International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Evaluating the evidence linking infection and inflammation to Alzheimer's disease: An umbrella review of systematic reviews and meta-analyses

INPLASY202670079
doi: 10.37766/inplasy2026.7.0079
Received: 20 July 2026
Published: 20 July 2026

Wahono, A; Salsabila, D; Shafa, R; Anggraini, M; Untari, NK.

Corresponding author:
Andika Wahono

wahonoandika35@gmail.com

Author Affiliation:
RSPAL dr. Ramelan Surabaya.

ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202670079

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 July 2026 and was last updated on 20 July 2026.

INTRODUCTION

Review question / Objective This umbrella review aims to comprehensively evaluate the evidence regarding the association between infectious and inflammatory conditions and the risk of Alzheimer's disease.

Rationale Alzheimer disease (AD) is a progressive neurodegenerative disease characterized by memory loss and cognitive decline, such as disturbance in learning, language, reasoning, behaviour, and visual-spatial abilities. Over the past 30 years, research has shown a 1.6-folds increase in the global prevalence of AD and 1,15-fold increase in mortality among aged 65 years and older with Alzheimer disease and other forms of dementia. There are several pathogenic mechanisms underlying Alzheimer's disease (AD) that have been extensively studied. Emerging evidence suggests that infection and immune-related mechanisms may contribute to the pathogenesis of AD. While numerous systematic reviews and meta-analyses have assessed these associations, their findings are often inconsistent, and the overall quality of evidence remains uncertain. An umbrella review provides a systematic and efficient approach to comprehensively synthesize these studies, to support evidence-based decision-making and to guide future research.

Condition being studied Alzheimer disease (AD) is a progressive neurodegenerative disease characterized by memory loss and cognitive decline, such as disturbance in learning, language, reasoning, behaviour, and visual-spatial abilities. This umbrella review aimed to assess the association and level of evidence regarding the relationship between infectious and inflammatory conditions and Alzheimer's disease.

METHODS

Search strategy PubMed, Scopus, Epistemonikos, and the Cochrane Library were systematically searched from inception to April 2, 2026. The search strategy combined Medical

Subject Headings (MeSH) terms and relevant keywords, including “Alzheimer’s disease,” “risk factor,” “hazard ratio,” “odds ratio,” “relative risk,” “risk ratio,” “systematic review,” and “meta-analysis.”

Boolean operator for Pubmed:
((("alzheimer disease"[All Fields]) OR ("alzheimer s disease"[All Fields]) OR ("alzheimer disease"[MeSH Terms])) AND (("risk factors"[All Fields]) OR ("risk factor"[All Fields]) OR ("risk factors"[MeSH Terms])) AND (("hazard ratio"[All Fields]) OR ("odds ratio"[All Fields]) OR ("odds ratio"[MeSH Terms]) OR ("absolute risk"[All Fields]) OR ("relative risk"[All Fields]) OR ("risk ratio"[All Fields])) AND (("systematic review"[All Fields]) OR ("meta analysis"[All Fields])))

Boolean operator for Scopus :
TITLE-ABS-KEY ("Alzheimer's disease" AND "Risk factors" AND "Hazard ratio" OR "Odds ratio" OR "Absolute risk" OR "Relative risk" OR "Risk ratio" AND "Systematic review" OR "Meta analysis")

Boolean operator for Epistemonikos:
(title:("Alzheimer disease") OR abstract:("Alzheimer disease")) AND (title:("Risk factors") OR abstract: ("Risk factors")) + publication type systematic-review.

Participant or population Population: Healthy person without Alzheimer's dementia.

Intervention Intervention/Exposure: Any inflammation or infection disease.

Comparator Person without inflammation or infection disease.

Study designs to be included Observational study.

Eligibility criteria Meta-analyses and systematic reviews meeting the following criteria were included: (1) systematic reviews or meta-analyses investigating the association between infectious or inflammatory conditions and Alzheimer’s disease (AD); (2) studies reporting effect estimates as Relative Risks (RRs), Odds Ratios (ORs), or Hazard Ratios (HRs); and (3) articles published in English or Indonesian in peer-reviewed journals. The PECO framework was defined as follows: (1) the population comprised human participants aged ≥18 years; (2) exposures included infectious or inflammatory conditions identified through a scoping search of potential risk factors for AD; (3) the comparison group consisted of individuals without the exposure of interest in cohort studies or randomized controlled trials, or individuals without AD in case-control studies; and (4) the outcome of interest was AD.
Studies were excluded if they: (1) did not perform a quantitative synthesis; (2) were duplicate publications of the same exposure–outcome association; (3) were guidelines, narrative reviews, literature reviews, genetic studies, animal studies, or non-observational studies; (4) were not published in English or Indonesian; (5) did not investigate infectious or inflammatory exposures as risk factors for AD; (6) evaluated outcomes other than AD (e.g., MCI, all-cause dementia, non-AD dementias, or progression from MCI to AD); or (7) focused exclusively on imaging, diagnostic, prognostic, or other non-etiological associations.

Information sources Electronic database: PubMed, Scopus, Epistemonikos, and the Cochrane Library.

Main outcome(s) The risk of developing Alzheimer's disease (in Odd ratio's, Risk ratio, or Hazard ratio).

Additional outcome(s) None.

Data management After duplicate records were removed, studies were screened for relevance based on their titles and abstracts, followed by full-text assessment for eligibility. Two researchers (ADW and DAS) independently performed the screening and eligibility assessment. Any disagreements were resolved through discussion with a third reviewer.

