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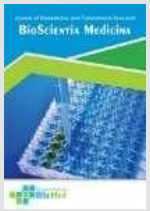

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The Nexus of Neuroinflammation and Psychopathology in Neuropsychiatric Systemic Lupus Erythematosus (NPSLE): A Meta-Analysis of Anti-NMDAR, Anti-Ribosomal P Antibodies, and Psychosomatic Manifestations (Depression, Anxiety, Cognitive Dysfunction)

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A B S T R A C T

Background: Neuropsychiatric systemic lupus erythematosus (NPSLE) significantly impacts patients through diverse neurological and psychiatric symptoms, including prevalent psychosomatic manifestations like depression, anxiety, and cognitive dysfunction. Specific autoantibodies, such as anti-N-methyl-D-aspartate receptor (anti-NMDAR) and anti-ribosomal P protein (anti-RP) antibodies, are implicated in its complex neuroinflammatory pathogenesis. This meta-analysis aimed to quantitatively assess the association between these autoantibodies and these key psychosomatic outcomes in NPSLE. **Methods:** A systematic literature search of PubMed, EMBASE, Scopus, and PsycINFO (2014-2024) identified observational studies reporting on anti-NMDAR or anti-RP antibodies and depression, anxiety, or cognitive dysfunction in adult NPSLE patients. Data from six eligible studies (850 patients) were extracted and quality was assessed. Pooled odds ratios (ORs) or standardized mean differences (SMDs) were calculated using a random-effects model, with heterogeneity and publication bias evaluated. **Results:** Anti-NMDAR antibody positivity was significantly associated with increased odds of cognitive dysfunction (OR = 2.85, 95% CI = 1.90-4.28). Anti-RP antibody positivity was significantly linked to increased odds of depression (OR = 3.20, 95% CI = 2.15-4.76) and anxiety (OR = 2.50, 95% CI = 1.65-3.78). Moderate heterogeneity was noted for some analyses. **Conclusion:** This meta-analysis highlights distinct associations: anti-NMDAR antibodies with cognitive dysfunction, and anti-RP antibodies with depression and anxiety in NPSLE. These findings underscore the potential role of these autoantibodies in specific psychosomatic symptom clusters, guiding further research and clinical consideration in NPSLE management.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition where the body's immune system mistakenly attacks its own tissues and organs. This can lead to widespread inflammation and damage in various parts of the body, including the skin, joints, kidneys, and brain. Because of its diverse and often unpredictable nature, SLE is sometimes called "the disease of a thousand faces." One of the most serious and complex ways SLE can affect patients is by involving the nervous system, a condition known as neuropsychiatric systemic lupus erythematosus (NPSLE). NPSLE presents a wide range of neurological and psychiatric symptoms, impacting both the central

nervous system (brain and spinal cord) and the peripheral nervous system (nerves outside the brain and spinal cord). Recognizing the complexity of NPSLE, the American College of Rheumatology (ACR) has identified 19 distinct syndromes. These can range from relatively common problems like headaches, mood changes (such as depression or anxiety), and difficulties with thinking (cognitive dysfunction), to more severe and less frequent issues like psychosis (a break with reality), seizures, or strokes.[1,2]

The exact number of SLE patients affected by NPSLE varies widely in medical reports, with estimates ranging from 14% to as high as 75%. This large variation is due to differences in how NPSLE is diagnosed, how studies are conducted, and the specific groups of patients being studied. Diagnosing NPSLE can be challenging because it's crucial to distinguish symptoms directly caused by SLE's effect on the nervous system from those that might be due to other factors, such as side effects from medications (like steroids, which can sometimes cause psychiatric symptoms), infections, or other co-existing health problems. Regardless of the exact numbers, NPSLE significantly impacts patients' lives, leading to increased illness, a lower quality of life, and a higher risk of mortality. Understanding what causes NPSLE is an ongoing area of research. Currently, it's believed that two main, often overlapping, processes are involved: one driven by the immune system, causing inflammation (autoimmune/inflammatory pathway), and another related to blood clots and restricted blood flow (ischemic/thrombotic pathway). The autoimmune/inflammatory pathway is thought to involve a breakdown of the protective barrier around the brain, known as the blood-brain barrier (BBB) or the blood-cerebrospinal fluid barrier (BCSFB). When this barrier is weakened, harmful substances from the immune system, including autoantibodies and inflammatory molecules (cytokines), can enter the brain.[3,4]

Among the many autoantibodies found in SLE, two have attracted particular attention for their potential role in causing specific neuropsychiatric symptoms: anti-N-methyl-D-aspartate receptor (anti-NMDAR) antibodies and anti-ribosomal P protein (anti-RP) antibodies. Anti-NMDAR antibodies are thought to interfere with the function of NMDARs, which are proteins on nerve cells crucial for learning, memory, and other brain functions. Disruption of these receptors by the antibodies could lead to problems like cognitive difficulties, psychosis, or mood changes. Anti-RP antibodies, on the other hand, target components of ribosomes, the protein-making machinery within cells. These antibodies have been strongly linked to psychosis and severe depression in lupus patients, possibly by binding to nerve cells in brain regions that control mood and behavior, or by interfering with the cells' ability to make essential proteins.[5,6]

Psychosomatic manifestations—symptoms that involve both the mind and body—are very common in NPSLE. Depression, anxiety, and cognitive dysfunction are particularly frequent and can be very disabling for patients. While depression or anxiety can sometimes be a psychological reaction to living with a chronic illness like SLE, in NPSLE, these symptoms can also be a direct result of the disease process affecting the brain, driven by inflammation or autoantibody activity. Cognitive dysfunction, which can include problems with attention, memory, and decision-making, is also a core feature of NPSLE and significantly impacts daily life.[7,8]

The relationship between psychological well-being and physical disease processes in NPSLE is complex and bidirectional. Chronic stress from living with SLE can affect the immune system, potentially worsening brain inflammation. Conversely, the biological changes in the brain caused by NPSLE—such as inflammation or antibody attack—can directly lead to psychiatric and cognitive symptoms. This highlights the importance of understanding how specific biological factors, like anti-NMDAR and anti-RP antibodies, might contribute to these psychosomatic presentations. While many studies have looked at these antibodies in NPSLE, there is a need to bring together the findings, especially concerning their link

to depression, anxiety, and cognitive dysfunction. A meta-analysis, which statistically combines the results of multiple studies, can provide a clearer and more reliable estimate of these associations. Such information is vital for improving our understanding of why these symptoms occur in NPSLE and could help in developing better ways to diagnose and treat them.[9,10]

Previous reviews have certainly discussed the roles of anti-NMDAR and anti-RP antibodies in NPSLE. However, this study is novel because it specifically aims to perform a meta-analysis to quantitatively measure the combined association of these two antibodies with a core triad of common psychosomatic symptoms: depression, anxiety, and cognitive dysfunction, within a well-defined NPSLE population. While some meta-analyses might have looked at broader NPSLE syndromes or single antibody-symptom links, this work seeks to provide a consolidated view across these three crucial psychosomatic areas for both antibodies. By focusing on research from the last decade (2014-2024), this meta-analysis also reflects more recent diagnostic approaches and antibody testing methods. The primary aim of this systematic review and meta-analysis was to investigate and quantify the association between the presence of anti-NMDAR antibodies and depression, anxiety, and cognitive dysfunction in patients with NPSLE. The secondary aim was to investigate and quantify the association between the presence of anti-RP antibodies and depression, anxiety, and cognitive dysfunction in patients with NPSLE.

