cognitive impairment, including apathy, anxiety, agitation, sleep disturbance, and depression [2,3]. These symptoms contribute substantially to functional dependency, institutional care needs, caregiver burden, and reduced quality of life. Among them, depression is particularly important because it may occur across different stages of the AD continuum and can complicate clinical assessment by overlapping with cognitive and behavioral manifestations of dementia [4]. Therefore, accurate recognition of depressive symptoms in individuals with AD is essential for appropriate diagnostic evaluation, clinical monitoring, and individualized management.

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Depression is the most clinically significant neuropsychiatric manifestation associated with AD. Depressive symptoms have been associated with poorer quality of life, greater functional limitations, and more complex clinical management, while neuropsychiatric symptom burden can increase distress and care demands among family caregivers [5,6]. Depression may reduce motivation, social engagement, and participation in daily activities, thereby compounding disability caused by cognitive impairment. Identifying depressive symptoms is therefore important for patient-centered care and appropriate clinical decision-making.

Despite its clinical importance, depression remains difficult to identify accurately in AD. Depressive features such as apathy, loss of interest, reduced initiative, psychomotor slowing, sleep or appetite changes, and social withdrawal overlap with cognitive and behavioral manifestations of dementia [7,8]. Progressive cognitive impairment may also affect patients' ability to recall or communicate affective symptoms, increasing reliance on caregiver observations and clinical judgement. The Cornell Scale for Depression in Dementia (CSDD), Geriatric Depression Scale (GDS), and depression-related items of the Neuropsychiatric Inventory (NPI) are commonly used; however, their performance may vary according to cut-off values, disease severity, care setting, and source of reporting. A recent diagnostic accuracy review found that the CSDD had the strongest evidence for depression case finding in people living with dementia, although diagnostic uncertainty remains [9–11]. Such limitations may contribute to under-recognition, misclassification, and inconsistency across AD studies.

Understanding factors associated with depression may improve diagnostic monitoring across the AD continuum. Evidence from dementia-focused cohorts indicates that previous depression is an important clinical factor associated with depressive symptoms in individuals with AD [12]. Depression can also emerge after AD diagnosis: a Swedish national cohort reported a greater than two-fold subsequent risk of major depression among people with AD without prior depression compared with matched controls, with the greatest risk in the first year after diagnosis [13, 14]. Longitudinal evidence in mild cognitive impairment (MCI) also suggests that persistently elevated depressive symptom trajectories are associated with later progression to AD dementia [15]. These findings support longitudinal assessment but do not establish causality.

Accurate recognition of depression is also important for evaluating treatment outcomes. Recent trials have reported mixed findings: vortioxetine did not significantly improve depressive symptoms compared with placebo in AD with depression, and adapted problem adaptation therapy did not improve the primary depression outcome at six months [16,17]. By contrast, a small caregiver-inclusive cognitive behavioral intervention reported encouraging improvement in clinician-rated depression at longer follow-up [18]. Differences in assessment instruments, treatment intensity, caregiver involvement, and follow-up duration may partly explain variation in outcomes.

Although recent studies have examined depression detection and management in dementia, uncertainty remains regarding diagnostic assessment, risk factors, longitudinal symptom patterns, and intervention outcomes in Alzheimer's disease (AD) across different stages of the disease continuum.

This narrative review aims to synthesize evidence published between 2021 and 2026. The primary focus is on diagnostic challenges in identifying depression in AD, including symptom overlap and limitations of assessment methods. Additional objectives include summarizing associated risk factors, depressive symptom trajectories, and evidence on pharmacological and non-pharmacological interventions.

2. Materials and Methods

This article presents a narrative synthesis of the literature on depression in Alzheimer's disease (AD) across the AD continuum. It examines three broad and interrelated domains: diagnostic challenges in identifying depressive symptoms, associated risk factors and longitudinal symptom trajectories, and pharmacological and non-pharmacological intervention outcomes. Particular attention is given to the clinical complexity of depression assessment in AD across different disease stages and care settings.

2.1 Search Strategy

The A non-systematic literature search was conducted to identify relevant studies on depression in Alzheimer's disease (AD) across the AD continuum. The aim was to capture key thematic areas, including diagnostic challenges in identifying depressive symptoms, associated risk factors, symptom trajectories, and pharmacological and non-pharmacological treatment approaches. Relevant literature was identified through searches of major biomedical databases, including PubMed/MEDLINE, Scopus, Web of Science, and PsycINFO, with supplementary articles retrieved from Google Scholar. Peer-reviewed studies published between 2021 and 2026 were considered for inclusion.

