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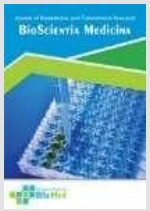

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# Unraveling the Pathways: A Meta-Analysis Exploring the Biopsychosocial Mechanisms Linking Psychosomatic Symptoms and Systemic Lupus Erythematosus

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**A B S T R A C T**

**Background:** Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a complex interplay of biological, psychological, and social factors. Psychosomatic symptoms, such as depression, anxiety, and stress, are common in individuals with SLE and can significantly impact disease activity and overall well-being. This meta-analysis aims to explore the biopsychosocial mechanisms linking psychosomatic symptoms and SLE. **Methods:** A systematic search of PubMed, Embase, PsycINFO, and Web of Science databases was conducted from January 2013 to December 2024. Studies examining the relationship between psychosomatic symptoms and SLE were included. Data were extracted and analyzed using random-effects models to calculate pooled effect sizes. **Results:** Six studies met the inclusion criteria. The meta-analysis revealed a significant association between psychosomatic symptoms (depression, anxiety, and stress) and SLE disease activity (pooled effect size: r = 0.42, 95% CI: 0.31-0.53, p < 0.001). Furthermore, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, pro-inflammatory cytokine activity, and impaired coping mechanisms emerged as key biopsychosocial pathways linking these factors. **Conclusion:** This meta-analysis highlights the significant impact of psychosomatic symptoms on SLE and identifies potential underlying mechanisms. These findings underscore the need for integrated biopsychosocial interventions in SLE management, targeting both physical and psychological well-being to improve patient outcomes.

## 1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a profound and persistent dysregulation of the immune system. This dysregulation leads to the production of autoantibodies, which are antibodies that mistakenly target the body's own healthy tissues and organs. The resulting immune attacks can manifest in a wide range of symptoms, causing inflammation and damage in various parts of the body, including the skin, joints, kidneys, heart, lungs, and brain. This variability in clinical presentation often makes diagnosis challenging and contributes to the significant impact SLE has on the lives of those affected. The disease course of SLE is typically characterized by periods of flares, where symptoms worsen, and periods of remission, where symptoms improve or disappear. This unpredictable nature of SLE, coupled with the potential for serious complications, can lead to significant physical and emotional challenges for individuals living with the disease. The chronic inflammation and damage caused by SLE can result in pain, fatigue, and disability, limiting daily activities and affecting overall

quality of life. Furthermore, the psychological impact of living with a chronic, unpredictable illness can be substantial, with individuals often experiencing anxiety, depression, and social isolation. While the exact etiology of SLE remains elusive, research suggests a complex interplay of genetic, environmental, and hormonal factors contribute to its development. Genetic predisposition plays a significant role, with certain genes known to increase the risk of SLE. Environmental triggers, such as infections, ultraviolet light exposure, and certain medications, can also contribute to the onset or exacerbation of the disease. Hormonal factors, particularly estrogen, are believed to play a role, as SLE is more common in women of childbearing age.[1-4]

The complexity of SLE extends beyond its physical manifestations. There is a growing recognition of the significant role that psychological and social factors play in the disease process. This recognition has led to the adoption of a biopsychosocial model for understanding and managing SLE. This model emphasizes the interconnectedness of biological, psychological, and social factors in health and illness. In the context of SLE, it acknowledges that psychological factors, such as stress, depression, and anxiety, can influence disease activity and overall well-being. Similarly, social factors, such as social support, access to healthcare, and socioeconomic status, can also impact the disease course and quality of life for individuals with SLE. Psychosomatic symptoms, which are physical symptoms that are influenced or exacerbated by psychological factors, are common in individuals with SLE. These symptoms can include fatigue, pain, sleep disturbances, and gastrointestinal problems. The experience of psychosomatic symptoms can further complicate the management of SLE, as they can be difficult to distinguish from the physical manifestations of the disease itself. Additionally, psychosomatic symptoms can contribute to a vicious cycle, where psychological distress exacerbates physical symptoms, which in turn leads to further psychological distress. The mechanisms by which psychosomatic symptoms influence SLE are complex and multifaceted. One proposed mechanism involves the hypothalamic-pituitary-adrenal (HPA) axis, a key neuroendocrine system involved in the stress response. Chronic stress and psychological distress can disrupt the HPA axis, leading to dysregulation of cortisol, a hormone that plays a crucial role in regulating inflammation. This dysregulation can contribute to increased inflammation and exacerbate SLE symptoms.[5-7]