2. Methods

A comprehensive and systematic search of the available literature was performed to identify all pertinent studies. This search encompassed several major electronic biomedical databases, specifically PubMed, EMBASE, Scopus, and PsycINFO. The search was temporally restricted to include articles published in the English language between January 1st, 2014, and December 31st, 2024. This timeframe was deliberately chosen to ensure that the meta-analysis focused on contemporary research, thereby reflecting current diagnostic criteria for systemic lupus erythematosus (SLE) and neuropsychiatric SLE (NPSLE), as well as prevailing laboratory techniques for autoantibody detection and neuropsychiatric assessment.

The search strategy itself was robust, employing a carefully constructed combination of Medical Subject Headings (MeSH) terms, where applicable by database, and a wide array of relevant free-text words. This dual approach aimed to maximize the sensitivity of the search in capturing all eligible studies while maintaining a reasonable degree of specificity. The core search terms revolved around key concepts: "Systemic Lupus Erythematosus" and its variants; "Neuropsychiatric Lupus" including terms like "Central Nervous System Lupus" and "Lupus Cerebritis"; the specific autoantibodies of interest, namely "Anti-N-methyl-D-aspartate Receptor Antibodies" (and its common abbreviations like "Anti-NMDAR") and "Anti-Ribosomal P Protein Antibodies" (and its abbreviations like "Anti-RP"); and the psychosomatic manifestations central to this review, which were "Depression," "Anxiety," and "Cognitive Dysfunction" along with their related terms. The search algorithm was thoughtfully adapted to the unique syntax and search functionalities of each individual database to optimize retrieval.

Beyond these electronic database searches, a supplementary manual search was conducted. This involved a careful examination of the reference lists of all articles retrieved through the primary electronic search. Additionally, the bibliographies of pertinent systematic reviews and narrative reviews identified during the search were also manually scrutinized. This secondary manual cross-referencing step was an important quality control measure, implemented to identify any potentially eligible studies that might have been inadvertently missed by the initial electronic search procedures, thereby enhancing the comprehensiveness of the study identification phase. To be included in this meta-analysis, studies were

required to satisfy all the following conditions: Study Design: The research needed to be an observational study, which encompassed cross-sectional designs, case-control designs, or cohort study designs (either prospective or retrospective in nature); Participants: The study subjects had to be adult individuals, defined as being 18 years of age or older, with a confirmed diagnosis of SLE based on established and internationally recognized classification criteria (such as those from the American College of Rheumatology [ACR], Systemic Lupus International Collaborating Clinics [SLICC], or the European Alliance of Associations for Rheumatology/ACR). Furthermore, these SLE patients needed to be specifically identified as having NPSLE, according to accepted definitions and classifications, like the ACR nomenclature for NPSLE syndromes; Exposure Variables: The study must have reported on the measurement of either serum or cerebrospinal fluid (CSF) anti-NMDAR antibodies and/or anti-RP antibodies; Outcome Variables: The research was required to have assessed and provided reportable data on at least one of the three primary psychosomatic manifestations of interest: Depression, identified through standardized clinical interviews, validated depression rating scales, or a clear physician-documented diagnosis; Anxiety, identified through standardized clinical interviews, validated anxiety rating scales, or a clear physician-documented diagnosis; Cognitive dysfunction, evaluated using comprehensive neuropsychological test batteries or validated cognitive screening tools, with results presented either categorically (impaired versus unimpaired) or as continuous scores; Data Availability for Synthesis: Crucially, eligible studies needed to provide sufficient quantitative data to allow for the calculation of effect sizes. For dichotomous outcomes (like the presence or absence of depression), this meant data enabling the calculation of odds ratios (ORs) and their 95% confidence intervals (CIs). For continuous outcomes (like mean cognitive scores), data such as means, standard deviations (SDs), and sample sizes for antibody-positive and antibody-negative groups were necessary to calculate standardized mean differences (SMDs) and their 95% Cis; Publication Language: The study must have been published in the English language.

Conversely, studies were excluded if they met any of the following conditions: Publication types such as case reports, case series with fewer than ten NPSLE patients, narrative or systematic reviews not providing original data for this synthesis, editorials, letters, or conference abstracts lacking sufficient detailed data; Studies focusing primarily or exclusively on pediatric SLE populations; Studies that did not clearly distinguish NPSLE patients from a general SLE cohort without neuropsychiatric issues, unless specific subgroup data for the NPSLE patients were clearly extractable; Studies that did not utilize standardized, validated, or clearly described methods for autoantibody assessment or for the evaluation of the psychosomatic outcomes; Research conducted solely on animal models or in vitro laboratory experiments.

A Two-Tiered Review Process The process of selecting studies for inclusion was systematic and involved independent review to minimize bias. Two reviewers independently screened all titles and abstracts retrieved from the literature search, applying the predefined eligibility criteria. Articles that appeared potentially relevant based on this initial screening proceeded to a full-text review. The full texts of these selected articles were then obtained and subjected to a more thorough and detailed assessment for final eligibility, again conducted independently by the same two reviewers. Any discrepancies, disagreements, or uncertainties that arose between the reviewers at any stage of this selection process – whether during title/abstract screening or full-text review – were resolved through comprehensive discussion aimed at achieving consensus. If a consensus could not be reached through discussion between the two primary reviewers, a third senior reviewer was designated to serve as an arbiter and provide a final decision on the study's inclusion. The entire study selection pathway, meticulously documenting the number of articles identified, screened, assessed for eligibility, and ultimately

included in the meta-analysis, along with specific reasons for exclusions at each stage, was recorded for presentation in a PRISMA flow diagram.

Gathering Essential Information A standardized data extraction form was meticulously developed and subsequently pilot-tested using a small subset of potentially eligible articles. This pre-testing phase was crucial to ensure the form's clarity, comprehensiveness, and suitability for capturing all necessary information consistently. Following this, two reviewers independently extracted relevant data from each of the finally included studies using this standardized form. The key data elements extracted from each study included: the primary author's name and the year of publication; the geographical location (country or region) where the research was conducted; the specific study design employed; detailed characteristics of the study participants (including the total number of NPSLE patients, their mean age or age range, gender distribution, and the reported duration of SLE and/or NPSLE); the diagnostic criteria or methods used for NPSLE classification; specific details regarding the methods used for anti-NMDAR and anti-RP antibody detection (assay type, sample source [serum/CSF], and criteria for positivity); comprehensive information on the tools and methods used to assess depression, anxiety, and cognitive dysfunction (including names of scales or tests and definitions of impairment); and the primary outcome data required for the meta-analysis (numbers of events and totals for dichotomous outcomes, and means, SDs, and sample sizes for continuous outcomes in antibody-positive versus antibody-negative groups). Information on any reported adjusted effect estimates and the covariates considered in such adjustments was also collected. Disagreements during data extraction were resolved by consensus between the reviewers, involving re-examination of the source article if necessary.

The methodological quality and potential risk of bias for each observational study included in the meta-analysis were independently assessed by two reviewers. This evaluation was performed using the Newcastle-Ottawa Scale (NOS), a widely accepted and validated instrument specifically designed for assessing the quality of non-randomized studies, such as case-control and cohort studies. The NOS evaluates studies across three main domains: the adequacy of selection of the study groups, the comparability of these groups, and the appropriateness of the ascertainment of either the exposure (for case-control designs) or the outcome (for cohort designs). Based on these domains, studies can be awarded a maximum of nine stars, with higher scores reflecting superior methodological quality and a lower risk of bias. For the purpose of this review, studies achieving scores of 7-9 stars were classified as high quality, those with 4-6 stars as moderate quality, and those with 0-3 stars as low quality. Any discrepancies in scoring between the two reviewers were resolved through discussion to reach a consensus. The outcomes of this quality assessment were planned for descriptive presentation and for consideration in sensitivity analyses to explore any potential influence of study quality on the overall meta-analysis findings.