Search terms were based on key concepts related to Alzheimer's disease, depression, diagnosis, risk factors, and interventions. The search was exploratory in nature, and no formalized search protocol or reproducible search algorithm was applied.

Study selection was guided by relevance to the objectives of the review and conceptual contribution to the topic. No structured screening procedure or methodological quality assessment was undertaken. The findings were synthesized narratively to provide an integrated overview of the existing literature.

2.2 Study Selection and Eligibility

A Study selection was conducted in a narrative manner based on the relevance of the identified literature to the objectives of the review. The purpose of this process was to include studies that contributed meaningfully to understanding depression in Alzheimer's disease (AD) across diagnostic, risk factor, and intervention domains. The review focused on studies addressing diagnosis and management of depression in Alzheimer's disease to ensure alignment with the primary objective of the study.

Articles retrieved from the selected databases were screened at the title and abstract level to assess their relevance to the topic. Full-text articles were then considered for inclusion based on their conceptual alignment with the review objectives **(Table 1).**

No formal systematic screening procedure, dual independent reviewer process, or structured quality appraisal was applied, as this study follows a narrative review design. The final included literature was selected to ensure broad thematic coverage across the AD continuum.

Table 1. Overview of Included Literature in the Narrative Review.

Category	Description
Population	Alzheimer's disease or Alzheimer's disease spectrum populations
Outcome	Depression, depressive symptoms, or mood-related disturbances
Focus	Diagnosis, risk factors, disease progression, and treatment approaches
Study Types	Quantitative, qualitative, mixed-methods, and review articles
Time Period	2021–2026 peer-reviewed literature
Language	English-language publications

2.3 Data Synthesis and Analysis

The findings of the included literature were synthesized using a narrative approach. Given the heterogeneity in study design, populations, and outcome measures, a quantitative synthesis was not performed.

The results were organized into three broad thematic domains: (i) diagnostic challenges in identifying depression in Alzheimer's disease, (ii) risk factors associated with depression across the Alzheimer's disease continuum, and (iii) pharmacological and non-pharmacological intervention approaches.

This thematic organization was used to provide a coherent and integrated interpretation of the evidence while highlighting key areas of consistency and variation across studies.

3. Results

3.1 Characteristics of Included Studies

A total of 20 studies were included in this narrative review. The included literature primarily consisted of large-scale cohort and database studies from the United States, along with intervention-based clinical studies from countries including China, Korea, Spain, Sweden, the United Kingdom, and Austria.

The included studies addressed multiple aspects of depression in Alzheimer's disease, including diagnostic challenges, risk factors, and intervention approaches. **Table 2** summarizes the characteristics of the included studies and their alignment with the main objectives of the review.

Table 2. Characteristics of studies and objective mapping.

Study	Design	Sample	Focus	Key Findings	Effect Size (95% CI)	Quality
[19]	Psychometric / DIF	14,077	Measurement bias in GDS	13/15 items showed DIF across cognitive status; measurement non-invariance identified	NR	Moderate
[20]	Factor analysis	511	Depression scale structure	CSDD factor structure varies in assisted living populations	NR	Moderate
[21]	Measurement study	NR	Racial measurement bias	CSDD showed measurement invariance issues across groups	NR	Low
[22]	Observational	NR	Depression symptoms in dementia	Neuropsychiatric symptoms vary across MCI/dementia stages	NR	Moderate
[23]	Multicohort analysis	AND	Risk factors	Prior depression associated with higher depressive symptoms in AD	OR 7.78 (95% CI 4.03–15.03)	High
[24]	Longitudinal cohort	3,770	Symptom trajectories	Depression linked with longitudinal symptom persistence	HR NR	Moderate
[25]	Neuropathology cohort	1,923	Risk factors	Depression associated with neuropathological changes	NR	Moderate
[30]	PET cohort	154	Biomarkers	Depressive symptoms linked with amyloid PET changes	NR	Moderate
[26]	ADNI cohort	303	Tau PET	Depression associated with tau accumulation trajectories	NR	High
[15]	Cohort	397	Conversion risk	Depressive symptoms predict AD conversion risk	HR NR	High
[27]	Longitudinal cohort	811	Conversion risk	Depression increases dementia conversion risk	HR NR	High
[28]	Mediation analysis	2,722	Neuroimaging	Hippocampal volume mediates depression–AD association	NR	High
[29]	Registry study	129,410	Post-diagnosis depression	Higher risk of major depression after AD diagnosis	HR >2 (NR CI)	High
[30]	RCT	100	Pharmacological	Vortioxetine not superior to placebo	NR	High
[17]	RCT	336	Psychotherapy	Short-term improvement at 6 months	NR	High
[31]	RCT	41 dyads	CBT intervention	Clinician-rated improvement observed	NR	Moderate
[32]	RCT	60	Neuromodulation	TPS reduced depressive scores (BDI-II)	NR	Moderate
[33]	RCT	NR	Multicomponent therapy	Mixed results across scales (GDS/HDRS)	NR	Moderate
[34]	Retrospective	105	Stimulation therapy	Symptom reduction observed post-intervention	NR	Low
[34]	Cohort	170	Treatment outcome	PHQ-9 improvement post-treatment	NR	Low