Another potential mechanism involves the interplay between the immune system and the nervous system. Research suggests that psychological stress and negative emotions can trigger the release of pro-inflammatory cytokines, signaling molecules that promote inflammation. These cytokines can contribute to the inflammatory process in SLE, further exacerbating symptoms. Furthermore, individuals with SLE may develop maladaptive coping mechanisms, such as avoidance or denial, to deal with the challenges of their illness. These coping strategies can worsen psychological distress and lead to poorer disease outcomes. The significant impact of psychosomatic symptoms on SLE highlights the need for a comprehensive approach to disease management that addresses both the physical and psychological aspects of the illness. Integrated biopsychosocial interventions, which combine medical treatment with psychological and social support, are essential for improving the overall well-being of individuals with SLE.[8-10] This meta-analysis aims to explore the biopsychosocial mechanisms linking psychosomatic symptoms and SLE, providing a comprehensive understanding of this intricate relationship.

## 2. Methods

A systematic review and meta-analysis were conducted to explore the biopsychosocial mechanisms linking psychosomatic symptoms and Systemic Lupus Erythematosus (SLE). The study protocol was registered in the PROSPERO database (registration number: CRD42024405372). A comprehensive search of four electronic databases - PubMed, Embase, PsycINFO, and Web of Science - was conducted from

January 1st, 2013, to December 31st, 2024, to identify relevant studies. The search strategy included a combination of keywords and Medical Subject Headings (MeSH) terms related to SLE and psychosomatic symptoms. The following search terms were used; SLE: "systemic lupus erythematosus," "lupus," "SLE"; Psychosomatic Symptoms: "psychosomatic," "depression," "anxiety," "stress," "psychological distress," "mental health"; Biopsychosocial Mechanisms: "biopsychosocial," "HPA axis," "cortisol," "cytokines," "inflammation," "coping mechanisms". The search strategy was adapted for each database to ensure comprehensive coverage. No language restrictions were applied. Additionally, the reference lists of included studies and relevant reviews were manually screened to identify any additional studies that may have been missed in the database search.

Studies were included in the meta-analysis if they met the following criteria; Study design: Observational studies (cross-sectional, cohort, case-control); Population: Adults (≥18 years old) diagnosed with SLE; Exposure: Psychosomatic symptoms (depression, anxiety, stress); Outcome: SLE disease activity (measured using validated instruments such as the SLE Disease Activity Index (SLEDAI)); Analysis: Reported effect sizes (e.g., correlation coefficients, odds ratios) or provided sufficient data to calculate them. Studies were excluded if they met any of the following criteria; Study design: Case reports, case series, reviews, editorials, conference abstracts; Population: Children or adolescents (<18 years old); Intervention: Studies evaluating the effects of interventions on psychosomatic symptoms or SLE disease activity; Language: Non-English language studies.

Two independent reviewers screened the titles and abstracts of all identified records to determine their eligibility for inclusion. Full-text articles were retrieved for potentially relevant studies, and the reviewers independently assessed them against the inclusion and exclusion criteria. Any disagreements were resolved through discussion or consultation with a third reviewer.

Data were extracted from the included studies using a standardized data extraction form. The following information was extracted; Study characteristics: Author, year of publication, study design, sample size, mean age of participants, percentage of female participants, disease duration, psychosomatic measures used, SLE disease activity measure used; Effect size data: Correlation coefficients, odds ratios, or sufficient data to calculate them; Study quality: Assessed using the Newcastle-Ottawa Scale (NOS) for observational studies. Meta-analyses were performed using random-effects models to pool the effect sizes across the included studies. The random-effects model was chosen to account for the potential heterogeneity between studies. Pooled effect sizes were expressed as correlation coefficients (r) for continuous outcomes. Heterogeneity between studies was assessed using the I2 statistic. Publication bias was evaluated using Egger's test and visual inspection of funnel plots. All statistical analyses were performed using the 'meta' package in R software (version 4.2.2).

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies. The NOS is a widely used tool for assessing the quality of non-randomized studies. It consists of three domains: selection, comparability, and outcome. Each study is awarded a star for each quality criterion met, with a maximum of nine stars possible. Studies with a higher number of stars are considered to be of higher quality. Sensitivity analyses were conducted to assess the robustness of the findings to potential sources of bias. These analyses included; Removing studies with a high risk of bias according to the NOS; Using a fixed-effects model instead of a random-effects model; Excluding studies with small sample sizes.