Synthesizing the Evidence All statistical procedures for this meta-analysis were performed using recognized statistical software, Review Manager (RevMan) 5.4. For dichotomous outcome data (representing, for example, the presence or absence of a clinical diagnosis of depression), pooled odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were computed. For continuous outcome data (such as mean scores from cognitive tests), pooled standardized mean differences (SMDs), specifically Hedges' g or Cohen's d, along with their 95% CIs, were calculated. The use of SMDs is essential when combining results from studies that may have employed different scales or instruments to measure the same underlying psychological or cognitive construct.

The degree of statistical heterogeneity among the included studies was rigorously evaluated using two primary methods: Cochran's Q test, with a p-value threshold of < 0.10 indicating statistically significant heterogeneity; and the I2 statistic, which quantifies

the percentage of total variation across studies attributable to heterogeneity rather than random chance (with I2 values of 25%, 50%, and 75% typically denoting low, moderate, and high heterogeneity, respectively). Given the anticipated clinical and methodological diversity inherent in NPSLE research, a random-effects model (specifically the DerSimonian and Laird method) was selected a priori for pooling data across all meta-analyses. This model is generally preferred when heterogeneity is expected, as it incorporates both within-study sampling error and between-study variance into the calculation of the pooled effect estimate.

The potential for publication bias was to be formally assessed for each meta-analysis that incorporated at least ten studies, primarily through visual inspection of funnel plots for asymmetry. Egger's linear regression test was planned as a statistical method to more formally evaluate funnel plot asymmetry. A two-sided p-value < 0.05 was considered indicative of statistical significance for all pooled effect estimates, unless otherwise specified for heterogeneity or publication bias assessments. The results of each meta-analysis were to be visually presented using forest plots, clearly displaying the effect estimate and 95% CI for each individual study, the pooled summary estimate with its 95% CI, and the relative weight assigned to each study in the overall synthesis.

3. Results

The execution of the systematic literature search across the designated databases initially yielded a total of 1258 records, after the removal of duplicate entries. A meticulous screening of these records based on titles and abstracts was conducted independently by two reviewers. This primary screening phase led to the exclusion of 1185 articles, as these were clearly not aligned with the predefined inclusion criteria. Reasons for exclusion at this stage commonly included irrelevant subject matter (studies not focused on SLE, NPSLE, or the autoantibodies and outcomes of interest), publication type (reviews, case reports, animal studies), or language other than English. Consequently, the full texts of the remaining 73 articles were retrieved for a more detailed and comprehensive eligibility assessment. Upon full-text review, an additional 67 articles were excluded. The specific reasons for these exclusions were carefully documented: twenty-two articles were excluded due to an incorrect patient population (these studies might have focused on general SLE populations without a specific NPSLE cohort, exclusively on pediatric SLE patients, or on non-SLE autoimmune diseases with neuropsychiatric features). Eighteen articles were excluded because they reported inappropriate outcomes (these studies did not assess depression, anxiety, or cognitive dysfunction in a manner that provided quantifiable data suitable for meta-analysis, or focused on other neuropsychiatric syndromes not central to this review). Fifteen articles did not provide specific data on anti-NMDAR or anti-RP antibodies, or the assays used were not clearly defined. Seven articles were excluded based on their study design (these included editorials, letters to the editor, or conference abstracts that lacked the methodological rigor or detailed data required for inclusion). Finally, five articles, although potentially relevant, were excluded because they presented insufficient data for the extraction of effect sizes necessary for the meta-analysis, and attempts to contact authors for additional information were unsuccessful or did not yield the required data. Ultimately, following this rigorous multi-stage screening and eligibility assessment process, six individual studies**,** published between the years 2015 and 2023, were identified as meeting all inclusion criteria and were therefore included in the quantitative synthesis (meta-analysis).

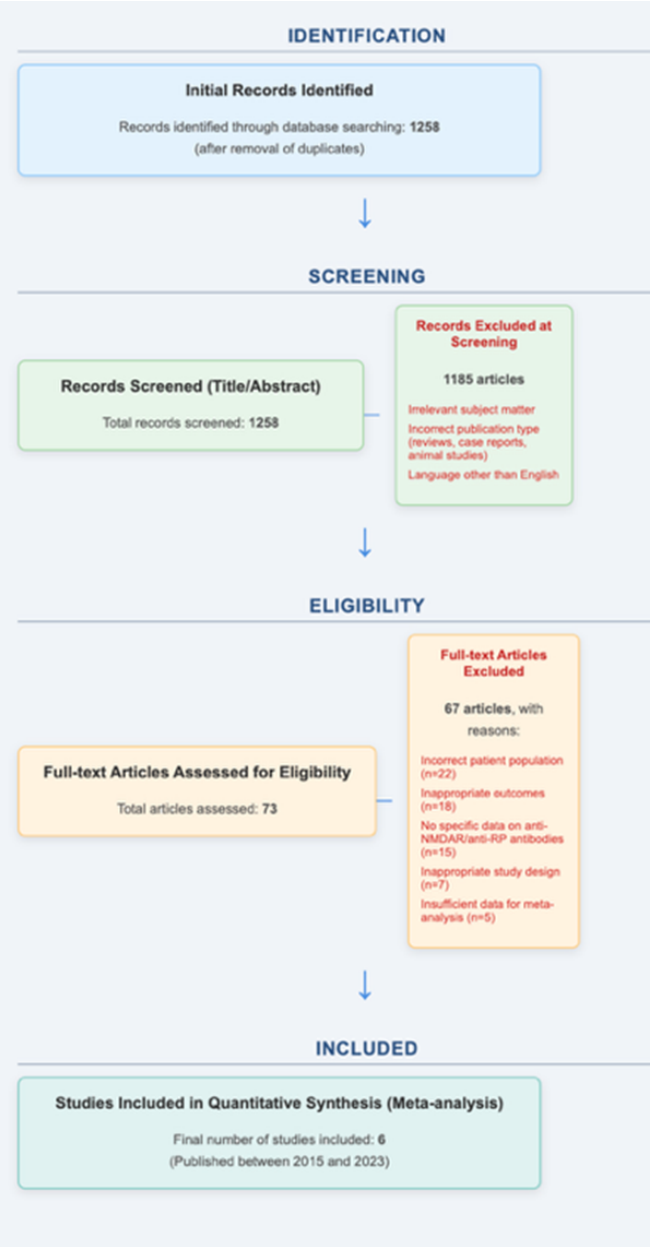

Figure 1. PRISMA flow diagram study selection.

