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REVIEW

Family History of Psychiatric Disorders as a Risk Factor for Post-Stroke Depression: A Systematic Review and Meta-Analysis

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Background: Currently, the evidence regarding the relationship between family history of psychiatric disorders and post-stroke depression (PSD) is inconsistent. Some observational studies did not consider a positive family history of psychiatric disorders as a definite risk factor. Furthermore, the bulk of research on the association between family history of psychiatric disorders and PSD comes from earlier studies that were frequently constrained by modest sample sizes. Therefore, we plan to use a meta-analysis approach to study this correlation.

Methods: We systematically reviewed the studies related to PSD and family history of psychiatric disorders from PubMed, Embase and EBSCO. The studies eligible for inclusion were peer-reviewed observational studies that reported an odds ratio or contained sufficient data to enable its calculation. We conducted a random-effects meta-analysis of the proportion of PSD patients with a reported positive family history of psychiatric disorders.

Results: Eleven studies published between 1990 and 2020 were included, comprising data on stroke patients. The meta-analysis revealed an elevated odds ratio of 1.73 (95% CI: 1.29–2.33; I^2 = 6.1%) for the development of PSD among stroke patients with a familial predisposition to psychiatric disorders. The findings of subgroup, sensitivity, and meta-regression analyses concurred with the primary analysis. According to GRADE, the overall certainty of the evidence was judged as moderate.

Conclusion: This study revealed moderate certainty of evidence, indicating that stroke patients with family history of psychiatric disorders have approximately a 1.73-fold risk of developing PSD compared to those without such a family history.

Keywords: Post-stroke depression, Meta-analysis, Family history of psychiatric disorders, Cerebrovascular disease

Introduction

According to data from the World Health Organization (WHO) in 2019, the global number of stroke patients reached 101 million. Stroke ranks as the second leading cause of death and remains one of the primary contributors to disability.[1] Stroke survivors often face severe sequelae that significantly impair their quality of life. Post-stroke depression (PSD), a common complication of cerebrovascular disease, further complicates stroke recovery.[2] PSD manifests with a wide range of symptoms, including persistent pain, diminished interest and pleasure, and fatigue or reduced vitality.[3] The prevalence of PSD among stroke patients is approximately 36.9%, markedly higher than the 12% observed in the general population.[4,5] This disparity highlights the urgent need for further research. PSD is associated with adverse outcomes such as elevated mortality rates, worsened functional impairment, and increased societal burden. These influences not only hinder stroke treatment but also increase both the likelihood and severity of poor patient prognosis.[6]

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Many studies have searched for PSD risk factors, but their findings clash because samples were small and PSD was defined differently.[7] Most research focused on brain damage in white matter, the prefrontal lobe and basal ganglia,[8] or on post-stroke rises in the C-reactive protein (CRP) and blood glucose,[9,10] while a family history of psychiatric illness was largely overlooked. Notably, family history often serves as a critical influencing factor in psychiatric disorders, and is readily obtainable through clinical medical history inquiries.[11] Therefore, we hypothesize that family history of psychiatric disorders may be a significant contributor to PSD and intend to validate this hypothesis via a meta-analysis. If confirmed, clinical attention for this high-risk PSD patient group should encompass not only stroke treatment but also the prevention and management of PSD, and enhanced social and familial support.

Currently studies demonstrate that a family history of psychiatric disorders is associated with a wide range of psychiatric conditions, including autism,[12] cancer-related depression[13] and postpartum depression.[14] With the increasing clinical availability of family history data, it has become a key foundation for predicting psychiatric illnesses or symptoms.[11,15] However, despite extensive observational studies on PSD, a family history of psychiatric disorders has not yet been conclusively identified as a risk factor.[7,16] Therefore, it is necessary to clarify the possible correlation between family history of psychiatric disorders and PSD. Therefore, it is essential to further clarify the possible correlation between a family history of psychiatric disorders and PSD. Although one study has documented an association between a family history of psychiatric disorders and the development of PSD,[17] the sample size was relatively small (n = 903), and it failed to account for potential confounding factors such as age and personal history of psychiatric disorders, nor did it include a bias assessment. Hence, a more comprehensive investigation into the link between a family history of psychiatric disorders and PSD is warranted. This meta-analysis aims to contribute clinically to the early screening, diagnosis and intervention of high-risk PSD populations, ultimately improving patient outcomes.

This systematic review and meta-analysis synthesizes existing evidence on the association between family psychiatric history and PSD, and compares how different outcome measures affect the results. Subsequently, we investigated whether the inclusion of PSD and potential confounding factors would influence the conclusions. Finally, we employed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to assess the certainty of the evidence.[18]

Methods

This review and meta-analysis were conducted in accordance with the guidelines outlined in the Cochrane Handbook.[19] The study protocol was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guideline,[20,21] registered in PROSPERO (CRD42024553100) on May 20, 2024.