Note: NR = Not reported; OR = Odds ratio; HR = Hazard ratio; CI = Confidence interval; DIF = Differential item functioning; AD = Alzheimer's disease; MCI = Mild cognitive impairment; GDS = Geriatric Depression Scale; CSDD = Cornell Scale for Depression in Dementia; NACC = National Alzheimer's Coordinating Center; ADNI = Alzheimer's Disease Neuroimaging Initiative; PET = Positron Emission Tomography; RCT = Randomized controlled trial; TPS = Transcranial pulse stimulation; PHQ-9 = Patient Health Questionnaire-9.

3.2 Diagnostic Challenges

Depression measurement in AD is complicated by symptom overlap (eg, psychomotor slowing, sleep/appetite disturbance, reduced initiative) and by the fact that cognitive impairment changes how individuals interpret and endorse depression items. Large-scale psychometric evidence from NACC indicates that the commonly used GDS-SF is not measurement-invariant: 13 of 15 items showed differential item functioning (DIF) by demographic and especially cognitive status (CDR level), meaning that item endorsement probabilities differ even at comparable latent depression levels [35,36]. Importantly, only two items ("hopelessness" and "worthlessness") were invariant across tested groups, reinforcing that raw total scores may not be comparable across cognitive stages in AD-continuum samples **(Figure 1).**

A second diagnostic challenge involves reliance on informant-reported neuropsychiatric symptoms. In a NACC-based analysis of participants with an AD diagnosis, informant traits (sex and spouse status) were associated with differences in informant-rated depression/dysphoria severity on the NPI-Q, even after modeling clinical and demographic factors—supporting the interpretation that "WHO reports" can influence observed depression severity. Care-setting differences also matter. A factor-analysis study in assisted living residents highlighted that the Cornell Scale for Depression in Dementia (CSDD) factor structure in assisted living may diverge from assumptions based on other contexts, implying potential construct drift and underscoring the need to use setting-validated factor solutions or

subscales [37,38].