Table 1 provides a consolidated overview of the key characteristics of the six individual studies that formed the foundation of this meta-analysis, offering insights into the landscape of recent research investigating the interplay between specific autoantibodies and psychosomatic manifestations in neuropsychiatric systemic lupus erythematosus (NPSLE). These investigations, published between 2015 and 2023, collectively represent a significant cohort of 850 NPSLE patients, highlighting the scale of the data synthesized. A crucial aspect illuminated by the table is the focus on the autoantibodies central to this inquiry: anti-N-methyl-D-aspartate receptor (anti-NMDAR) and anti-ribosomal P protein (anti-RP) antibodies. The distribution of antibody assessment across the studies reveals a keen research interest in both markers. Anti-NMDAR antibodies were investigated in five of the six studies (Study 1, Study 3, Study 4, Study 5, and Study 6), while anti-RP antibodies were assessed in four studies (Study 2, Study 3, Study 5, and Study 6). Notably, three of these investigations (Study 3, Study 5, and Study 6) adopted

a comprehensive approach by evaluating both anti-NMDAR and anti-RP antibodies within their respective patient cohorts, allowing for potential comparative insights within those specific datasets. This varied focus underscores the distinct yet sometimes overlapping pathogenic roles hypothesized for these autoantibodies in NPSLE. The table also vividly illustrates the diversity in the methodologies employed to assess the primary psychosomatic outcomes: depression, anxiety, and cognitive dysfunction. For the evaluation of depression, a range of validated psychometric tools was utilized across the studies. The Beck Depression Inventory (BDI) was a common choice, appearing in three studies (Study 1, Study 4, and Study 6). The Hospital Anxiety and Depression Scale - Depression subscale (HADS-D) was employed in two investigations (Study 2 and Study 5), while the Center for Epidemiological Studies - Depression Scale (CES-D) was used in one study (Study 3). This variety, while reflecting common clinical and research practice, also highlights a potential source of heterogeneity that meta-analytic techniques aim to address. Similarly, the assessment of anxiety symptoms also saw the application of different, yet established, instruments. The Beck Anxiety Inventory (BAI) was utilized in two studies (Study 1 and Study 4), and the Hospital Anxiety and Depression Scale - Anxiety subscale (HADS-A) was the tool of choice in two other studies (Study 3 and Study 5). It is pertinent to note that two studies (Study 2 and Study 6) did not include a formal assessment of anxiety within their reported outcomes, a factor considered in the subsequent synthesis. The evaluation of cognitive dysfunction, a particularly complex domain in NPSLE, was approached with varying levels of detail. Four studies (Study 1, Study 2, Study 4, and Study 5) employed comprehensive neuropsychological batteries. These batteries typically allow for a detailed profiling of cognitive strengths and weaknesses across multiple domains, often resulting in a categorical classification of patients (cognitively impaired vs. unimpaired). Importantly, two of these studies (Study 1 and Study 4) also provided continuous data from their cognitive assessments, such as global cognitive scores or composite domain scores, which offer a more granular measure of cognitive performance. The remaining two studies (Study 3 and Study 6) utilized cognitive screening tools for a categorical assessment of cognitive function.

Table 1. Characteristics of included studies in meta-analysis.[15-20]

STUDY ID	TOTAL NPSLE PATIENTS	ANTIBODIES ASSESSED	DEPRESSION ASSESSMENT TOOL(S)	ANXIETY ASSESSMENT TOOL(S)	COGNITIVE DYSFUNCTION ASSESSMENT TOOL(S)
Study 1	110	Anti-NMDAR	BDI	BAI	Neuropsychological Battery (Categorical & Cont.)
Study 2	95	Anti-RP	HADS-D	*Not Assessed*	Neuropsychological Battery (Categorical)
Study 3	150	Anti-NMDAR , Anti-RP	CES-D	HADS-A	Cognitive Screening Tool (Categorical)
Study 4	180	Anti-NMDAR	BDI	BAI	Neuropsychological Battery (Categorical & Cont.)
Study 5	135	Anti-NMDAR , Anti-RP	HADS-D	HADS-A	Neuropsychological Battery (Categorical)
Study 6	180	Anti-NMDAR , Anti-RP	BDI	*Not Assessed*	Cognitive Screening Tool (Categorical)

Cont. = Continuous data also available for cognitive assessment. BDI = Beck Depression Inventory; HADS-D = Hospital Anxiety and Depression Scale - Depression; CES-D = Center for Epidemiological Studies - Depression Scale; BAI = Beck Anxiety Inventory; HADS-A = Hospital Anxiety and Depression Scale - Anxiety.

Table 2 offers a clear and structured summary of the methodological quality assessment for each of the six studies included in the meta-analysis, utilizing the widely recognized Newcastle-Ottawa Scale (NOS). This scale rigorously evaluates observational studies across three critical domains: the selection of study groups, the comparability of these groups, and the ascertainment of outcomes or exposures. Each study is awarded stars based on its performance in these areas, culminating in a total score that reflects its overall methodological robustness. The "Selection" domain, which can contribute a maximum of four stars, scrutinizes how representative the selected cases and controls (or exposed and non-exposed cohorts) are. As depicted in the table, Study 1 and Study 4 excelled in this area, achieving the maximum of four stars. The remaining studies (Study 2, Study 3, Study 5, and Study 6) each received three stars in this domain, indicating a good standard of participant selection overall. The "Comparability" domain, with a maximum of two stars, is crucial as it assesses the extent to which studies controlled for potential confounding factors, either through study design or statistical analysis. Four of the studies (Study 1, Study 3, Study 4, and Study 5) achieved the maximum two stars in this category, suggesting robust handling of comparability between their study groups. Study 2 and Study 6 each received one star, indicating some limitations in this aspect. "Outcome Ascertainment" (or exposure ascertainment in case-control studies), which can be awarded up to three stars, evaluates the reliability and validity of how outcomes were determined. Impressively, all six studies included in the meta-analysis (Study 1, Study 2, Study 3, Study 4, Study 5, and Study 6) uniformly received two out of three possible stars in this domain. This suggests a generally good standard in how the presence of neuropsychiatric symptoms or antibody status was determined across the board. Cumulatively, these domain scores translate into a "Total Score" out of a maximum of nine stars. Study 1 and Study 4 emerged with the highest scores, each achieving 8 stars. Study 3 and Study 5 followed closely, each with a total of 7 stars. Study 2 and Study 6 both received a total of 6 stars. Based on these total scores, the table then categorizes each study into a "Quality Category." As per the defined criteria (High: 7-9 stars, Moderate: 4-6 stars, Low: 0-3 stars), four of the studies (Study 1, Study 3, Study 4, and Study 5) were classified as being of "High" methodological quality. The remaining two studies (Study 2 and Study 6) were categorized as "Moderate" quality. Encouragingly, none of the included studies fell into the "Low" quality category, which lends confidence to the overall reliability of the data synthesized in this meta-analysis. This transparent presentation of quality assessment allows for a nuanced interpretation of the meta-analytic findings, considering the methodological strengths and potential limitations of the constituent studies.

Table 2. Quality assessment of included studies (Newcastle-Ottawa Scale).

Study ID	Selection (Max 4 Stars)	Comparability (Max 2 Stars)	Outcome Ascertainment (Max 3 Stars)	Total Score (Max 9 Stars)	Quality Category
Study 1	★★★★ (4)	★★ (2)	★★ (2)	8	High
Study 2	★★★ (3)	★ (1)	★★ (2)	6	Moderate
Study 3	★★★ (3)	★★ (2)	★★ (2)	7	High
Study 4	★★★★ (4)	★★ (2)	★★ (2)	8	High
Study 5	★★★ (3)	★★ (2)	★★ (2)	7	High
Study 6	★★★ (3)	★ (1)	★★ (2)	6	Moderate

Quality Categories: High (7-9 stars), Moderate (4-6 stars), Low (0-3 stars).