Eligibility Criteria, Data Sources, and Search Strategy

The studies included in this analysis examined the family history of psychiatric disorders as a contributing factor to the increased risk of developing PSD from 1 week to 2 years after stroke, with a subsequent time-related subgroup analysis. The family history of psychiatric disorders was defined as any psychiatric disorders in close or distant relatives obtained through registration, validated instruments, or self-reported data. Definitions of PSD and post-stroke depressive symptoms were based on registers (eg, prescribed antidepressant medications; Hamilton Rating Scale for Depression (HAM-D); The Hospital Anxiety and Depression Scale (HADS); or equivalent to the diagnostic criteria for minor and major depression in Diagnostic and Statistical Manual of Mental Disorders (DSM)-III and DSM-IV), clinical interviews, or validated instruments.[22] To ensure temporal validity, in cohort studies, data on family history of psychiatric disorders must have been collected prior to the onset of PSD. Additionally, eligible studies were required to either directly report an odds ratio (OR) quantifying the association or provide sufficient data for its calculation. Finally, inclusion criteria restricted the articles to peer-reviewed articles published in English.

Comprehensive searches were conducted in PubMed, Embase, and EBSCO on October 22, 2024, without any restrictions on language or year of publication. The same search strategy was applied across all three databases. Free-text terms were used for the search, with the following strategy: ((((post stroke) OR (post cerebral infarction) OR (post cerebral vascular accident) OR (post cerebral ischaemia) OR (post cerebral haemorrhage)) AND ((depression) OR (depressive disorder) OR (minor depressive disorder and dysthymia))) OR (depression after stroke)) OR (depressive

disorder after stroke). A thorough reference screening and citation tracking were also performed in Web of Science to identify relevant studies. The search was updated on May 8, 2025, before finalizing the review, to ensure inclusion of the most recent literature. Detailed search strings and their construction methods were provided in the study protocol.[14]

Selection Process and Data Extraction

Records retrieved from database searches were imported into EndNote for deduplication. Screening was independently conducted by four reviewers (Hao Zhang, Zhe Wang, Zhiqi Li, and Qingxiong Ma) in two phases: initial title/abstract screening followed by full-text assessment. Studies with discordant judgments during title/abstract screening proceeded to full-text review. Disagreements at the full-text screening stage were resolved by a fifth reviewer (Guo Li). Reasons for exclusion at the full-text review were documented in the PRISMA flowchart.

When studies lacked OR or provided insufficient data for OR calculation, corresponding authors were contacted via Email (maximum three attempts) to obtain missing information before exclusion. To prevent overlapping cohorts in the meta-analysis: 1) Studies with populations already included in the review were excluded; 2) For multiple reports on identical cohorts, only the study with the largest population size was retained; 3) All articles meeting inclusion criteria were incorporated regardless of whether samples had been reused in other studies.

Data extraction was performed by two reviewers (Zhe Wang and Hao Zhang) using a predefined Microsoft Excel template. To ensure consistency and accuracy, both reviewers initially extracted data from eleven articles. Discrepancies were resolved through discussion until consensus was achieved prior to proceeding with full extraction.

Risk of Bias Assessment

Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for the cohort studies, with dual independent evaluations followed by consensus resolution of discrepancy. The NOS comprises 8 items, awarding up to 9 stars for highest quality.[23] Cross-sectional studies were appraised via the Agency for Healthcare Research and Quality's (AHRQ) criteria (11 items scored "yes"/"no"/"unclear"), where 11 points indicate maximal quality,[24] with higher scores denoting lower bias risk (eMethod 1 in Supplement for details).

Data Synthesis and Statistical Analysis Meta-Analyses

Meta-analyses employed random-effects models using Stata 11.0 "meta" module. When studies reported both unadjusted and adjusted ORs, primary analyses exclusively incorporated adjusted estimates, while unadjusted values were reserved for sensitivity analyses. For multiple post-stroke timepoints, the estimates closest to stroke onset were selected for primary analysis, with remaining data utilized in time-stratified secondary analyses based on PSD assessment timing. Statistical heterogeneity was evaluated using the Cochran's Q test and quantified with I^2 statistics.