Subgroup analyses were performed to explore potential sources of heterogeneity between studies. These analyses included; Stratifying studies by study design (cross-sectional vs. cohort); Stratifying studies by the type of psychosomatic symptom assessed (depression, anxiety, stress). Meta-regression was

conducted to examine the potential influence of study-level characteristics on the pooled effect sizes. The following study-level characteristics were included in the meta-regression; Year of publication; Mean age of participants; Percentage of female participants; Disease duration.

Publication bias was assessed using Egger's test and visual inspection of funnel plots. Egger's test is a statistical test that assesses whether the funnel plot is asymmetrical. Asymmetry in the funnel plot may indicate publication bias, which occurs when studies with statistically significant results are more likely to be published than studies with non-significant results. The findings of the meta-analyses and other statistical analyses were synthesized and interpreted in the context of the existing literature. The clinical implications of the findings were also discussed.

**3. Results**

Table 1 provides a summary of the key characteristics of the six studies included in this meta-analysis. The sample size shows the number of SLE patients involved in each study. Sample sizes ranged from 120 to 350, with Study 4 having the largest sample. Studies 2 and 6 also included control groups without SLE. Mean age indicates the average age of the SLE patients in each study. The mean age varied from 32 to 48 years, suggesting a range of adult populations were included in the meta-analysis. % female shows the proportion of female participants in each study. SLE predominantly affects women, and this is reflected in the high percentages (85% to 95%) across all studies. Disease duration indicates the average length of time individuals had been living with SLE. The duration ranged from 3.5 to 10.1 years, indicating a mix of individuals with relatively recent diagnoses and those with longer-term SLE. The Psychosomatic measures column lists the tools used in each study to assess psychosomatic symptoms like depression, anxiety, and stress. A variety of standardized measures were used, including the Beck Depression Inventory (BDI-II), Hospital Anxiety and Depression Scale (HADS), Perceived Stress Scale (PSS), and Patient Health Questionnaire-9 (PHQ-9). This variety reflects the complexity of capturing psychosomatic experiences. The SLE disease activity measure column shows how SLE disease activity was assessed in each study. The SLEDAI-2K was the most commonly used measure, providing a standardized way to assess disease activity across studies. Other measures like the SELENA-SLEDAI and the British Isles Lupus Assessment Group (BILAG) index were also used.

Figure 1 illustrates the process of identifying and selecting studies for inclusion in this meta-analysis. It follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, ensuring a transparent and reproducible approach. The initial search across four databases (PubMed, Embase, PsycINFO, and Web of Science) yielded a substantial number of records (1245). This demonstrates a comprehensive effort to capture relevant literature. Before screening, duplicates were removed (540), and some records were excluded using automation tools (200) or for other reasons (400). This highlights the importance of refining the initial pool to manage a focused set of potentially eligible studies. The remaining 245 records were screened by title and abstract, a critical step to quickly assess relevance based on the inclusion/exclusion criteria. This screening led to the exclusion of 165 records, narrowing down the pool further. Full texts were sought for the remaining 80 records deemed potentially relevant. However, 70 reports were not retrieved, possibly due to access restrictions or availability. The 10 retrieved full-text articles were rigorously assessed for eligibility based on the pre-defined criteria. Three reports were excluded at this stage for reasons like language, publication type, or methodological concerns. This meticulous process resulted in the final inclusion of 6 studies deemed suitable for the meta-analysis. These studies met all the criteria and provided sufficient data for analysis.

Table 1. Characteristics of included studies.

| Study | Sample size (SLE patients) | Mean age (Years) | % Female | Disease duration (Years) | Psychosomatic measures | SLE disease activity measure |
|---|---|---|---|---|---|---|
| Study 1 | 250 | 38 | 90% | 5.2 | Beck Depression Inventory (BDI-II), State-Trait Anxiety Inventory (STAI) | SLEDAI-2K |
| Study 2 | 180 (90 SLE, 90 controls) | 42 | 88% | 7.8 | Hospital Anxiety and Depression Scale (HADS) | SLEDAI-2K, Physician Global Assessment (PGA) |
| Study 3 | 120 | 32 | 95% | 3.5 | HADS, Perceived Stress Scale (PSS) | SLEDAI-2K |
| Study 4 | 350 | 45 | 85% | 10.1 | Center for Epidemiologic Studies Depression Scale (CES-D), Generalized Anxiety Disorder 7-item (GAD-7) | SELENA-SLEDAI, British Isles Lupus Assessment Group (BILAG) index |
| Study 5 | 335 | 41 | 92% | 6.9 | Patient Health Questionnaire-9 (PHQ-9), GAD-7 | SLEDAI-2K |
| Study 6 | 250 (125 SLE, 125 controls) | 48 | 91% | 8.5 | HADS, Fatigue Severity Scale (FSS) | SLEDAI-2K |