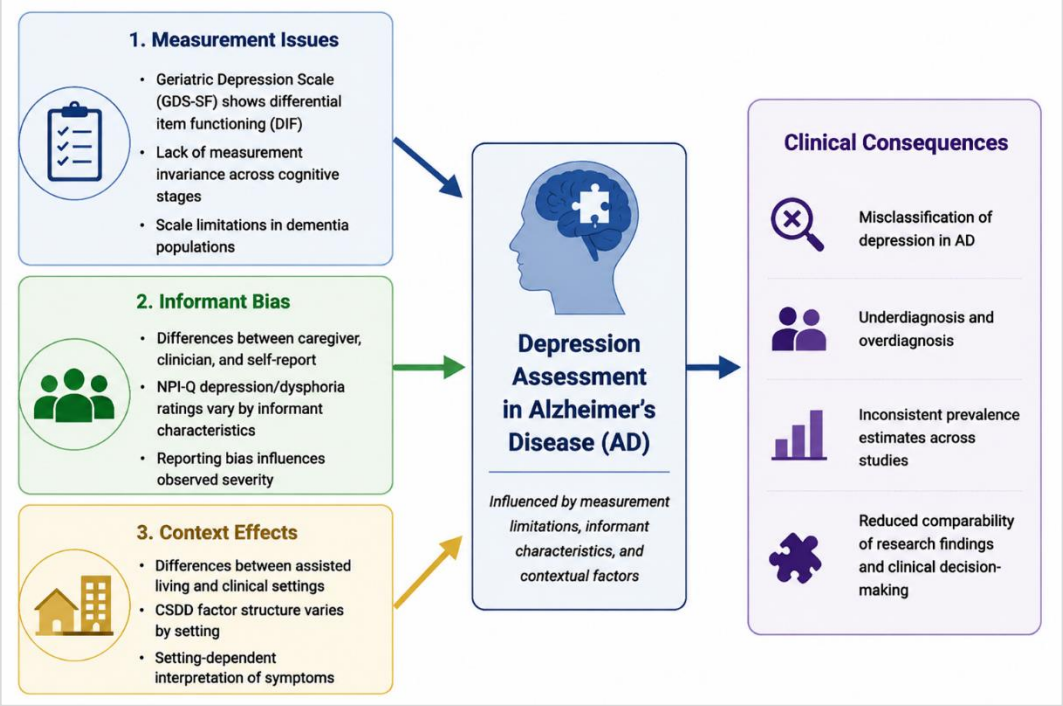


Figure 1. Conceptual framework of diagnostic challenges in depression assessment in Alzheimer's disease. Measurement issues, informant bias, and contextual variability contribute to differences in symptom interpretation and diagnostic outcomes across AD populations.

3.3 Risk Factors and Predictors

3.3.1 Clinical and Historical Predictors

In a multicohort analysis **(Figure 2),** a history of depression was identified as a significant predictor of depressive symptoms in Alzheimer's disease. Across datasets such as NACC, BDR, and ADNI, prior depression showed a consistent association with subsequent depressive symptoms (OR 7.78; 95% CI 4.03–15.03). However, this estimate was derived from a single analytical framework and should be interpreted with caution due to limited variable availability across cohorts [23,39]. Registry-based evidence further suggests an increased risk of depression following AD diagnosis. In Swedish registry

data, incident depression was higher among individuals with AD compared to controls, with an elevated adjusted hazard ratio observed in both men and women. The risk appeared highest in the first year after diagnosis and remained elevated over subsequent years [27].

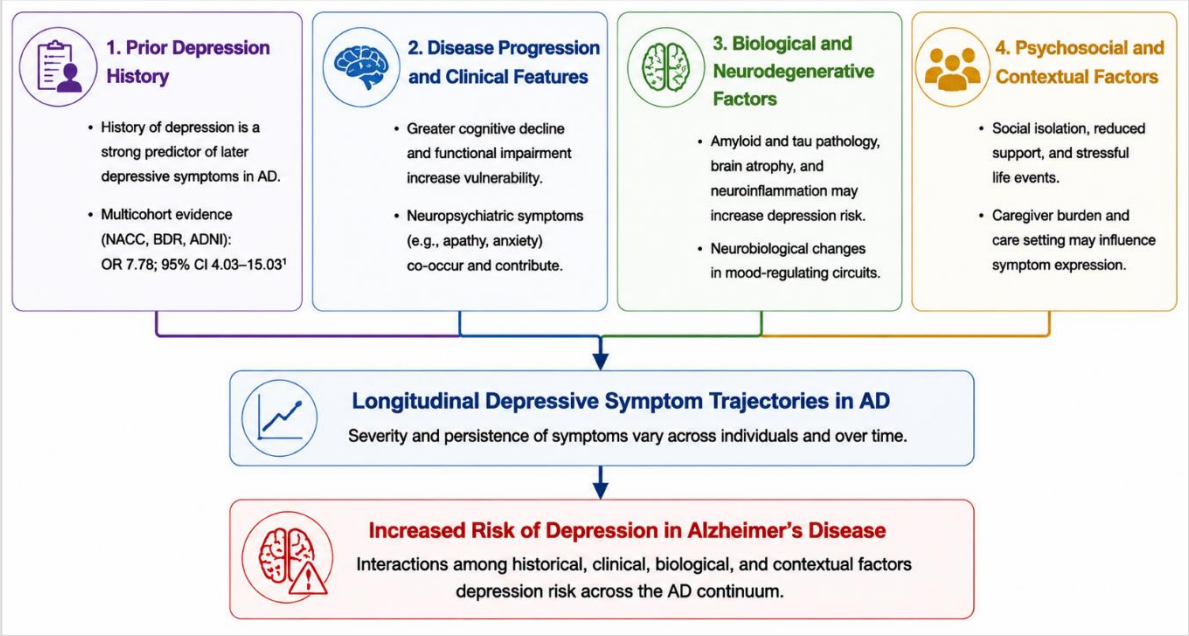


Figure 2. Conceptual framework of factors associated with depression risk in Alzheimer's disease. Clinical history, disease progression, biological vulnerability, and psychosocial factors interact to influence longitudinal depressive symptom trajectories across the AD continuum.