Primary analysis examined the overall association between family history of psychiatric disorders and PSD; secondary analyses stratified associations by PSD assessment timing and diagnostic criteria for family history of psychiatric disorders and PSD; subgroup analyses considered study design, geographical region, sample type, and cumulative/point prevalence estimates; sensitivity analysis compared adjusted/unadjusted estimates, and excluded high-bias-risk studies (eMethod 1 in the Supplement). Meta-regression analyses assessed covariate effects (age, personal psychiatric history) and study-level bias risk on pooled OR, with publication bias evaluated via funnel plot symmetry[25] and the Peters' regression test.[26]

Quality of Evidence

The GRADE framework was used to systematically rate the certainty of evidence from this meta-analysis assessing the association between family history of psychiatric disorders and PSD. The methodology assesses evidence quality through five domains: study limitations (eg, risk of bias), inconsistency across results, indirectness of evidence, imprecision of effect estimates, and publication bias. Based on this assessment, the certainty of evidence is categorized into four levels (high to very low).[18]

Results

Search Results

Database searches identified 23,005 articles. After removing 8089 duplicates and excluding 14,916 records through title/abstract screening, 938 full-text articles were assessed. Of these, 925 were excluded for not meeting inclusion criteria, yielding 13 eligible articles. Three articles had overlapping samples and the largest sample size study was retained, excluding the other 2 articles (Figure 1). Consequently, 11 articles were included in the final analysis, including those identified through citation tracking.[16,27–36]

Study Characteristics

Table 1 summarized key characteristics and bias risk assessments of the 11 included studies. Geographically, studies originated from Asia (n = 3), Australia (n = 3), Europe (n = 2), and America (n = 3). Sample sizes varied considerably (range: 61–1732), totaling 3747 post-stroke patients across 4 cohort and 7 cross-sectional studies. The assessment of family history of psychiatric

