International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Evaluating the Diagnostic Utility of Galectin-3 in Alzheimer's Disease: A Systematic Review and Meta-Analysis

INPLASY202650003

doi: 10.37766/inplasy2026.5.0003

Received: 30 April 2026

Published: 1 May 2026

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ADMINISTRATIVE INFORMATION

Support - The authors declare that they did not receive any funding for this research.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202650003

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 1 May 2026 and was last updated on 1 May 2026.

INTRODUCTION

Review question / Objective P: Patients diagnosed with Alzheimer's disease (AD) based on established clinical criteria (NINCDS-ADRDA or NIA-AA). I: Measurement of Galectin-3 (Gal-3) levels in serum and/or cerebrospinal fluid (CSF) using enzyme-linked immunosorbent assay (ELISA). C: Healthy controls (HC) without Alzheimer's disease. O: (1) Pooled Gal-3 levels comparing AD patients and healthy controls. (2) Comparison of Mini-Mental State Examination (MMSE) scores between AD patients and healthy controls. (3) Subgroup analysis of Gal-3 levels stratified by specimen type (serum vs. CSF). (4) Subgroup analysis of Gal-3 levels stratified by geographic region.

Rationale Alzheimer's disease is the most prevalent cause of dementia worldwide, and neuroinflammation has emerged as a critical contributor to its pathogenesis. Galectin-3, a beta-galactoside-binding lectin predominantly expressed by activated microglia in the central nervous system, has been linked to neuroinflammatory processes in AD and is detectable in both serum and CSF. Several individual studies have reported elevated Gal-3 levels in AD patients compared to healthy controls; however, these studies have been limited by small sample sizes, heterogeneous methodologies, and varying specimen types. To date, no comprehensive systematic review and meta-analysis has rigorously synthesized the available evidence on Gal-3 as a diagnostic biomarker for AD. A quantitative synthesis is therefore warranted to determine the pooled effect size of Gal-3 elevation in AD and to explore potential sources of heterogeneity through subgroup analyses.

Condition being studied Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. Alongside these classical hallmarks, neuroinflammation—particularly microglial activation—has emerged as

a driving force in disease progression. Genome-wide association studies have identified variants in innate immunity-related genes (TREM-2, CD33, CR1, MEF2C) that confer significant risk for developing AD. Galectin-3 is predominantly expressed by activated microglia in the CNS and acts as an endogenous ligand for TLR4 and TREM-2, both key regulators of the neuroinflammatory cascade in AD. Gal-3-positive microglia cluster around Aβ plaques and tau aggregates in AD brain tissue, and genetic deletion of Gal-3 in transgenic mouse models reduces Aβ burden and improves cognitive performance. From a biomarker perspective, Gal-3 is detectable in both serum and CSF, making it a candidate for non-invasive or minimally invasive diagnostic assessment. However, pooled quantitative evidence on its diagnostic utility remains limited.

METHODS

Search strategy A comprehensive literature search was performed across three electronic databases—PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus—from inception through April 2026. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords using the following Boolean logic: ("galectin-3" OR "Gal-3" OR "LGALS3") AND ("Alzheimer" OR "Alzheimer's disease" OR "AD" OR "dementia" OR "cognitive impairment"). No language restrictions were applied. Reference lists of included studies and relevant review articles were manually screened to identify additional eligible studies.

Participant or population Patients diagnosed with Alzheimer's disease based on established clinical criteria, including the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria or the National Institute on Aging–Alzheimer's Association (NIA-AA) criteria, compared with healthy controls.

Intervention Measurement of Galectin-3 (Gal-3) levels in serum and/or cerebrospinal fluid (CSF) using enzyme-linked immunosorbent assay (ELISA) in the Alzheimer's disease patient group.

Comparator Measurement of Galectin-3 (Gal-3) levels in serum and/or cerebrospinal fluid (CSF) using enzyme-linked immunosorbent assay (ELISA) in the healthy control group.

Study designs to be included Published original research articles with cross-sectional, cohort, or case-control study designs that compared Gal-3 levels between patients diagnosed with Alzheimer's disease and healthy controls.