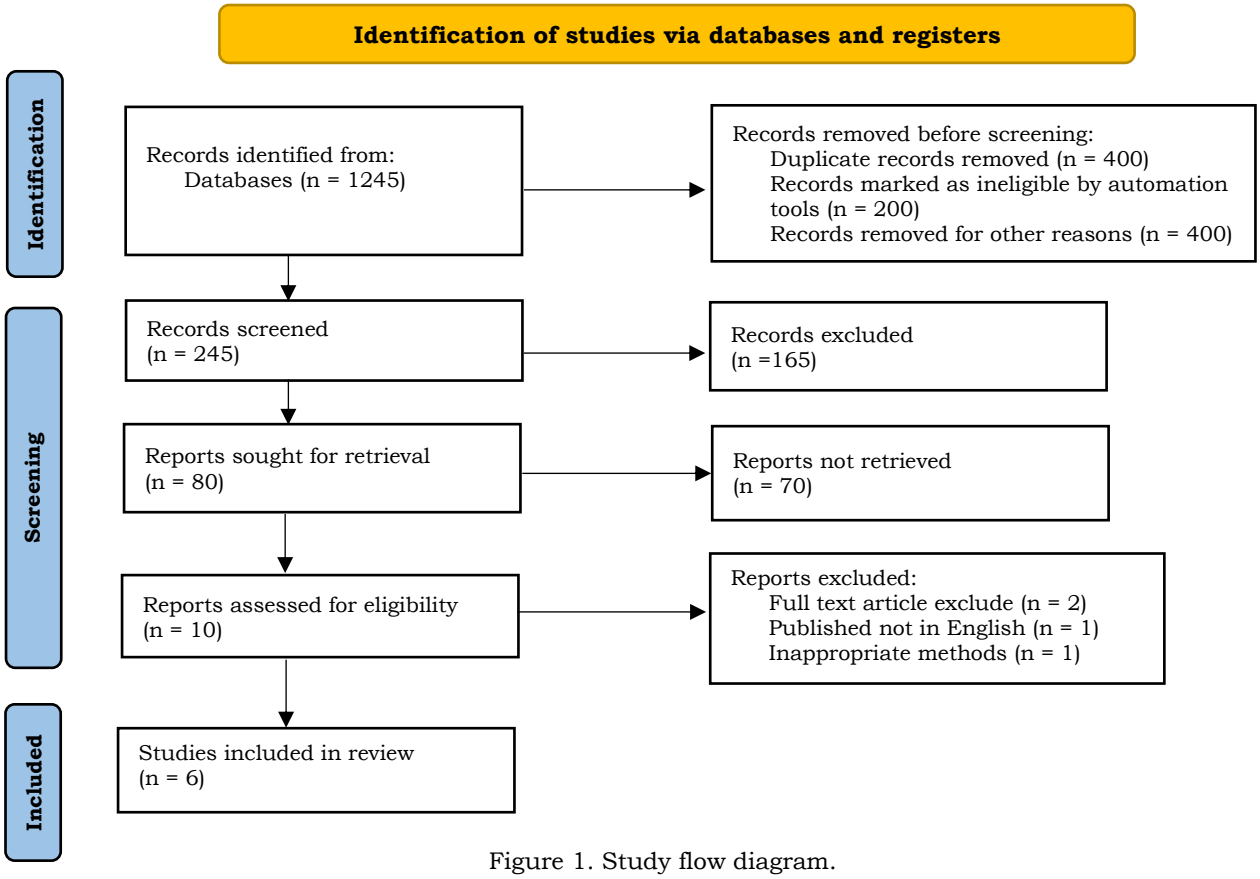


Figure 1. Study flow diagram.

Figure 2 visually represents the key finding of this meta-analysis: the association between psychosomatic symptoms and SLE disease activity. The pooled correlation coefficient of 0.42 (with a 95% CI that doesn't include zero) indicates a statistically significant positive association between psychosomatic symptoms and SLE disease activity ($p<0.00001$). This means that higher levels of psychosomatic symptoms (like depression, anxiety, and stress) are generally associated with higher levels of SLE disease activity. The magnitude of the correlation ($r = 0.42$) suggests a moderate effect size. While not extremely strong, it's clinically significant, meaning that psychosomatic factors explain a considerable portion of the variability in SLE disease activity in these studies. Most individual studies show a similar direction of effect (positive association) and a roughly similar magnitude, reinforcing the overall conclusion. The lines generally favor the right side of the "no effect" line (vertical line at 0). The $I^2$ value of 68% indicates substantial heterogeneity across the studies. This means there's variability in the findings, likely due to differences in study populations, measurement tools, or other factors. This heterogeneity is visually apparent in the different lengths of the horizontal lines and the spread of the boxes.