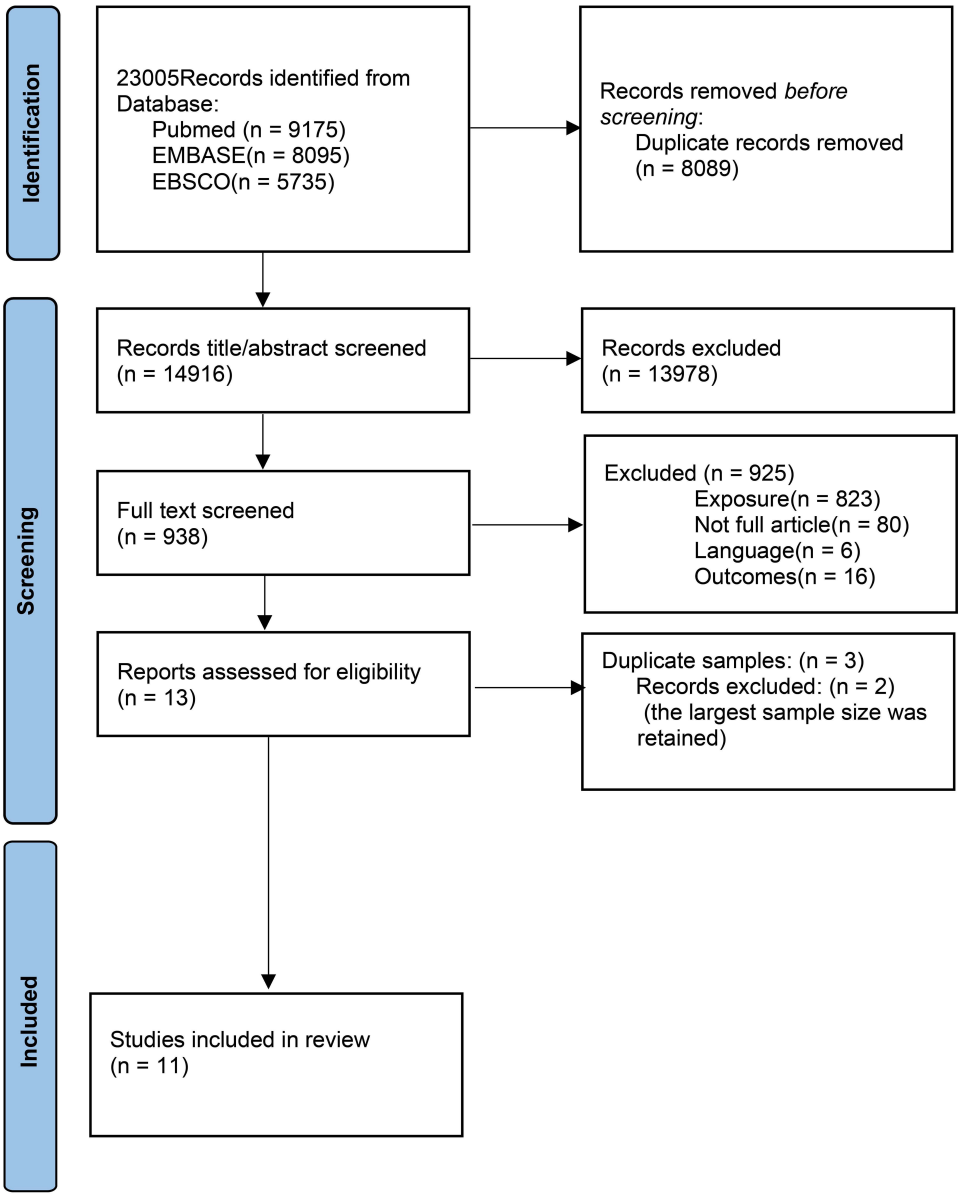

Figure 1 PRISMA Flowchart of Study Selection. According to the PRISMA protocol, identify and screen studies through databases and registries.

Table 1 Characteristics of Included Studies

Administrative Information		Sample		Methods			
Source	**Location**	**Sample Size Population, No.**	**Sample Characteristics**	**Study Design**	**Family Psychiatry Assessment Method**	**PSD Assessment Method**	**PSD Assessment Post-Stroke (Weeks)**
Castillo, 1993[16]	America	309	Selected group	Cross-sectional	Self-reports or other ways	Clinical interview	0–12
Chan, 2024[27]	Asia	1732	Registers	Cross-sectional	Registers	Registers	27–104
González-Torrecillas, 1995[28]	Europe	165	Selected group	Cross-sectional	Self-reports or other ways	Validated instrument	13–26
Leentjens, 2006[30]	Europe	190	Selected group	Cohort	Validated instrument	Clinical interview	27–104
Liang-Po Hsieh, 2005[29]	Asia	207	Selected group	Cohort	Self-reports or other ways	Validated instrument	27–104
Paradiso,1998[33]	America	301	Selected group	Cross-sectional	Self-reports or other ways	Clinical interview	0–12
Philip L. P. Morris, 1990[32]	Oceania	104	Selected group	Cross-sectional	Validated instrument	Clinical interview	27–104
Philip L. P. Morris, 1992[31]	Oceania	99	Selected group	Cohort	Validated instrument	Clinical interview	13–26
Robinson, 2000[34]	America	343	Registers	Cross-sectional	Registers	Registers	27–104
Storor, 2006[35]	Oceania	61	Selected group	Cross-sectional	Self-reports or other ways	Clinical interview	0–12
Zhao, 2020[36]	Asia	236	Selected group	Cohort	Self-reports or other ways	Clinical interview	0–12

Abbreviation: PSD, Post-Stroke Depression.

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disorders was conducted utilizing various methods, including self-reported questionnaires (n = 2), registry data review (n = 2), validated questionnaires or scales (n = 3), and unspecified approaches (n = 4). PSD was evaluated using validated instruments (n = 2), clinical interviews (n = 7), and national registries (n = 2), with assessments conducted 1 week to 2 years post-stroke. Cohort studies demonstrated low-to-moderate bias risk (NOS scores: 7 to 9), while cross-sectional studies showed a wider range of scores (AHRQ scores: 4 to 10), reflecting a more variable degree of potential bias (eMethod 1 in the Supplement).

Primary Analysis and Secondary Analyses

Primary analysis has shown that family history of psychiatric disorders has been significantly associated with increased PSD risk (pooled OR=1.73; 95% CI: 1.29–2.33; I^2= 6.1%) (Figure 2).

The results of secondary analyses were shown as follows.

1. PSD Assessment Timing: The highest OR occurred >26 weeks post-stroke (OR=2.02; 95% CI, 1.37–3.00), though statistically comparable with assessments at ≤12 weeks (OR=1.45; 95% CI, 0.70–2.99) and at 13–26 weeks (OR=1.57; 95% CI, 0.78–3.13) (Figure 3).
2. Assessment of family history of psychiatric disorders: validated instruments yielded the strongest association (OR=1.90; 95% CI, 1.13–3.17), followed by registries (OR=1.83; 95% CI, 1.02–3.30) and self-reporting (OR=1.70; 95% CI, 0.92–3.14) (eFigure 1 in the Supplement).
3. PSD diagnostic method: no significant differences emerged across clinical interviews (OR=1.63; 95% CI, 1.11–2.38), registries (OR=1.83; 95% CI, 1.02–3.30), or validated instruments (OR=2.37; 95% CI, 0.53–10.60) (eFigure 2 in the Supplement).