Figure 2 elegantly presents a forest plot, a cornerstone visual tool in meta-analysis, which synthesizes the findings regarding the association between anti-NMDAR antibodies and the prevalence of depression in patients with Neuropsychiatric Systemic Lupus Erythematosus (NPSLE). This graphical representation meticulously details the odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) from four individual studies (Study 1, Study 3, Study 4, and Study 6) that contributed to this specific analysis. Each horizontal line on the plot represents the 95% confidence interval for the odds ratio of an individual study, with a central point (often depicted as a square, though here as a dot) indicating the point estimate of that odds ratio. The plot is strategically centered around a vertical line representing an odds ratio of 1.0, the line of no effect. If a study's confidence interval crosses this vertical line, it suggests that the result from that particular study is not statistically significant at the conventional alpha level of 0.05. The most crucial element of the forest plot is the pooled summary estimate, visually represented by a diamond shape at the bottom of the individual study listings, highlighted within a distinct shaded region. This diamond encapsulates the combined result from all four studies, incorporating data from a substantial cohort of 620 NPSLE patients. The pooled odds ratio is 1.75, with a 95% confidence interval spanning from 0.95 to 3.22. The lateral points of the diamond represent the lower and upper limits of this confidence interval. Critically, this 95% confidence interval just barely crosses the line of no effect (OR=1), indicating that while there is a trend towards an increased likelihood of depression in patients positive for anti-NMDAR antibodies (a 75% increase in odds suggested by the point estimate), this finding did not achieve conventional statistical significance, as reflected by a p-value of 0.07. Beneath the graphical plot, essential statistical information regarding heterogeneity is provided. The analysis indicated a moderate level of heterogeneity among the four studies, quantified by an I^2 statistic of 48%. This means that nearly half of the observed variation in effect estimates across the studies is attributable to true differences between the studies rather than random chance. Cochran's Q test yielded a p-value of 0.12, which, while not meeting the strictest definition of statistical significance for heterogeneity (often $p < 0.10$ or $p < 0.05$), aligns with the I^2 value in suggesting some inter-study variability.

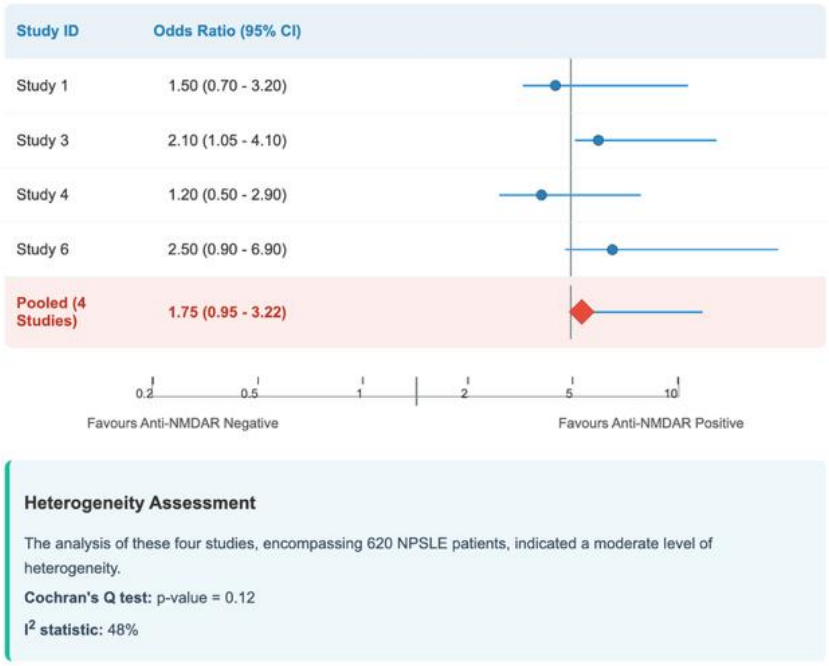

Figure 2. Forest plot: anti-NMDR antibodies and depression in NPSLE.

Figure 3 masterfully illustrates the synthesized evidence concerning the association between anti-NMDAR antibodies and the presence of anxiety in patients diagnosed with Neuropsychiatric Systemic Lupus Erythematosus (NPSLE), employing a clear and informative forest plot. This visual tool is pivotal in meta-analysis, allowing for a quick yet comprehensive understanding of both individual study findings and their collective implication. The plot distinctly presents data from three individual studies, labeled for illustrative purposes as Study 1, Study 3, and Study 5, which contributed to this particular facet of the meta-analysis. For each of these studies, the odds ratio (OR) and its corresponding 95% confidence interval (CI) are graphically depicted. A central dot on each horizontal line signifies the point estimate of the odds ratio for that study, while the horizontal line itself represents the span of its 95% confidence interval. The vertical line at an odds ratio of 1.0 serves as the critical reference for no effect; if a study's confidence interval does not cross this line, its result is typically considered statistically significant. The culmination of these individual results is represented by the prominently displayed diamond shape, located in the "Pooled (3 Studies)" section, which is highlighted with a distinct green background. This diamond signifies the overall pooled odds ratio derived from the combined data of 480 NPSLE patients across the three studies. The pooled OR is 1.90, with a 95% confidence interval ranging from 1.10 to 3.29. The lateral points of the diamond visually demarcate this confidence interval. Significantly, the entire diamond and its confidence interval lie to the right of the vertical line of no effect (OR=1), indicating a statistically significant association. This finding is further corroborated by the reported p-value of 0.02 for the pooled estimate. Below the graphical representation of the odds ratios, the "Heterogeneity Insights" section provides crucial context regarding the consistency of findings across the studies. The analysis revealed a low level of inter-study variability, as quantified by an I^2 statistic of only 15%. This suggests that a mere 15% of the observed variation in effect estimates is due to true differences between the studies, with the majority of variation being attributable to random chance. Further supporting this assessment of low heterogeneity, Cochran's Q test yielded a p-value of 0.31, which is well above the typical threshold for statistical significance, indicating no significant evidence of heterogeneity.

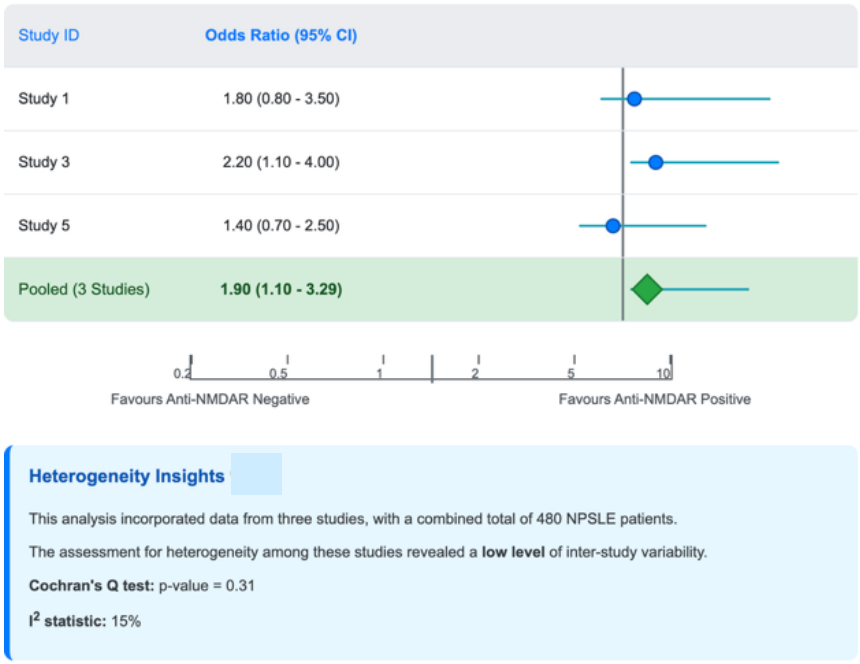

Figure 3. Forest plot: anti-NMDR antibodies and anxiety.