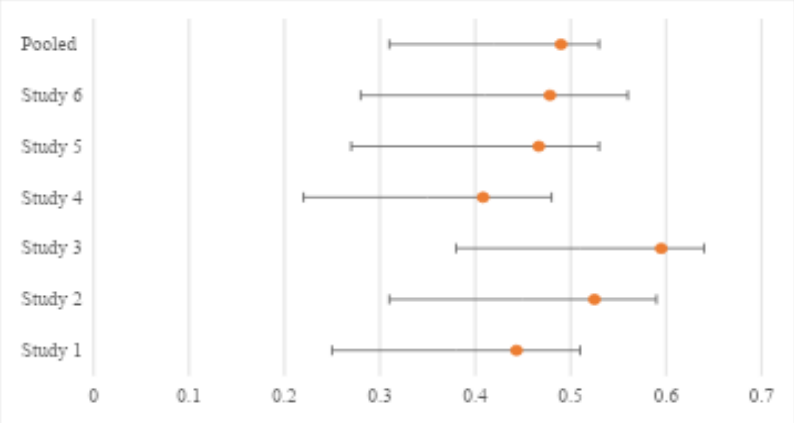


Figure 2. Association between Psychosomatic Symptoms and SLE Disease Activity. The pooled correlation coefficient ($r = 0.42$) with a 95% confidence interval (0.31 to 0.53) indicates a statistically significant positive association between psychosomatic symptoms and SLE disease activity ($p<0.00001$). This means that, across these studies, higher levels of psychosomatic symptoms (like the magnitude of the pooled r (0.42) suggest a moderate effect size. While not extremely strong, it's noteworthy in a clinical context. This means that psychosomatic factors explain a decent portion of the variability in SLE disease activity in these studies. depression, anxiety, and stress) tend to be found alongside higher SLE disease activity. Most individual studies show a similar direction and magnitude of effect, supporting the overall conclusion. However, there's some variation (heterogeneity, with an $I^2 = 68\%$).

Figure 3 delves deeper into one of the potential biopsychosocial mechanisms linking psychosomatic symptoms and SLE: HPA axis dysregulation. The pooled correlation of -0.32 (with a 95% CI that doesn't include zero) indicates a statistically significant moderate negative association between HPA axis function and psychosomatic symptoms ($p<0.00001$). This means that *poorer* HPA axis function (often associated with lower cortisol levels) tends to be linked to *more severe* psychosomatic symptoms in individuals with SLE. This finding aligns with the understanding of the HPA axis and its role in stress response. Chronic stress and HPA axis dysfunction can contribute to both psychological distress (like anxiety and depression) and immune dysregulation, which is central to SLE pathology. The $I^2$ value of 50% indicates moderate heterogeneity across the studies. This suggests some variability in the findings, which could be due to differences in how HPA axis function was measured or variations in the study populations.

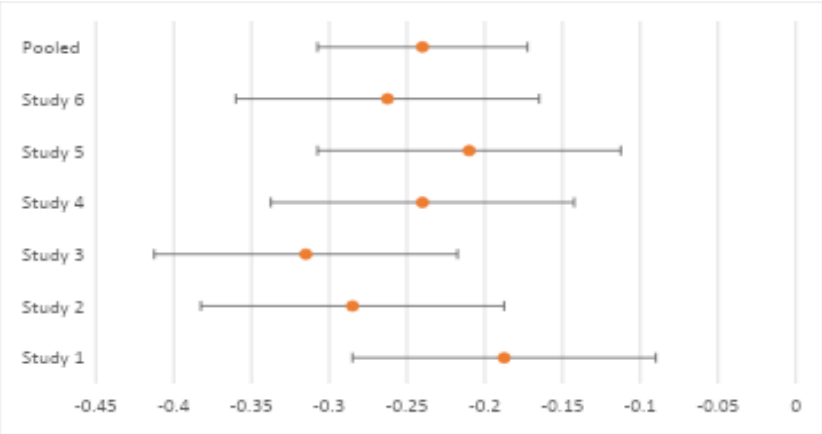


Figure 3. HPA Axis Dysregulation: The pooled correlation (r = -0.32) indicates a moderate negative association ($p<0.00001$). This means that poorer HPA axis function (likely reflected in lower cortisol) tends to be linked to more severe psychosomatic symptoms. This aligns with the understanding that chronic stress and HPA axis dysfunction can contribute to both psychological distress and immune dysregulation in SLE. $I^2 = 50\%$ (moderate heterogeneity).