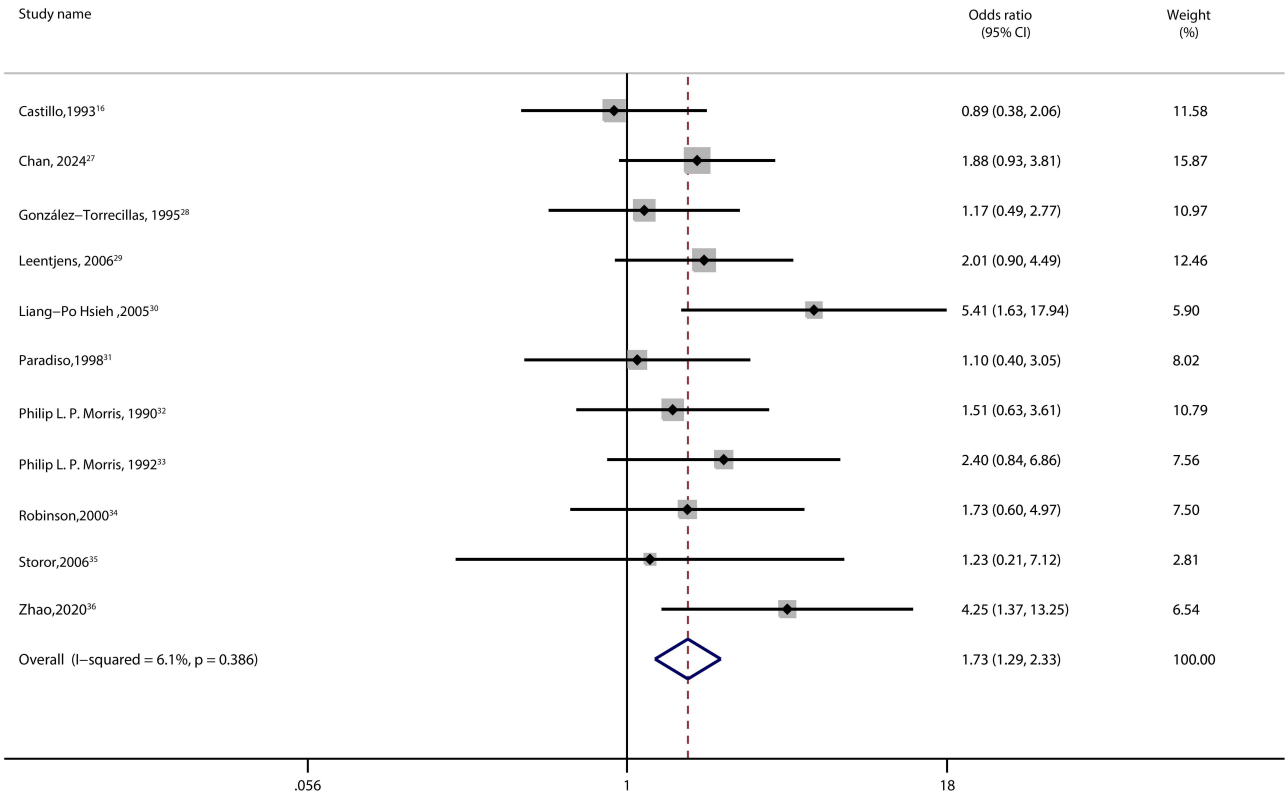

Figure 2 Primary Analysis. Pooled association between family history of psychiatric disorders and PSD.
Abbreviations: PSD, Post-stroke depression; 95% CI, 95% Confidence Interval.