3.3.2 Symptom Trajectories and AD Progression

Two studies based on the highlighted how the cross-sectional snapshots of depression presence or absence can minimize the prognostic value. In Mild Cognitive Impairment (MCI) participants, consistent moderate and high depressive symptoms were observed over 36 months, and it was later converted to AD dementia, where the moderate to low trajectory was Hazard Ration (HR) of 2.36, and high vs low HR was 3.79, but a linear dosage response has a relationship of 36-month conversion hazard [15,40]. Alzheimer's Disease Neuroimaging Initiative (ADNI) analysis by [24] found three depressive symptoms trajectory clusters in the MCI, and the study assessed sex-specific analytical effects **(Table 3).** However, in men, there was a mild increase in the trajectories, and these were linked with dementia conversion risks vs persistent low symptoms. On the other hand, no significant link was found among women. These findings indicate consistency and an increase over time; it is clinically informative, and it affects gender, as inconsistency is assessed in existing studies.

Table 3. Clinical and Historical Predictors of Depression in Alzheimer's Disease Across Multiple Cohorts.

Study	Population	Trajectory Cluster	HR vs Low	Sex-specific Notes	Follow-up (months)
[15]	MCI participants	Moderate	2.36	Both sexes combined	36
[15]	MCI participants	High	3.79	Both sexes combined	36
[27]	ADNI MCI	Low	Reference	–	36
[27]	ADNI MCI	Moderate	1.5	Men slight increase, women NS	36
[27]	ADNI MCI	High	2.5	Men high linked to conversion, women NS	36

Abbreviations: MCI = Mild Cognitive Impairment; ADNI = Alzheimer's Disease Neuroimaging Initiative; HR = Hazard Ratio; NS = Not Significant.

3.3.3 Biomarker and Neuroimaging Correlates

The study by associated depressive symptoms with the pathophysiology of AD. The preclinical cohort in the US found increasing depressive symptoms with time, and these were linked with higher longitudinal accumulation of amyloid in the frontal region that increases complications of emotional control. The study by followed ADNI tau-PET, that spanned normal cognition, dementia, and MCI, and depressive symptoms are correlated with increased accumulation rates of tau, particularly in participants with positive amyloid [26,41]. The results also found that depression can lead to potentially ongoing progression of tau pathology among AD patients **(Figure 3).**

The study by was based on NACC neuroimaging analysis and was based on structural aspects. It was based on a large sample size, including 886 AD and 1836 cognitively normal participants, where AD patients were showing an increased prevalence of significant depressive symptoms. However, the mediation analysis indicates a partial mediation of the hippocampal atrophy between AD severity and depression [28].