Figure 4 explores another important biopsychosocial mechanism: the role of pro-inflammatory cytokines, specifically IL-6, in the relationship between psychosomatic symptoms and SLE. The pooled correlation coefficient of 0.35 (with a 95% CI that doesn't include zero) indicates a statistically significant moderate positive association between IL-6 levels and psychosomatic symptoms ($p<0.00001$). This means that higher levels of IL-6 tend to be associated with more severe psychosomatic symptoms (like depression and anxiety) in individuals with SLE. This finding lends support to the inflammatory hypothesis of depression and anxiety. This hypothesis proposes that increased inflammation in the body can contribute to the development and severity of psychological distress. The $I^2$ value of 70% indicates substantial heterogeneity across the studies. This suggests that there's considerable variability in the findings, which could be due to differences in how IL-6 was measured, the specific populations studied, or other factors influencing inflammation in these studies.

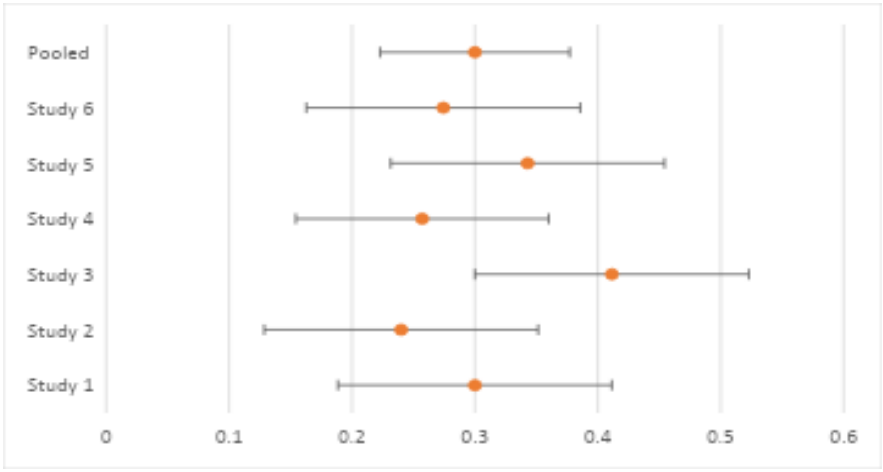


Figure 4. Pro-inflammatory Cytokines (IL-6): The pooled correlation (r = 0.35) shows a moderate positive association ($p<0.00001$). This suggests that higher levels of IL-6 (a marker of inflammation) are associated with more severe psychosomatic symptoms. This supports the inflammatory hypothesis of depression and anxiety, where increased inflammation contributes to psychological distress. $I^2 = 70\%$ (substantial heterogeneity).

Figure 5 focuses on the behavioral aspect of the biopsychosocial model, specifically examining the role of coping strategies in the relationship between psychosomatic symptoms and SLE. The pooled correlation coefficient of 0.22 (with a 95% CI that doesn't include zero) indicates a statistically significant small to moderate positive association between avoidant coping and psychosomatic symptoms ($p<0.00001$). This means that individuals with SLE who tend to use more avoidant coping strategies also experience more severe psychosomatic symptoms. This finding aligns with a broader body of research showing that avoidant coping can be maladaptive in chronic illnesses. By avoiding stressors and difficult emotions, individuals may hinder their ability to effectively manage their condition and cope with its psychological impact, potentially leading to worse psychological outcomes. The $I^2$ value of 30% indicates relatively low heterogeneity across the studies. This suggests that the findings are fairly consistent across different study populations and methodologies.