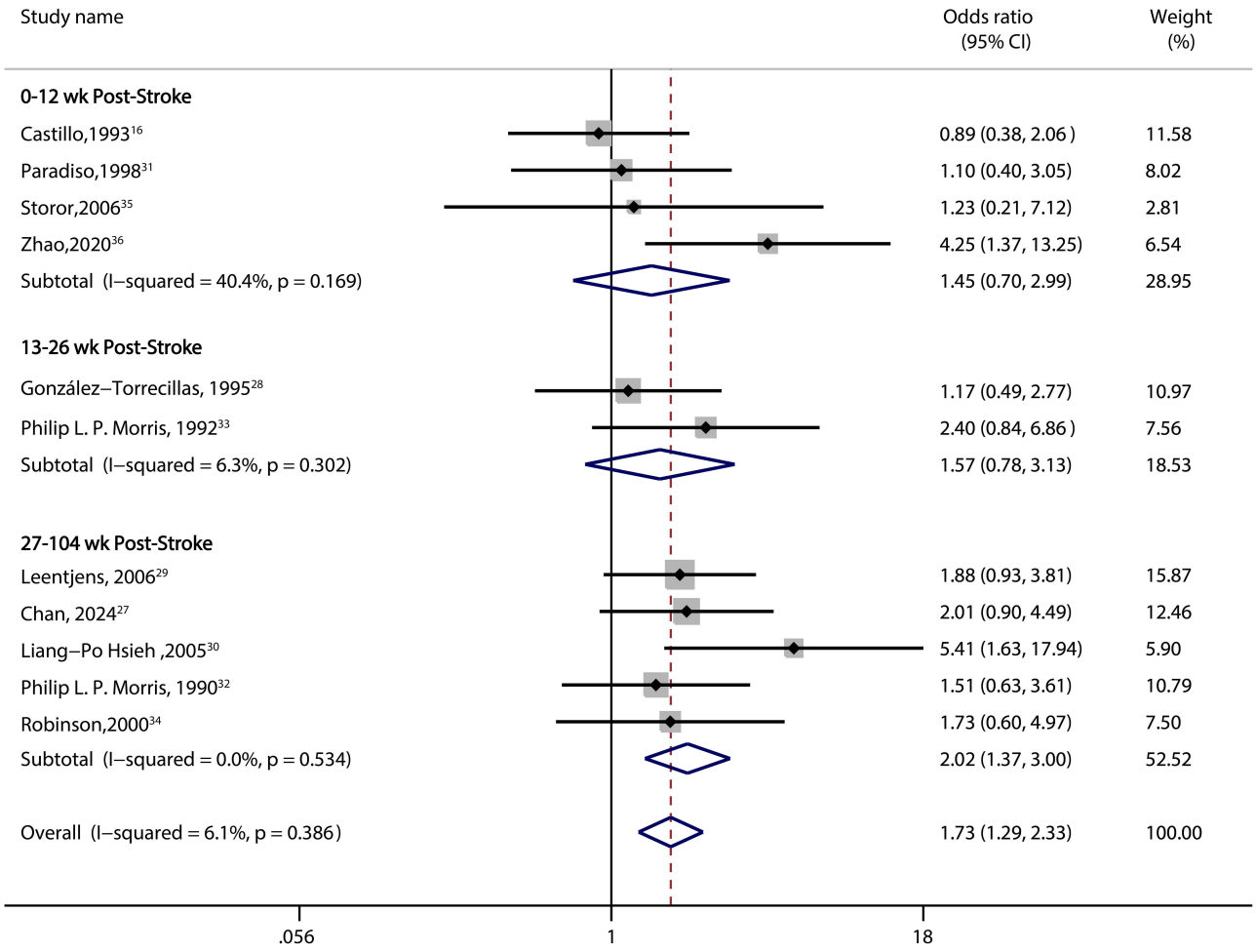

Figure 3 Stratified Analysis by Post-Stroke Depression Assessment Time. Stratified analysis based on different assessment times of PSD, divided into three subgroups: 0–12 weeks, 13–26 weeks, and 27–104 weeks.
Abbreviations: PSD, Post-stroke depression; 95% CI, 95% Confidence Interval.

Subgroup, Sensitivity, and Meta-Regression Analysis

Results from subgroup, sensitivity, and meta-regression analyses consistently aligned with primary findings. Crucially, overlapping 95% CIs across subgroups indicated no statistically significant divergence as demonstrated between registry-based samples (OR=1.83; 95% CI, 1.02–3.30) and hospital-selected groups (OR=1.73; 95% CI, 1.18–2.54), suggesting generalizability across sample types (eFigure 3 in the Supplement). Furthermore, country-stratified analysis revealed significantly lower PSD risk in American studies (OR=1.13; 95% CI, 0.65–1.97) compared to Asian cohorts (OR= 3.03; 95% CI, 1.54–5.97) (eFigure 4 in the Supplement).

Subgroup analyses were conducted across various dimensions, including study design (eFigure 5 in the Supplement), comparisons between cumulative and point prevalence estimates (eFigure 6 in the Supplement), sensitivity analyses employing different statistical methods (eFigure 7 in the Supplement), and the exclusion of studies with high bias risk (eFigure 8 in the Supplement). These analyses did not alter the study outcomes. Similarly, the meta-regression analyses, which evaluated participant characteristics such as age and psychiatric history, as well as the risk of bias score, did not significantly affect the results (eFigures 9 and 10 in the Supplement).

