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INPLASY

Relationship between Vitamin D Level and Post-stroke Depression: A Systematic Review and Meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 May 2026 and was last updated on 13 May 2026.

INTRODUCTION

Review question / Objective Population (P): Adult patients with a confirmed diagnosis of stroke (ischemic or hemorrhagic), regardless of age or sex.
Intervention/Exposure (I): Low vitamin D levels or vitamin D deficiency.
Comparator (C): Stroke patients with normal or sufficient vitamin D levels.
Outcome (O): Incidence or prevalence of post-stroke depression (PSD), measured by validated psychiatric diagnostic criteria (DSM/ICD) or standardized psychometric scales (e.g., HAMD, PHQ-9).
Study Design (S): Observational studies, including cohort, case-control, or cross-sectional studies.
Review Question/Objective:
To systematically evaluate and synthesize the evidence on whether low vitamin D levels are associated with post-stroke depression in adult stroke patients, and to determine if vitamin D deficiency is an independent risk factor for PSD after adjusting for potential confounding factors.

Condition being studied The condition being studied in this systematic review is post-stroke depression (PSD). PSD is a common neuropsychiatric complication that occurs following a cerebrovascular accident (stroke), affecting approximately 30% of stroke survivors. It is characterized by the presence of depressive symptoms such as persistent sadness, loss of interest or pleasure in activities, changes in appetite or sleep, fatigue, impaired concentration, and feelings of worthlessness. PSD can significantly impair physical recovery, cognitive function, and overall quality of life, and it has been associated with poorer rehabilitation outcomes, increased dependence in daily activities, and higher long-term mortality. The development of PSD is influenced by a combination of biological, psychological, and social factors, including the severity of the stroke, pre-existing mental health conditions, functional disability, social support, and nutritional status. Early identification and management of PSD are crucial to improving the

recovery trajectory and overall well-being of stroke survivors.

METHODS

Participant or population The participants included in this systematic review are adult patients who have experienced a confirmed stroke, including both ischemic and hemorrhagic subtypes, regardless of age, sex, or ethnicity. Eligible participants are those whose stroke diagnosis has been verified through standard clinical criteria and neuroimaging (CT or MRI). The review focuses on stroke survivors assessed for post-stroke depression (PSD) using validated psychiatric diagnostic frameworks (DSM or ICD) or standardized psychometric scales such as the Hamilton Depression Rating Scale (HAMD) or Patient Health Questionnaire (PHQ-9). Participants with pre-existing depression prior to the stroke were excluded in the original studies to ensure that the assessment reflects post-stroke onset depressive symptoms.

Intervention In this systematic review, the "intervention" corresponds to the exposure of interest, which is low vitamin D levels or vitamin D deficiency in adult stroke patients. Vitamin D status is typically measured by circulating 25-hydroxyvitamin D [25(OH)D] concentrations in the blood. The review evaluates whether individuals with lower vitamin D levels are more likely to develop post-stroke depression (PSD) compared to those with sufficient or normal vitamin D levels.
No therapeutic intervention (e.g., supplementation) is directly assessed in this review; instead, the focus is on observational comparisons of naturally occurring differences in vitamin D status among stroke survivors and their association with PSD incidence or severity.

Comparator The comparator in this systematic review consists of stroke patients with normal or sufficient vitamin D levels. These participants serve as the reference group against which the association between low vitamin D levels and post-stroke depression (PSD) is evaluated. By comparing stroke survivors with deficient versus adequate vitamin D status, the review aims to determine whether low vitamin D is associated with an increased risk of developing PSD, after accounting for potential confounding factors.

Study designs to be included This review will include observational studies, specifically cohort, case-control, and cross-sectional designs, that investigate the association between vitamin D levels and post-stroke depression in adult stroke patients. Only studies providing quantitative data on vitamin D status and PSD outcomes will be considered.