Eligibility criteria The included studies met the following criteria: (1) original research articles (cross-sectional, cohort, or case-control design); (2) AD diagnosis based on established clinical criteria such as the NINCDS-ADRDA or NIA-AA criteria; (3) measurement of Gal-3 concentrations in serum and/or CSF using ELISA; (4) inclusion of a healthy control group; and (5) reporting of sufficient quantitative data (mean ± standard deviation or data convertible thereto) for meta-analytic synthesis.

The studies were excluded based on the following criteria: (1) animal-only studies without human data; (2) did not measure Gal-3 levels; (3) did not include an AD patient group or a healthy control comparator; (4) publication types such as reviews, editorials, conference abstracts, or case reports; or (5) used duplicated datasets from other included studies.

Information sources A comprehensive literature search was performed across PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus from database inception through April 2026. Reference lists of included studies and relevant review articles were manually screened to identify additional eligible studies.

Main outcome(s) Pooled Galectin-3 levels: standardized mean difference (SMD) of Gal-3 concentrations between AD patients and healthy controls across serum and CSF measurements.

Additional outcome(s) (1) Comparison of Mini-Mental State Examination (MMSE) scores between AD patients and healthy controls. (2) Subgroup analysis of Gal-3 levels stratified by specimen type (serum vs. CSF). (3) Subgroup analysis of Gal-3 levels stratified by geographic region (West Asia, East Asia, Europe). (4) Evaluation of publication bias via funnel plot.

Data management Two reviewers (PJH and CHL) independently screened titles and abstracts for initial eligibility. Full texts of potentially relevant articles were assessed against predefined inclusion and exclusion criteria. Discrepancies were resolved through discussion and consensus. Data were independently extracted by two reviewers using a standardized data collection form. The extracted information included first author, year of publication, country, study design, sample size (AD and HC groups), participant demographics (age, sex distribution), detected

specimen type (serum, CSF, or both), assay methodology, Gal-3 concentration values (mean ± SD), MMSE scores, and diagnostic criteria employed. Two reviewers (PJH and CHL) independently verified data extraction, with any disagreements settled by consulting a third reviewer (MML).

Quality assessment / Risk of bias analysis The methodological quality of included studies was assessed using the modified Newcastle-Ottawa Scale (NOS) adapted for cross-sectional studies. This scale evaluates three domains: selection (representativeness and selection of cohorts, ascertainment of exposure), comparability (adjustment for confounders), and outcome (assessment of outcome). Each study received a score out of 7 stars, with higher scores indicating superior methodological quality.

Strategy of data synthesis All meta-analyses were performed using Review Manager version 5.4 (The Cochrane Collaboration). A random-effects model (DerSimonian-Laird method) was used for all analyses given the expected clinical and methodological heterogeneity across studies. Continuous outcomes (Gal-3 levels, MMSE scores) were expressed as standardized mean differences (SMD) with corresponding 95% confidence intervals (CI). Statistical heterogeneity was evaluated using the Cochran Q test and quantified by the I^2 statistic. An I^2 value of 0–25% was considered low, 25–50% moderate, 50–75% substantial, and greater than 75% considerable heterogeneity. Publication bias was evaluated visually using a funnel plot. A two-tailed P value < 0.05 was considered statistically significant.

Subgroup analysis Prespecified subgroup analyses were conducted based on: (1) specimen type (serum vs. CSF) and (2) geographic region (West Asia, East Asia, Europe) to explore potential sources of heterogeneity.

Sensitivity analysis Given the small number of included studies (n = 4), formal sensitivity analysis was limited. The consistency of findings across subgroup analyses by specimen type and geographic region served as a robustness check for the pooled results.

Language restriction No language restrictions were applied in this study.

Country(ies) involved Taiwan.

Other relevant information The bibliometric analysis using VOSviewer was performed to visualize keyword co-occurrence networks and identify research hotspots related to Galectin-3, providing insight into the intellectual structure of the field.

Keywords Galectin-3, Alzheimer's disease, biomarker, cerebrospinal fluid, serum, meta-analysis, systematic review, neuroinflammation, microglia.

Dissemination plans The findings of this systematic review and meta-analysis will be submitted for publication in a peer-reviewed journal. The study protocol was registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY).

Contributions of each author

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