Publication Bias

Visual inspection of the funnel plot (Figure 4) suggested a potential small-study bias; however, the Peters' regression test did not confirm this hypothesis. Furthermore, after excluding smaller studies yielding extreme results (OR=1.51; 95% CI,

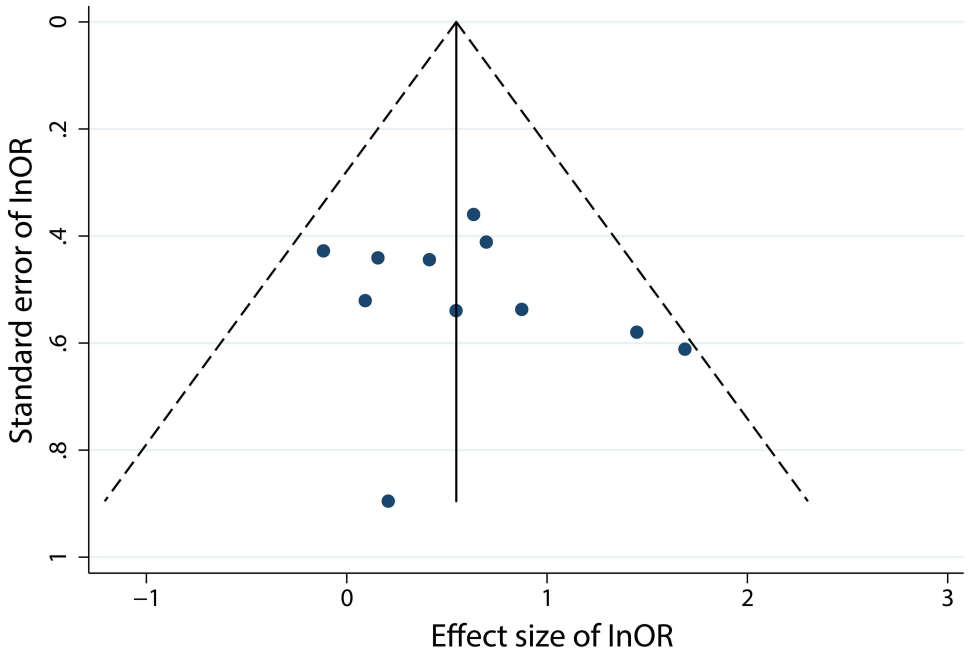

Figure 4 Funnel Plot. The funnel plot shows each study's OR against its sample size, with the two diagonal lines marking pseudo-95% confidence limits that separate regions of differing statistical significance. lnORs, the natural logarithm of odds ratios.

1.11–2.06),[29,35,36] the recalculated pooled OR slightly decreased but remained statistically indistinguishable from the original primary analysis (OR=1.73; 95% CI, 1.29–2.33) (eFigures 11 and 12 in the Supplement). These findings imply that publication bias did not significantly affect the overall conclusions.

For the three studies with sample duplication,[7,16,37] a sensitivity analysis was conducted using the one-by-one exclusion method. The results indicated minimal bias in this meta-analysis, with findings remained stable and were unaffected by any single study (eFigures 13–15 in the Supplement).

Quality of the Evidence

The GRADE framework rated the overall certainty of the evidence linking a family history of psychiatric disorders to PSD as moderate (eTable 1 in the Supplement).

Discussion

Findings from Systematic Review and Meta-Analysis

The systematic review and meta-analysis revealed a 1.73-fold risk of developing PSD among individuals with family history of psychiatric disorders compared to those without. Subgroup analyses, including cohort and cross-sectional studies, yielded consistent findings, which further supports the significance of family psychiatric history in PSD development. These conclusions are consistent with with previous systematic reviews and meta-analyses.[38,39] The observed low heterogeneity further strengthened the reliability of our findings.

Potential Mechanistic Insights into Family Psychiatric History and PSD

Studies investigating the etiological mechanisms of PSD corroborate our findings, highlighting family history of psychiatric disorders as a potent risk factor for PSD. A positive family history of psychiatric disorders may elevate the likelihood of PSD, and potential explanations are as follows.

Firstly, stroke, as a severe stressful event, may impose significant psychological burdens on individuals.[40] Stroke patients with a family history of psychiatric disorders may possess susceptibility genes associated with emotion regulation and stress response.[41] When these susceptibility genes encounter the intense stress of stroke, they may

produce a synergistic amplification effect, significantly increasing the incidence of PSD. Although individual genes exert only modest and nonspecific effects through complex pathways,[42] notable candidates include Brain-Derived Neurotrophic Factor (BDNF),[43,44] and Heat-Shock Proteins (HSP) genes.[45]

Notably, a Danish population-based cohort study identified an elevated risk of a broad spectrum of disorders, encompassing psychotic, mood, anxiety, personality, and substance use disorders, among offspring of parents with severe psychiatric disorders.[46] These findings underscore the link between family psychiatric history and PSD, suggesting that genetic traits may be transmitted across generations, heightening vulnerability to psychiatric disorders and, consequently, PSD.