Eligibility criteria Inclusion criteria:

Studies must involve adult stroke patients (ischemic or hemorrhagic) with PSD assessment using validated diagnostic tools (DSM, ICD) or standardized psychometric scales (HAMD, PHQ-9).
Studies must report quantitative data on vitamin D levels (25-hydroxyvitamin D) and allow calculation of effect sizes (e.g., mean differences, odds ratios).
Publications in English or Chinese peer-reviewed journals.

Exclusion criteria:

Duplicate publications reporting the same dataset; only the most complete study is included.
Studies lacking sufficient data on vitamin D levels or PSD outcomes.
Non-original research articles, including case reports, case series, commentaries, editorials, conference abstracts, and review articles.
Participants with pre-existing depression prior to stroke to avoid confounding PSD assessment.
Interventional studies (e.g., vitamin D supplementation trials) are excluded, as the review focuses on observational associations.

Information sources The systematic review will identify relevant studies through a comprehensive search of multiple electronic bibliographic databases, including PubMed, Web of Science, the Cochrane Library, China National Knowledge Infrastructure (CNKI), and WanFang Data Knowledge Service Platform. The search will cover all records from database inception to the most recent available date. Both free-text keywords and controlled vocabulary terms (e.g., MeSH) related to stroke, post-stroke depression, and vitamin D will be used to ensure sensitivity and comprehensiveness.

In addition to database searching, the review will include manual screening of reference lists from relevant articles to identify additional eligible studies. Where necessary, correspondence with study authors will be undertaken to obtain missing data or clarify unclear information. Grey literature, such as conference abstracts and theses, will be considered only if they provide sufficient quantitative data for inclusion.

This multi-source approach is intended to minimize publication bias and ensure a thorough capture of

all studies examining the association between vitamin D status and post-stroke depression.

Main outcome(s) The main outcome of this review is post-stroke depression (PSD) in adult stroke patients. PSD is assessed using validated psychiatric diagnostic criteria (DSM or ICD) or standardized psychometric scales such as the Hamilton Depression Rating Scale (HAMD) or Patient Health Questionnaire (PHQ-9). The outcome is measured as the incidence or prevalence of PSD, typically occurring within weeks to months following the stroke event.

The review also evaluates the association between vitamin D levels (25-hydroxyvitamin D) and PSD. Effect measures include standardized mean differences (SMDs) comparing vitamin D levels between PSD and non-PSD groups, and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) quantifying the risk of PSD in participants with low versus sufficient vitamin D, controlling for potential confounders.

These measures allow the review to determine both the magnitude of difference in vitamin D levels and the independent association between vitamin D status and PSD risk.

Quality assessment / Risk of bias analysis The methodological quality of the included primary studies will be assessed using the Newcastle-Ottawa Scale (NOS), a validated tool for evaluating non-randomized observational studies. The NOS evaluates studies across three key domains:
Selection of participants – assessing the representativeness and adequacy of the exposed (PSD) and non-exposed (non-PSD) cohorts, or the case and control definitions in case-control studies.
Comparability of groups – evaluating the study's control for potential confounding factors, such as age, sex, stroke severity, and comorbidities.
Outcome or exposure ascertainment – assessing the validity and reliability of PSD diagnosis and vitamin D measurement, including the use of standardized tools and laboratory methods.

Each study is scored with a maximum of nine stars, with higher scores indicating lower risk of bias. Studies scoring 7 stars or above are classified as high quality, while lower scores indicate moderate or higher risk of bias.

Quality assessment will be conducted independently by two reviewers, and any disagreements will be resolved through discussion or consultation with a third senior reviewer. This ensures objectivity and consistency in evaluating the risk of bias.

The NOS assessment informs the interpretation of results and is used to perform sensitivity analyses to examine the impact of study quality on pooled outcomes.