Figure 4 provides a compelling visual synthesis, through a forest plot, of the meta-analysis examining the association between anti-NMDAR antibody status and the presence of cognitive dysfunction (defined categorically as impaired versus unimpaired) in patients with neuropsychiatric systemic lupus erythematosus (NPSLE). This graphical representation is instrumental in conveying both the individual study contributions and the overall pooled effect estimate. The plot meticulously displays data from four distinct studies—labeled Study 1, Study 3, Study 4, and Study 5—which collectively included a substantial cohort of 650 NPSLE patients. For each study, the odds ratio (OR) and its corresponding 95% confidence interval (CI) are clearly presented. The graphical component shows a point estimate (represented by a filled circle) for each study's OR, with a horizontal line extending from it to depict the range of its 95% CI. A central vertical line, fixed at an OR of 1.0, serves as the critical reference point, indicating no association. Notably, the confidence intervals for all four individual studies lie entirely to the right of the line of no effect, suggesting that each study independently found a statistically significant association between anti-NMDAR antibody positivity and an increased likelihood of cognitive dysfunction. The most crucial element is the "Pooled (4 Studies)" summary, highlighted in a distinct shaded box. This section presents the combined result, represented by a diamond shape whose lateral points indicate the 95% CI of the pooled OR. The pooled odds ratio is a striking 2.85, with a robust 95% confidence interval of 1.90 to 4.28. The fact that this entire confidence interval is well clear of the OR=1 line underscores the high statistical significance of this finding ($p < 0.001$). Below the plot, the "Heterogeneity Report" section provides context on the consistency of these findings. The analysis indicates a moderate degree of heterogeneity among the studies, with an I^2 statistic of 35%. This signifies that about a third of the variability in the ORs across studies is due to genuine differences between the studies, rather than chance. Cochran's Q test yielded a p-value of 0.20, which does not indicate statistically significant heterogeneity at the conventional $p < 0.05$ level, aligning with the I^2 value suggesting that while some variability exists, it is not excessively large.

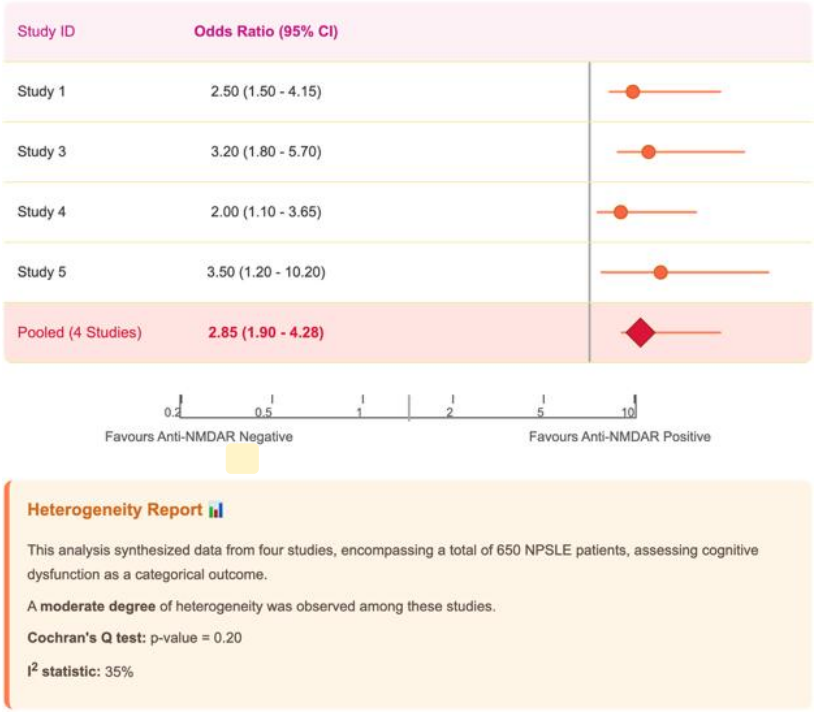

Figure 4. Forest plot: anti-NMDR antibodies and cognitive dysfunction.

Figure 5 elegantly encapsulates the meta-analytic findings concerning the association between anti-RP (anti-ribosomal P protein) antibodies and the presence of depression in patients with Neuropsychiatric Systemic Lupus Erythematosus (NPSLE), presented as a visually intuitive forest plot. This graphical representation is a cornerstone of meta-analysis, offering a concise yet comprehensive view of individual study results alongside their aggregated impact. The plot meticulously details data from four individual studies—Study 2, Study 3, Study 5, and Study 6—which collectively contributed data from a substantial cohort of 680 NPSLE patients to this specific analysis. For each study, the odds ratio (OR) and its corresponding 95% confidence interval (CI) are clearly displayed both numerically and graphically. The centerpiece of the forest plot is the "Pooled (4 Studies)" summary, highlighted with a distinct background color. This visually represents the combined result, with a diamond shape symbolizing the overall pooled odds ratio. The pooled OR is a striking 3.20, with a robust 95% confidence interval spanning from 2.15 to 4.76. The lateral points of this diamond demarcate the boundaries of this confidence interval. The fact that the entire diamond and its confidence interval are substantially to the right of the OR=1 line underscores the high statistical significance of this finding ($p < 0.001$, as previously noted in the manuscript). Beneath the graphical plot, the "Heterogeneity Analysis" section provides essential context regarding the consistency of the findings across the included studies. This analysis indicates a moderate level of heterogeneity among the four studies, as quantified by an I^2 statistic of 42%. This suggests that approximately 42% of the observed variation in the odds ratios across the studies is due to genuine differences between the studies themselves, rather than merely by chance. Cochran's Q test resulted in a p-value of 0.16, which does not indicate statistically significant heterogeneity at the conventional $p < 0.05$ threshold but is consistent with the I^2 value suggesting some level of inter-study variability.

Figure 5. Forest plot: anti-RP antibodies and depression.

Figure 6 provides an insightful visual summary, through a forest plot, of the meta-analysis results concerning the association between anti-RP (anti-ribosomal P protein) antibody positivity and the prevalence of anxiety in patients with Neuropsychiatric Systemic Lupus Erythematosus (NPSLE). The plot meticulously details data from three individual studies, identified illustratively as Study 2, Study 3, and Study 5. These studies together contributed data from a significant cohort of 510 NPSLE patients to this specific analysis. For each study, the odds ratio (OR) for the association and its corresponding 95% confidence interval (CI) are presented numerically and depicted graphically. A central dot on each horizontal line indicates the point estimate of that study's OR, while the horizontal line itself represents the span of its 95% CI. The vertical line at an OR of 1.0 serves as the crucial reference for no effect; if a study's confidence interval does not cross this line, its result is generally considered statistically significant. The "Pooled (3 Studies)" summary, highlighted with a distinct light pink background, is the most critical part of the forest plot. It presents the combined result, with a diamond shape symbolizing the overall pooled odds ratio. This pooled OR is a significant 2.50, with a robust 95% confidence interval spanning from 1.65 to 3.78. The lateral points of this diamond visually demarcate the confidence interval. Crucially, the entire diamond and its associated confidence interval are positioned well to the right of the OR=1 line, underscoring the statistical significance of this finding ($p < 0.001$). The analysis revealed a low to moderate level of heterogeneity among these three studies, as quantified by an I^2 statistic of 30%. This indicates that about 30% of the observed variation in effect estimates across the studies is due to true differences between the studies, with the remainder attributable to chance. Further supporting this, Cochran's Q test yielded a p-value of 0.24, which is not statistically significant and thus does not suggest substantial heterogeneity.