Secondly, environmental factors play a significant role in the recovery of stroke patients. Unfavorable living conditions may undermine recovery motivation, exacerbate depressive moods, and create a vicious cycle. Stroke patients with a family history of psychiatric disorders often lack adequate familial support.[47]

Thirdly, sociocultural factors were equally critical. Attitudes toward illness, disability, and emotional expression varied across cultural background and social norms.[48] These factors shape the likelihood and quality of family and social responses, thereby influencing both the likelihood and severity of improvement in the patient's psychological recovery trajectory.[49]

Implications of the Findings

Investigating the association between family history of psychiatric disorders and PSD offers valuable insights for developing effective symptom alleviation and prevention strategies. This highlights the potential utility of incorporating a self-reported family psychiatric history screening into routine post-stroke care to facilitate early identification of high-risk patients.[50]

To reduce the occurrence of PSD as a significant clinical concern, we propose the following measures. Firstly, implement early screening and intervention by closely monitoring the emotional states in stroke patients with family history of psychiatric disorders and detecting depressive symptoms at initial stages. Clinicians should pay immediate attention to post-stroke emotional changes and conduct regular assessments.[51] Secondly, develop comprehensive treatment plans encompassing primary disease management, pharmacotherapy, psychotherapy, and physical rehabilitation. Aggressive management of the index stroke is essential to reduce the likelihood and severity of subsequent emotional complications.[52,53] Furthermore, psychological support should be strengthened. Family members and society must provide adequate care and support to help patients establish positive life attitudes, while encouraging participation in interest groups or rehabilitation activities to enhance self-confidence and improve quality of life.[52,54] Establishing social support networks, including maintaining connections with family, friends, and community, fosters a supportive social environment. Lastly, communities should enhance social support systems by increasing follow-up frequency, delivering professional home-care guidance, securing government subsidies to alleviate financial burdens, and organizing rehabilitation activities and social gatherings-all collectively contributing to patients' recovery and community reintegration.[55,56]

By quantifying the elevated PSD risk faced by stroke survivors with a family history of psychiatric disorders, our findings enable stroke survivors with a family history of psychiatric disorders to discuss personalized early screening and preventive care with clinicians, access targeted psychosocial resources, and adopt proactive self-management strategies that may shorten depressive episodes, accelerate functional recovery, and improve long-term quality of life.

Our findings inform future prevention research targeting individuals with familial psychiatric predispositions, with these steps being crucial for identifying PSD risks while ensuring judicious resource allocation.

Strengths and Limitations

This systematic review has several strengths: strict adherence to the pre-specified protocol, rigorous search criteria implementation, and the independent execution of study screening, data extraction, and quality assessment by four reviewers. These measures collectively mitigate reporting biases and enhance the validity of our findings. Nevertheless, certain limitations were also acknowledged. First, the assessment of family history of psychiatric disorders in included studies relied primarily on self-report or unspecified methodologies (n = 6), which introduced methodological

heterogeneity. Substantial variation in self-reported questionnaire phrasing—without standardized approaches—combined with limited literature detailing depression diagnostic criteria and severity grading, constrained our ability to examine how specific psychiatric diagnoses or kinship relationships modulate PSD risk.[57] Consequently, definitive conclusions regarding assessment specificity cannot be drawn. Second, underreporting of psychiatric disorders due to social desirability bias (often stemming from disease stigmatization) likely caused misclassification,[58] suggesting that the true association between family history of psychiatric disorders and PSD risk may be more pronounced than observed.

Our inclusion criteria were restricted to English-language publications, resulting in the exclusion of six non-English articles during full-text screening. This constituted a minor proportion of excluded studies and is unlikely to introduce significant bias. Furthermore, our analysis exclusively incorporated peer-reviewed research.[59] Notably, funnel plot analysis showed no evidence of substantial small-study biases, and subsequent subgroup analysis excluding one small sample size study with extreme outcomes did not alter the primary findings.

Conclusions

This meta-analysis, which synthesized eleven studies, demonstrate that stroke patients with family history of psychiatric disorders face a 1.73-fold risk of developing PSD compared to those without. Crucially, family psychiatric history can be conveniently ascertained through brief self-reported questions. Implementing this approach in clinical assessments may enhance PSD risk prediction, enabling early identification of high-risk individuals for timely, tailored interventions to prevent PSD or mitigate its adverse consequences.

Author Contributions

Guo Li had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Hao Zhang and Zhe Wang are co–first authors. Study concept and design: Hao Zhang, Zhe Wang, Zhiqi Li, and Qingxiong Ma. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Hao Zhang and Zhe Wang. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Hao Zhang. Obtained funding: Guo Li. Study supervision: Guo Li.

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Disclosure

The authors report no conflicts of interest in this work.

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