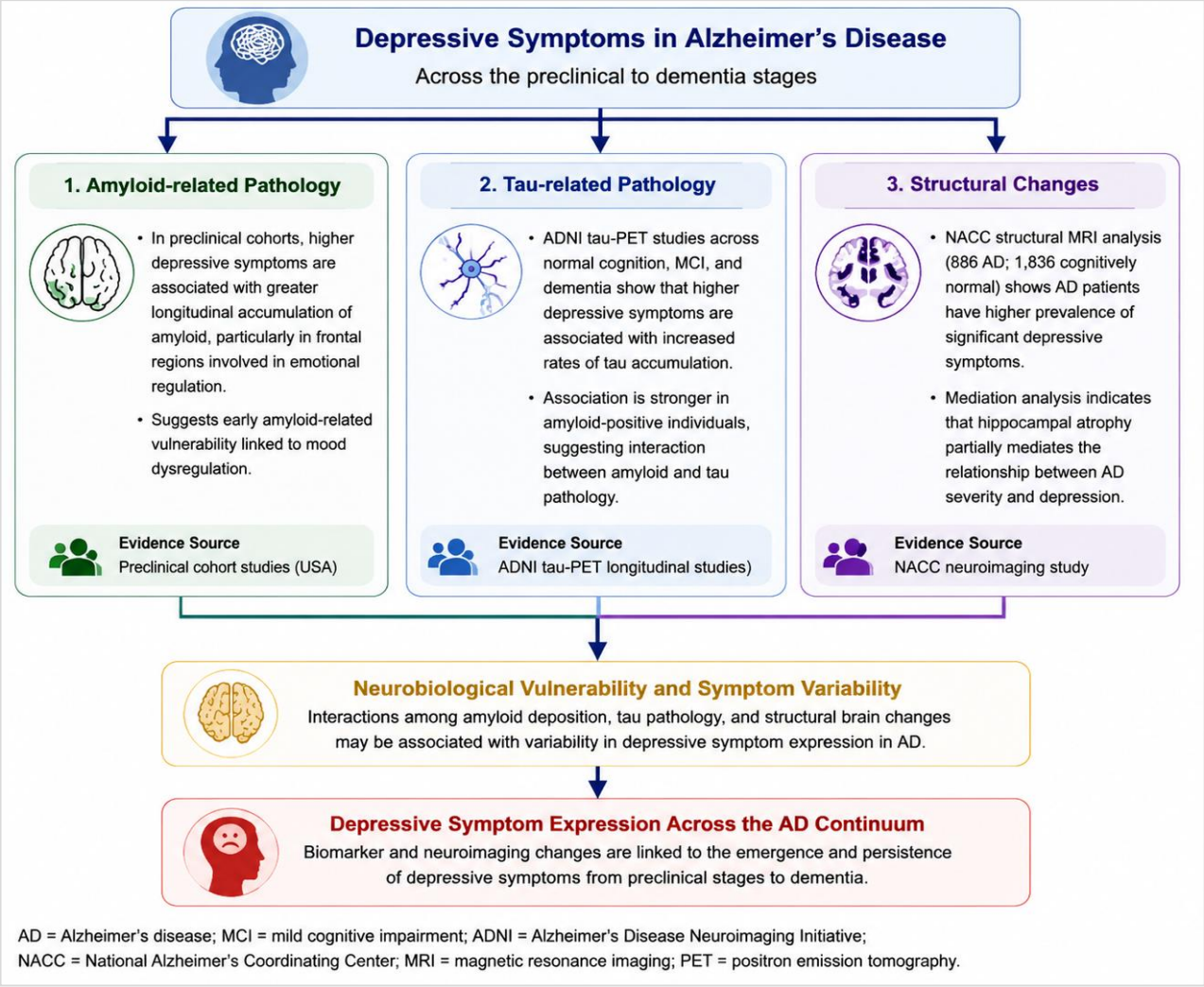


Figure 3. Conceptual framework summarizing biomarker and neuroimaging correlates of depressive symptoms in Alzheimer's disease. Amyloid pathology, tau accumulation, and structural brain changes may contribute to variability in depressive symptom expression across the AD continuum.

3.3.4 Cognitive and Functional Consequences

The burden of neuropsychiatric symptoms includes dysphoria and depression domains that can signal future cognitive decline. Furthermore, in NACC USD longitudinal modeling, an increased baseline severity of neuropsychiatric symptoms indicates an increased

decline in executive functions over four years. Moreover, a memory clinic study with biomarkers validated the diagnosis. The depression prevalence is assessed by the neuropathology aspects, where depression was most frequent in the clinically diagnosed AD and its pathology, as well as in biomarker-negative cohorts [24,42]. In this aspect, depression was common in the group with non-AD pathology contributions.

3.4 Evidence-based Interventions

The results from the existing studies about intervention studies vary regarding treatment modality, intensity of treatment, duration of follow-up, and tools for depression assessment, that lead to higher clinical and methodological heterogeneity.

3.4.1 Pharmacologic Therapy

The RCT of double-blind placebo control assessed the impact of vortioxetine among 100 AD patients with depression [30]. There were insignificant results between the depressive symptoms differences for 12 weeks with CSDD applied as a primary result, and there was no meaningful indication within functional and secondary mood outcomes [43].

3.4.2 Psychotherapeutic and Behavioral Interventions

An RCT-based study was conducted, followed by the Problem Adaptation Therapy (PATH) within dementia services, and no significant benefits were found on primary depression outcomes. However, a small benefit was observed after 3 months, and this durability was not supported until 6 months [16]. On the other hand, conducted a CBT-based program including caregiver components, indicating large clinician-rated depression improvements at 12 months, but it was a small RCT, and clinician-rated depression was assessed [44]. The study by conducted a long-duration mindfulness followed by routine activities for two years, and the study reported a significant prevention of depression onset and larger effects of active comparators and control on GDS/HDRS/NPI-Q outcomes [33]. However, the generalizability is based on the feasibility of high-frequency attrition patterns and practices. The analysis was based on participants attending almost or equal to 75% of sessions.

3.4.3 Neuromodulation and Stimulation Therapies

In a sham-controlled crossover RCT (n=60 ITT), TPS did not show a significant overall primary cognitive condition × session interaction, but subgrouping by age suggested benefit in younger participants. Importantly for this review, per-protocol analyses showed significant Beck Depression Inventory (BDI-II) reduction after verum TPS at 3 months [32].

A retrospective pseudo-stimulation inpatient study reported greater reductions on depression scales (SDS and HAMD) and improved MMSE for iTBS-rTMS versus control, with fewer "ineffective treatment" cases (5 vs 14). However, the retrospective design and allocation by treatment protocol (rather than randomization) imply substantial confounding risk [45].