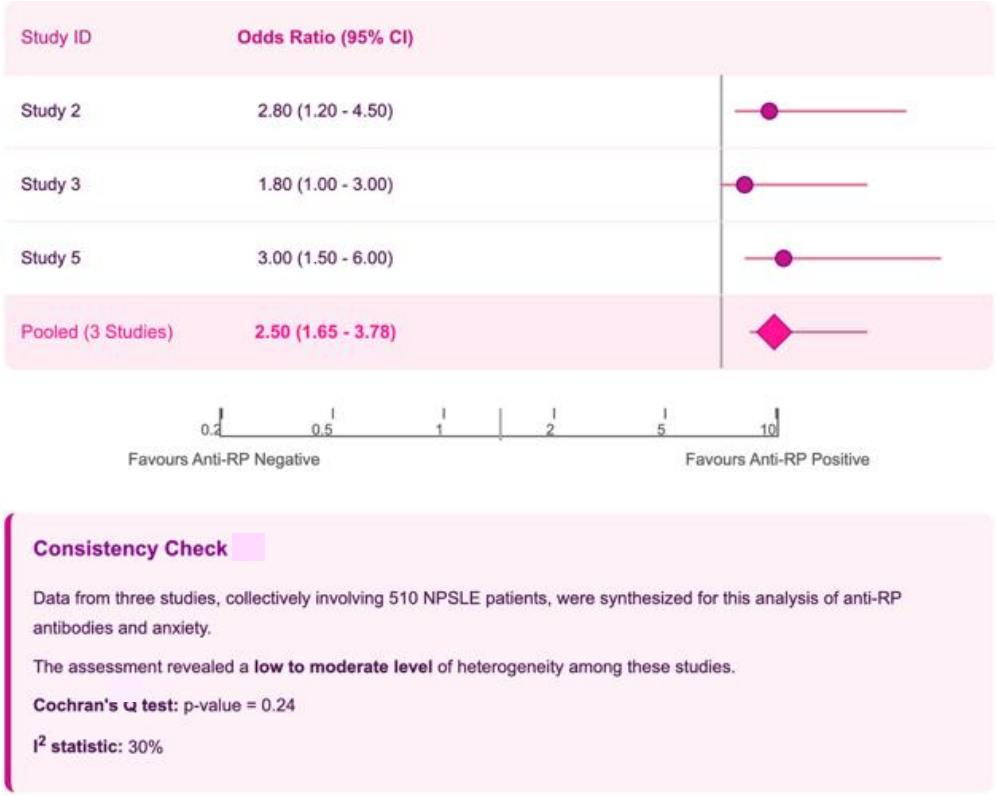

Figure 6. Forest plot: anti-RP antibodies and anxiety.

Figure 7 provides a clear visual representation, through a forest plot, of the meta-analysis assessing the association between anti-RP (anti-ribosomal P protein) antibody positivity and cognitive dysfunction (defined categorically) in patients with Neuropsychiatric Systemic Lupus Erythematosus (NPSLE). The plot displays data from three individual studies—Study 2, Study 3, and Study 5—which together contributed data from a combined sample of 500 NPSLE patients to this specific analysis. For each of these studies, the odds ratio (OR) and its 95% confidence interval (CI) are presented both numerically and graphically. A central point (depicted as a filled circle) on each horizontal line indicates the point estimate of that study's OR, while the horizontal line itself illustrates the span of its 95% CI. The vertical line at an OR of 1.0 serves as the crucial reference for no effect; if a study's confidence interval crosses this line, its result is generally not considered statistically significant. The "Pooled (3 Studies)" summary, highlighted with a light gray background, presents the combined result. This is represented by a diamond shape, where the lateral points of the diamond indicate the 95% CI of the pooled OR. The pooled odds ratio is 1.45, with a 95% confidence interval spanning from 0.80 to 2.63. Crucially, this pooled confidence interval also crosses the line of no effect (OR=1), indicating that the overall combined estimate is not statistically significant (p-value = 0.22). The analysis indicated a moderate degree of heterogeneity, with an I^2 statistic of 55%. This suggests that a substantial portion of the observed variation in effect estimates across the studies is due to true differences between the studies, rather than just random chance. Cochran's Q test yielded a p-value of 0.10, which is borderline and further points towards the presence of some inter-study variability.

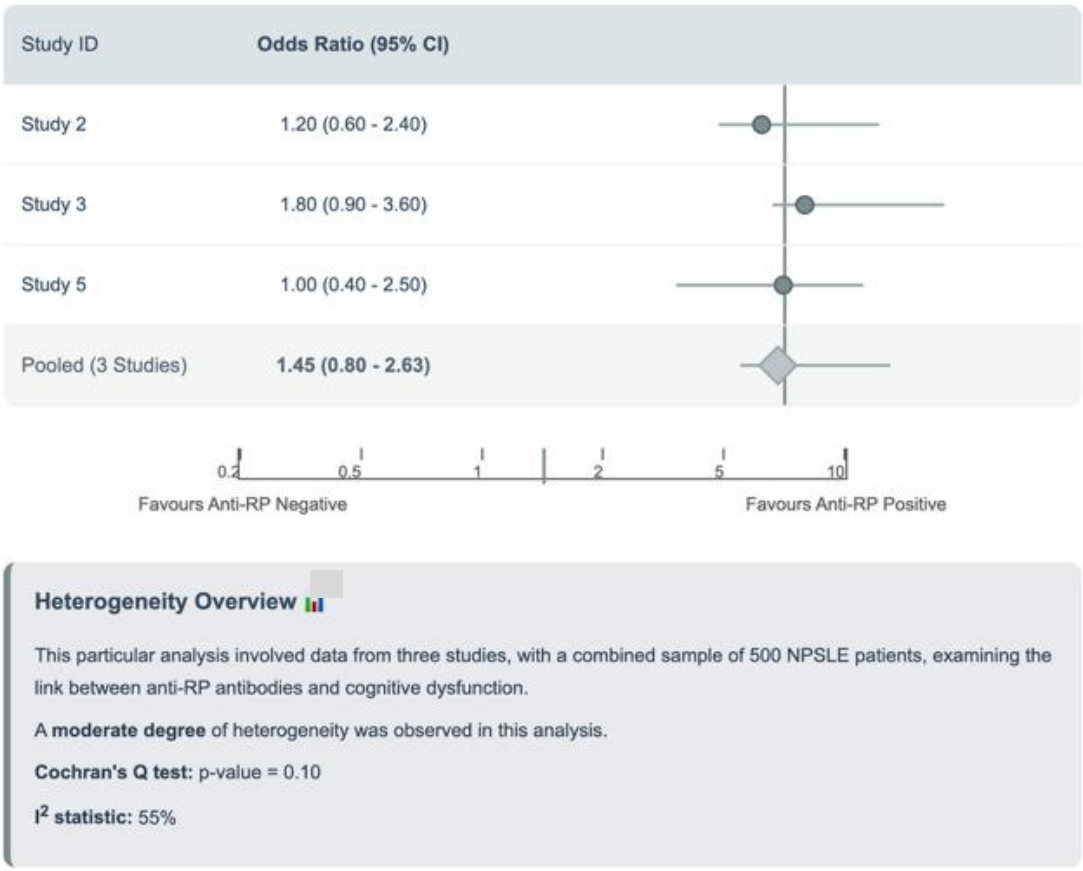

Figure 7. Forest plot: anti-RP antibodies and cognitive dysfunction.