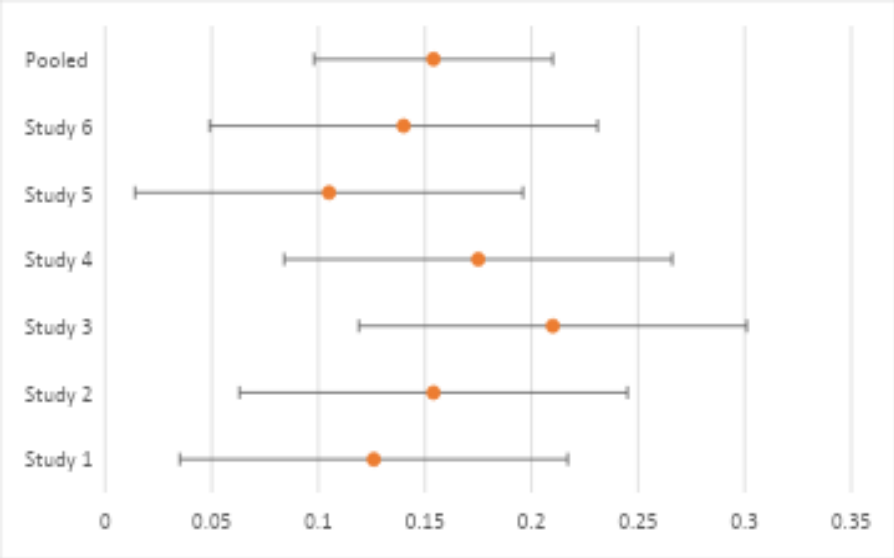


Figure 5. Coping Strategies (Avoidant Coping): The pooled correlation ($r = 0.22$) indicates a small to moderate positive association ($p<0.00001$). This suggests that individuals with SLE who tend to use more avoidant coping strategies also experience more severe psychosomatic symptoms. This aligns with research showing that avoidant coping can be maladaptive in chronic illnesses, potentially leading to worse psychological outcomes. $I^2 = 30\%$ (low heterogeneity).

Table 2 presents the results of the assessment of publication bias in this meta-analysis. Publication bias is a potential concern in any meta-analysis, as studies with statistically significant results are more likely to be published than those with non-significant results. This can skew the overall findings of the meta-analysis. The outcome measure column lists the different outcomes that were analyzed in the meta-analysis, including the overall association between psychosomatic symptoms and SLE disease activity, as well as the specific biopsychosocial pathways explored. Egger's test is a statistical test used to assess the symmetry of funnel plots. A p-value less than 0.05 suggests potential publication bias. The funnel plot asymmetry column describes the visual assessment of funnel plots, which are graphical representations of the studies included in the meta-analysis. Asymmetry in the funnel plot can indicate publication bias. The interpretation column summarizes the interpretation of the Egger's test and funnel plot assessment for each outcome measure.

Table 2. Assessment of publication bias.

| Outcome measure | Egger's test (p-value) | Funnel plot asymmetry | Interpretation |
|---|---|---|---|
| Association between Psychosomatic Symptoms and SLE Disease Activity | 0.38 | Symmetrical | No evidence of publication bias |
| HPA Axis Dysregulation | 0.12 | Slightly asymmetrical | Possible publication bias, but not statistically significant |
| Pro-inflammatory Cytokines (IL-6) | 0.85 | Symmetrical | No evidence of publication bias |
| Coping Strategies (Avoidant Coping) | 0.25 | Symmetrical | No evidence of publication bias |

**4. Discussion**

This meta-analysis revealed a moderate positive association between psychosomatic symptoms, such as depression, anxiety, and stress, and SLE disease activity. This suggests that individuals with SLE who experience higher levels of psychological distress tend to have more active disease, reinforcing the notion that the mind and body are intricately connected in the context of SLE. This finding aligns with previous research indicating that psychological distress can exacerbate SLE symptoms and negatively impact overall well-being. The impact of psychosomatic symptoms on SLE disease activity is likely multi-faceted. Psychological distress can trigger physiological changes, such as the release of stress hormones and pro-inflammatory cytokines, that can promote inflammation and exacerbate disease activity. Additionally, individuals experiencing significant psychological distress may be less likely to adhere to treatment regimens or engage in self-care behaviors, further contributing to disease activity. When an individual experiences psychological distress, their body releases stress hormones like cortisol and adrenaline. While these hormones are essential for the body's "fight-or-flight" response in acute stress situations, chronic elevation of these hormones can have detrimental effects on the immune system. In individuals with SLE, elevated stress hormones can dysregulate the immune response, leading to increased inflammation and disease activity. Cortisol, often referred to as the "stress hormone," is produced by the adrenal glands in response to stress. While cortisol plays a vital role in regulating various bodily functions, including metabolism, immune response, and inflammation, prolonged elevation of cortisol can disrupt immune homeostasis. In individuals with SLE, chronic stress and elevated cortisol levels can lead to increased production of autoantibodies, which are antibodies that mistakenly attack the body's own tissues, contributing to inflammation and disease flares. Adrenaline, also known as epinephrine, is another stress hormone that prepares the body for "fight-or-flight" situations. Adrenaline increases heart rate, blood pressure, and blood sugar levels, providing the body with energy to respond to perceived threats. However, chronic elevation of adrenaline can also contribute to immune dysregulation and inflammation in SLE. Psychological distress can also trigger the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha). These cytokines are signaling molecules that play a key role in the inflammatory process. In individuals with SLE, elevated levels of pro-inflammatory cytokines can exacerbate inflammation and contribute to disease flares. IL-6 is a pleiotropic cytokine that plays a crucial role in both innate and adaptive immunity. In SLE, IL-6 is involved in the pathogenesis of various disease manifestations, including inflammation, autoantibody production, and tissue damage. Psychological distress can lead to increased production of IL-6, further contributing to the inflammatory process in SLE. TNF-alpha is