3.4.4 Multi-domain Precision Medicine

A retrospective uncontrolled evaluation of a short-term ReCODE program in 170 mild–moderate AD participants reported PHQ-9 improvement from 12.64±5.86 to 8.70±5.04 (mean difference 3.96; 95% CI 3.34–4.57; $p<0.0001$), with Wilcoxon $r=0.46$ and ~80% improving **(Figure 4)**. The authors explicitly framed findings as associative/hypothesis-generating due to the uncontrolled design and selection restrictions (baseline PHQ-9≥10 and follow-up available) [34].

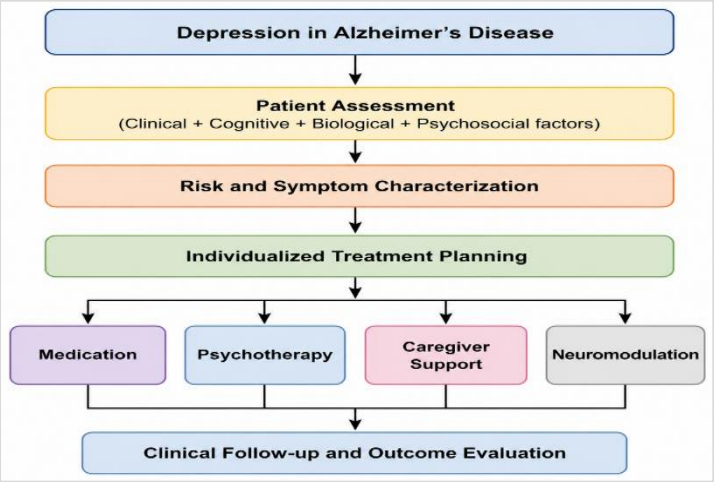


Figure 4. Conceptual framework for personalized management of depression in Alzheimer's disease. Clinical, cognitive, biological, and psychosocial factors inform individualized assessment and treatment selection, followed by outcome evaluation and ongoing clinical follow-up.

3.5 Assumptions and Limitations

This review has several limitations. The literature was identified through a non-systematic search strategy, which may introduce selection bias and limit the comprehensiveness of the evidence. The included studies also varied in design, population characteristics, and outcome measures, which reduces direct comparability across findings. In addition, heterogeneity in depression assessment methods and reliance on informant-based reporting across studies may have influenced the consistency of reported outcomes. As a result, the findings should be interpreted as a qualitative synthesis of the available evidence rather than a comprehensive or definitive evaluation of the literature.

1. Discussion

In this review, we found that depression in Alzheimer's disease (AD) represents a heterogeneous neuropsychiatric syndrome that is challenging to assess reliably. Its manifestation varies across cognitive stages, demographic groups, and neurobiological profiles, complicating both diagnosis and intervention strategies. Commonly used depression screening tools do not consistently capture the construct across populations, highlighting the limitations of current assessment methods. Moreover, variability in risk factors, symptom trajectories, and intervention outcomes underscores the need for comprehensive evidence synthesis. These findings should be interpreted as a synthesis of heterogeneous observational and interventional evidence rather than definitive conclusions.

In a large National Alzheimer's Coordinating Center (NACC) dataset, differential item functioning (DIF) analysis of the Geriatric Depression Scale–Short Form (GDS-SF) indicated measurement variability across cognitive stages, with evidence of DIF observed in a substantial proportion of items. This suggests that several questionnaire items may function differently depending on cognitive status, particularly in relation to symptoms such as hopelessness and worthlessness [19,46]. These findings highlight limitations in the use of a single cut-off score across mild cognitive impairment (MCI) and dementia stages and may partly contribute to variability in reported prevalence estimates across studies.

Evidence from risk-factor analyses further indicates a consistent association between prior history of depression and subsequent depressive symptoms in Alzheimer's disease. In a multicohort analysis, previous depression was identified as a significant correlate of higher odds of depressive symptoms; however, this variable was available in only a subset of contributing datasets [23]. Additionally, longitudinal evidence from the ADNI cohort suggests that depressive symptom trajectories persist following MCI diagnosis and may be associated with a graded increase in risk of progression to Alzheimer's dementia [15,47].

All findings suggest a shift from single-time-point assessment of depression toward a trajectory-based understanding of risk in Alzheimer's disease. Evidence from intervention studies indicates mixed and variable effects across pharmacological and non-pharmacological approaches. A double-blind randomized controlled trial reported that vortioxetine did not significantly reduce depressive symptoms compared to placebo in Alzheimer's disease. In contrast, pragmatic psychotherapy trials demonstrated modest short-term improvements in depressive symptoms measured by the Cornell Scale for Depression in Dementia at 6 months, although these effects were not consistently sustained over longer follow-up periods [16,30,48] Similarly, cognitive-behavioral and multicomponent interventions (CBTAC) showed improvements in clinician-rated depressive outcomes; however, the evidence remains limited and requires further

replication. Neuromodulation approaches, including transcranial pulse stimulation, also reported reductions in depressive symptom scores in randomized trials, but findings are preliminary and based on limited samples [27,31,44] .