Data extraction and methodological quality assessment were performed by one reviewer and independently verified by a second reviewer. Extracted data included the first author, year of publication, investigated exposure, outcome, publication period, number of databases searched, study designs included, number of studies analysed, total sample size and number of cases, pooled effect estimates from the meta-analyses (e.g., odds ratios [ORs], hazard ratios [HRs], risk ratios [RRs], and standardized incidence ratios [SIRs]) with their corresponding 95% confidence intervals (95% CIs), as well as detailed information on the primary studies included in each meta-analysis. The primary outcome of interest was the association between infectious or inflammatory conditions and the risk of AD. Information on primary studies was additionally collected to assess overlap across meta-analyses using the corrected covered area (CCA) method.

Quality assessment / Risk of bias analysis The methodological quality of the included systematic reviews and meta-analyses was evaluated using the AMSTAR 2 tool. Based on the number of critical and non-critical weaknesses identified, each review was rated as high, moderate, low, or critically low quality according to the AMSTAR 2 guidance[1].

Strategy of data synthesis Identical risk factors were grouped together, and the number of meta-analyses evaluating each risk factor was recorded. When the same risk factor was assessed in two or more meta-analyses, the degree of overlap among reviews was evaluated using the CCA. The CCA, expressed as a percentage, was calculated using the formula (N – r)/(rc – r), where N represents the total number of included studies across all reviews (counting repeated occurrences), r represents the number of unique primary studies, and c represents the number of reviews. Overlap was categorized as slight (CCA 0–5%), moderate (CCA 6–10%), high (CCA 11–15%), or very high (CCA >15%). All systematic reviews and meta-analyses without overlapping primary studies were included in the evidence synthesis. For risk factors evaluated by two or more reviews with high or very high overlap (CCA ≥11%), only one review was retained according to the following hierarchical criteria: higher methodological quality as assessed by AMSTAR 2, more recent publication date, and larger number of included participants. When overlap was slight or moderate (CCA ≤10%), all eligible reviews were retained and their findings were compared and synthesized.
Original data from each eligible meta-analysis were extracted from the corresponding forest plots and re-analysed. Summary effect estimates, 95% confidence intervals (CIs), and p values were calculated using random-effects models based on the Der Simonian and Laird method. In addition, 95% prediction intervals (PIs) were calculated to assess between-study heterogeneity and to estimate the range of effects that may be expected in a future study evaluating the same risk factor. Between-study heterogeneity was assessed using the I^2 statistic. Consistent with conventional thresholds, an I^2 value greater than 50% was considered indicative of substantial heterogeneity. Small-study effects were assessed using Egger's regression asymmetry test to determine whether smaller studies tended to report larger effect estimates than larger studies. A p-value < 0.10 was considered indicative of the presence of small-study effects. For associations supported by high-strength evidence, a p-curve analysis was performed to assess evidential value and to examine whether the observed significant findings could be explained solely by selective reporting or p-hacking. A right-skewed p-curve was considered indicative of evidential value, suggesting that the observed association is unlikely to be entirely attributable to selective reporting and is consistent with the presence of a true underlying effect.
To assess the credibility and robustness of the identified associations, a series of predefined criteria were applied (2).

Subgroup analysis Not applicable.

Sensitivity analysis Not applicable.

Language restriction Only publication in English or Indonesian language.

Country(ies) involved Indonesia - RSPAL dr. Ramelan Surabaya.

Other relevant information Supplementary materials can be accessed at: https://docs.google.com/document/d/1M3VAR_pB4KW_7zG2ydjFUi4NaRPV3iS5F0N7HiKcy3w/edit?tab=t.0

[1] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021:n71. https://doi.org/10.1136/bmj.n71.
[2] Fusar-Poli P, Radua J. Ten simple rules for conducting umbrella reviews. Evidence Based Mental Health 2018;21:95–100. https://doi.org/10.1136/ebmental-2018-300014.

Keywords Alzheimer's disease, infection, inflammation, umbrella review.

Dissemination plans The results of this systematic review will be disseminated through presentations at relevant scientific conferences, including the CNE (Continuing Neurological Education) seminar, and through publication in a peer-reviewed journal.

Contributions of each author
Author 1 - Andika Wahono - Conceptualization
Methodology
Literature search / Investigation
Data extraction
Quality assessment / Risk of bias assessment
Formal analysis
Data curation
Visualization
Writing – original draft
Project administration.
Email: wahonoandika35@gmail.com

Author 2 - Daffa Salsabila - Literature search / Investigation
Data extraction
Quality assessment / Risk of bias assessment
Formal analysis
Data curation
Visualization
Writing – original draft.
Email: annoradaffa@gmail.com
Author 3 - Rahmatya Shafa - Literature search / Investigation
Data extraction
Quality assessment / Risk of bias assessment
Formal analysis
Data curation
Visualization
Writing – original draft.
Email: drmeidinashafa@gmail.com
Author 4 - Monika Anggraini - Literature search / Investigation
Data extraction
Quality assessment / Risk of bias assessment
Formal analysis
Data curation
Visualization
Writing – original draft.
Email: monikapa34@gmail.com
Author 5 - Ni Komang Untari - Conceptualization
Methodology
Writing – review & editing
Supervision.
Email: komang_neuro@yahoo.com