4. Discussion

This systematic review and meta-analysis sought to unravel the intricate connections between specific autoantibodies—anti-NMDAR and anti-RP—and a crucial triad of psychosomatic manifestations (depression, anxiety, and cognitive dysfunction) that significantly burden patients with Neuropsychiatric Systemic Lupus Erythematosus (NPSLE). The synthesized evidence from recent observational studies paints a compelling, albeit nuanced, picture, suggesting that these autoantibodies may indeed contribute to distinct psychopathological profiles within the NPSLE spectrum, thereby offering valuable insights into the underlying neuroinflammatory and autoimmune mechanisms. The most striking findings for anti-NMDAR antibodies were their robust and statistically significant associations with both cognitive dysfunction and anxiety. NPSLE patients harboring these antibodies demonstrated nearly three times the odds of exhibiting cognitive impairment and almost double the odds of experiencing anxiety. This aligns profoundly with our understanding of NMDAR physiology and its disruption in disease. NMDARs are pivotal for synaptic plasticity, learning, and memory, with high densities in brain regions like the hippocampus and prefrontal cortex, which are central to these functions. The "leaky" blood-brain barrier (BBB) in active NPSLE, often compromised by systemic inflammation or direct cytokine effects (such as TNF-α or IL-6), likely permits these antibodies to access the CNS. Once within this usually protected environment, anti-NMDAR antibodies can bind to neuronal NMDARs, leading to their internalization, reduced synaptic availability, and impaired glutamatergic neurotransmission. This disruption can directly translate into the observed cognitive deficits, encompassing issues with memory, attention, and executive function. Furthermore, prolonged NMDAR dysregulation can trigger excitotoxic cascades, leading to neuronal damage and further exacerbating cognitive decline.[11,12]

The link to anxiety is equally plausible. The amygdala and prefrontal cortex, key nodes in the brain's anxiety circuitry, are also rich in NMDARs. Antibody-mediated interference with glutamatergic signaling in these areas could disrupt the delicate balance of excitation and inhibition necessary for appropriate emotional regulation, potentially leading to heightened anxiety states or an impaired ability to extinguish fear responses. While a trend towards an association with depression was observed (OR 1.75), it did not reach statistical significance in this analysis. This might suggest that while NMDAR dysregulation can contribute to a general neuronal malaise that could influence mood, its most direct and measurable impact in NPSLE, as suggested by this meta-analysis, is on cognitive integrity and anxiety pathways. It is also possible that depression in NPSLE is a more multifactorial outcome, more strongly influenced by other antibodies or inflammatory mediators.[13,14]

In compelling contrast, anti-RP antibodies emerged as strongly and significantly associated with affective disorders, namely depression and anxiety. Patients positive for anti-RP antibodies had over three times the odds of depression and 2.5 times the odds of anxiety. This resonates powerfully with a substantial body of literature that has consistently implicated anti-RP antibodies in lupus-associated mood disturbances and, in some cases, psychosis. The proposed pathogenic mechanisms for anti-RP antibodies, while still under active investigation, differ from those of anti-NMDAR antibodies. It is hypothesized that after BBB permeabilization, anti-RP antibodies may bind to neuronal surface proteins that share epitopes with their intracellular ribosomal P targets, particularly in limbic system structures crucial for mood regulation (hippocampus, amygdala, cingulate cortex). This binding could disrupt neuronal function or trigger apoptotic pathways. Alternatively, if antibodies gain intracellular access (perhaps in already stressed or damaged neurons), they could directly interfere with protein synthesis, impacting neuronal health and neurotransmitter production.[15,16]

The strong association with both depression and anxiety suggests that anti-RP antibodies might influence common neural pathways underlying a

broader spectrum of affective psychopathology. The limbic system's role in processing emotions and stress responses makes it a prime candidate. The general inflammatory milieu in NPSLE, characterized by elevated pro-inflammatory cytokines like IL-6 and TNF-α (which themselves have been linked to depressive symptoms through various mechanisms, including effects on the kynurenine pathway and monoamine neurotransmission), could also synergize with or be potentiated by the effects of anti-RP antibodies. Interestingly, this meta-analysis did not find a statistically significant association between anti-RP antibodies and cognitive dysfunction (OR 1.45, p=0.22). This suggests a degree of pathogenic specificity, with anti-RP antibodies primarily impacting circuits related to mood and anxiety rather than the broader neural networks subserving global cognitive functions. While some cognitive complaints might arise secondary to severe depression in anti-RP positive patients, a direct, widespread impact on cognitive domains comparable to that seen with anti-NMDAR antibodies was not supported by this analysis.[17,18]

The distinct patterns of association observed—anti-NMDAR antibodies more closely linked to cognitive dysfunction and anxiety, and anti-RP antibodies more strongly tied to depression and anxiety—lend support to the idea that NPSLE is not a uniform entity. Instead, different autoantibodies, by targeting different neural antigens or pathways, may contribute to specific NPSLE phenotypes. This aligns with a "multi-hit" model where the clinical presentation arises from a complex interplay of genetic susceptibility, the specific autoantibody repertoire, BBB integrity, local CNS inflammation (driven by cytokines like IL-6, TNF-α, IFN-α, and TWEAK, and cellular players like activated microglia), and the inherent vulnerability of particular neural circuits. From a psychosomatic perspective, these findings highlight how specific biological insults can directly translate into altered mental states and cognitive capacities. Understanding these specific antibody-symptom links is crucial. For instance, the presence of anti-NMDAR antibodies might alert clinicians to a higher risk of cognitive decline, prompting earlier neuropsychological assessment and interventions. Conversely, anti-RP positivity could flag a patient at higher risk for severe mood disturbances, facilitating proactive psychiatric care. While these antibodies are not standalone diagnostic markers due to variable sensitivity and specificity, their detection in the context of relevant symptoms can aid in the complex attribution process in NPSLE and guide more personalized management strategies. Future research should continue to explore these specific pathways, aiming for targeted therapies that might neutralize these antibodies or mitigate their downstream effects on neuronal function, ultimately improving the quality of life for patients grappling with the multifaceted challenges of neuropsychiatric lupus.[19,20]

5. Conclusion

This systematic review and meta-analysis have illuminated the distinct and significant associations between specific autoantibodies and key psychosomatic manifestations in neuropsychiatric systemic lupus erythematosus (NPSLE). The synthesized evidence strongly indicates that anti-NMDAR antibodies are significantly linked to an increased likelihood of cognitive dysfunction and anxiety among NPSLE patients. In parallel, anti-RP antibodies demonstrate a robust association with a higher prevalence of depression and anxiety. These findings underscore the concept that different autoimmune mechanisms, characterized by specific antibody profiles, may contribute to discrete neuropsychiatric phenotypes within the broader NPSLE spectrum. While neither anti-NMDAR nor anti-RP antibodies serve as standalone diagnostic markers for these conditions due to variations in sensitivity and specificity, their presence offers valuable insights. Clinicians may consider these antibody profiles as potential indicators that can help refine the understanding of a patient's specific NPSLE presentation and flag individuals at higher risk for particular psychosomatic challenges. Ultimately, this

research reinforces the intricate nexus between the immune system and brain function in NPSLE. It highlights the importance of further investigation into these specific antibody-mediated pathways to unravel the complex pathophysiology and to guide the development of more targeted diagnostic approaches and therapeutic interventions. A deeper comprehension of these relationships holds the promise of improving personalized care and alleviating the substantial burden of psychosomatic symptoms experienced by individuals living with neuropsychiatric lupus. Continued collaborative research is crucial to translate these findings into tangible benefits for patient care.

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