Overall, the evidence suggests that depression in Alzheimer's disease is a complex and heterogeneous condition influenced by clinical, cognitive, and methodological factors. Prior literature indicates an association between depression and later Alzheimer's disease, although variations in measurement tools and cut-off thresholds may influence reported effect estimates. The present review also highlights evidence of differential item functioning (DIF) in commonly used depression scales across cognitive stages, suggesting potential variability in measurement validity in dementia populations. Taken together, these findings support the need for longitudinal, stage-sensitive, and methodologically standardized approaches to studying depression in Alzheimer's disease rather than relying on single-time-point assessments or uniform treatment expectations [26].

This biomarker-linked evidence suggests a complex and heterogeneous relationship between depressive symptoms and Alzheimer's disease (AD), with potential involvement of biologically distinct subtypes. In cognitively unimpaired older adults, depressive symptoms have been associated with longitudinal changes in brain activity within emotion-related cortical regions. This supports the possibility that affective changes may be linked to early neurobiological alterations in a subset of individuals; however, this relationship is not consistent across all studies.

Large-scale individual-level analyses indicate that depressive symptoms are not consistently associated with amyloid pathology and may show variable or inverse associations in mild cognitive impairment (MCI) populations[15,49,50]. These inconsistencies highlight the need for biomarker-stratified approaches rather than single-mechanism explanations of depression in AD.

From a clinical perspective, these findings support a shift toward stage-sensitive, longitudinal, and multi-informant approaches for depression assessment in Alzheimer's disease. Evidence of differential item functioning (DIF) in commonly used scales such as the Geriatric Depression Scale–Short Form suggests that identical scores may reflect different underlying symptom burdens across cognitive stages [51]. This limits the direct comparability of depression severity across disease severity levels.

In terms of treatment implications, evidence from randomized trials indicates that standard antidepressant approaches, such as vortioxetine, may have limited efficacy in Alzheimer's disease. Pragmatic psychotherapy trials suggest modest benefits in selected patients, but effects vary across studies and follow-up periods. Similarly, multicomponent and caregiver-inclusive interventions (e.g., CBTAC) may show clinical benefit in some settings; however, current evidence is limited by issues of replication, scalability, and methodological heterogeneity [52].

From a policy perspective, evidence from national registry data suggests an increased risk of depression following Alzheimer's disease (AD) diagnosis, highlighting the importance of incorporating systematic depression surveillance into dementia care pathways. These findings support the integration of structured follow-up systems and improved access to psychosocial services for individuals living with dementia. In addition, there is a need to strengthen care delivery models through coordinated multidisciplinary teams within memory clinics and long-term care settings, including appropriate support for caregivers [53].

The included evidence is derived from a combination of large cohort studies and randomized controlled trials, including major research infrastructures such as ADNI and NACC, which provide relatively well-powered analyses of risk factors and clinical outcomes. However, several limitations should be considered. Heterogeneity in measurement approaches, including differences in depression scales, dementia staging methods, and rating procedures, may affect comparability across studies. In addition, selection bias in observational cohorts such as recruitment of research volunteers, exclusion of severe depressive cases, and limited population diversity may reduce the generalizability of findings to real-world clinical settings.

1. Conclusions

Depression in Alzheimer's disease is a common and clinically important condition; however, it remains challenging to diagnose and manage due to variability in diagnostic criteria, assessment tools, and overlap with cognitive symptoms. Evidence from studies published between 2021 and 2026 suggests that these factors may contribute to under recognition and misclassification of depressive symptoms in both clinical and research settings. Findings indicate that stage-sensitive and multi-informant assessment approaches, including caregiver input, may improve diagnostic accuracy. Reported risk factors include prior history of depression, neurobiological vulnerability, and psychological stressors, although their contributions vary across populations and study designs.

Evidence on treatment approaches remains mixed. Pharmacological interventions show limited and inconsistent benefits, while some non-pharmacological and individualized approaches demonstrate potential benefits in selected studies; however, overall evidence remains inconclusive. Future research should focus on large-scale longitudinal studies using standardized, dementia-specific depression measures to improve comparability and strengthen clinical decision-making.

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