Strategy of data synthesis Data from eligible studies will be synthesized using quantitative meta-analysis where possible. For the comparison of vitamin D levels between patients with and without post-stroke depression (PSD), standardized mean differences (SMDs) with 95% confidence intervals (CIs) will be calculated to account for differences in measurement scales across studies. For the association between low vitamin D levels and PSD risk, adjusted odds ratios (ORs) with 95% CIs from multivariate analyses will be pooled.

Heterogeneity among studies will be assessed using Cochran's Q test and the I^2 statistic. An I^2 0.1 will indicate low-to-moderate heterogeneity, warranting a fixed-effects model, whereas $I^2 \geq 50\%$ or $p \leq 0.1$ will indicate substantial heterogeneity, prompting use of a random-effects model.

Potential sources of heterogeneity will be explored through subgroup analyses, for example stratifying by PSD diagnostic tool, stroke subtype, or study quality. Publication bias will be evaluated using funnel plots and Egger's regression test, and, if detected, the Duval and Tweedie trim-and-fill method will be applied to adjust pooled estimates.

All statistical analyses will be conducted using the R statistical software with appropriate meta-analysis packages. Results will be presented as forest plots for effect sizes, and tables summarizing study characteristics, quality scores, and main findings. Sensitivity analyses will be performed to examine the impact of high-risk-of-bias studies on the overall conclusions.

Subgroup analysis Subgroup analyses will be conducted to explore potential sources of heterogeneity and to examine whether the association between vitamin D levels and post-stroke depression (PSD) differs across specific study or patient characteristics. Planned subgroup analyses include:

PSD diagnostic tool – comparisons between studies using the Hamilton Depression Rating Scale (HAMD), Patient Health Questionnaire (PHQ-9), or DSM/ICD criteria to assess whether

differences in diagnostic methods influence effect estimates.
Stroke subtype – analyses separating ischemic stroke from all-stroke populations to evaluate whether stroke type modifies the relationship between vitamin D status and PSD.
Study quality – comparisons between high-quality (NOS ≥7) and moderate/low-quality studies (NOS <7) to assess the impact of methodological rigor on pooled results.
Timing of outcome assessment – if data allow, examining whether early versus late PSD assessment (e.g., within weeks vs. months post-stroke) affects the observed associations.

Subgroup analyses will use the same meta-analytic methods as the primary synthesis, calculating SMDs for vitamin D levels and adjusted ORs for PSD risk within each subgroup. These analyses aim to clarify sources of heterogeneity and identify conditions under which the association between vitamin D deficiency and PSD is stronger or weaker.

Sensitivity analysis Sensitivity analyses will be performed to assess the robustness and reliability of the review's findings. These analyses will examine whether the overall results are influenced by specific studies or methodological decisions. Planned sensitivity analyses include:

Exclusion of low-quality studies – studies with Newcastle-Ottawa Scale (NOS) scores below 7 will be removed to determine the effect of study quality on pooled estimates.
Influence of individual studies – a leave-one-out analysis will be conducted, sequentially excluding each study to assess whether any single study disproportionately affects the overall results for both vitamin D levels (SMDs) and adjusted PSD risk (ORs).
Effect of study design – sensitivity analyses will explore whether results differ when including only cohort studies versus case-control or cross-sectional studies.
Adjustment for publication bias – where asymmetry is detected in funnel plots, the trim-and-fill method will be applied, and results will be compared to unadjusted pooled estimates to assess potential bias.

These sensitivity analyses will help ensure that conclusions drawn regarding the association between vitamin D deficiency and post-stroke depression (PSD) are robust, reliable, and not unduly influenced by individual studies, study quality, or methodological choices.

Country(ies) involved All authors of this systematic review are affiliated with institutions in China (The Second People's Hospital of Lianyungang & The Oncology Hospital of Lianyungang, Jiangsu, China).

Keywords Post-stroke depression; Vitamin D; 25-hydroxyvitamin D; Stroke; Meta-analysis; Observational studies; Risk factors; Neuropsychiatric complications.

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