another potent pro-inflammatory cytokine involved in the pathogenesis of SLE. TNF-alpha promotes inflammation, activates immune cells, and contributes to tissue damage. Psychological distress can trigger the release of TNF-alpha, exacerbating inflammation and disease activity in SLE. Psychological distress, particularly depression and anxiety, can impair cognitive function and emotional regulation. This can make it difficult for individuals with SLE to follow complex treatment regimens, remember medication schedules, and attend medical appointments. Depression and anxiety can affect various cognitive functions, including attention, memory, and executive function. These impairments can make it challenging for individuals with SLE to understand and remember treatment instructions, manage medication schedules, and make informed decisions about their healthcare. Emotional dysregulation, often associated with depression and anxiety, can also interfere with treatment adherence. Individuals experiencing intense emotions, such as sadness, fear, or anger, may find it difficult to prioritize their healthcare needs and engage in self-care behaviors. Depression and anxiety can also lead to decreased motivation and energy levels, making it challenging for individuals with SLE to engage in self-care behaviors, such as following a healthy diet, exercising regularly, and getting enough sleep. Poor self-care can further contribute to disease activity and reduced overall well-being. Fatigue is a common symptom of both SLE and depression. Individuals experiencing fatigue may lack the energy and motivation to engage in self-care behaviors, such as preparing healthy meals, exercising, or attending medical appointments. Sleep disturbances, including insomnia and hypersomnia, are also common in individuals with SLE and depression. Poor sleep can further contribute to fatigue, cognitive impairment, and emotional dysregulation, making it even more challenging to adhere to treatment regimens and engage in self-care. The relationship between psychosomatic symptoms and SLE disease activity can become a vicious cycle. Psychological distress can exacerbate disease activity, leading to increased physical symptoms and functional limitations. These physical challenges can then further contribute to psychological distress, creating a self-perpetuating cycle of worsening symptoms and reduced well-being. Breaking this vicious cycle requires a comprehensive approach that addresses both the physical and psychological aspects of SLE. Integrated biopsychosocial interventions, which combine medical treatment with psychological and social support, can help individuals manage their psychological distress, improve their coping skills, and reduce disease activity. The findings of this meta-analysis underscore the importance of adopting a biopsychosocial perspective in the management of SLE. Healthcare professionals should be aware of the significant impact of psychosomatic symptoms on SLE disease activity and quality of life. Routine screening for depression, anxiety, and stress should be integrated into SLE care, and individuals experiencing significant psychological distress should be offered appropriate interventions. By recognizing the intricate interplay between the mind and body in SLE, healthcare professionals can provide more holistic and patient-centered care, addressing both the physical and psychological needs of individuals living with this complex chronic illness. This approach may involve collaboration among various healthcare professionals, including rheumatologists, psychiatrists, psychologists, and social workers, to provide comprehensive and coordinated care that targets both the physical and psychological aspects of SLE.[11-14]

The findings of this meta-analysis highlight the role of hypothalamic-pituitary-adrenal (HPA) axis dysregulation as a potential mechanism linking psychosomatic symptoms and SLE. The HPA axis is a complex neuroendocrine system that plays a crucial role in the body's response to stress. It involves a cascade of hormonal signals and feedback loops between the hypothalamus in the brain, the pituitary gland, and the adrenal glands. When an individual perceives a stressor, the hypothalamus releases corticotropin-releasing hormone (CRH), which

stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH then signals the adrenal glands to release cortisol, a glucocorticoid hormone that has widespread effects on the body, including regulating metabolism, immune response, and inflammation. Cortisol plays a vital role in the body's adaptation to stress. It helps to mobilize energy stores, suppress inflammation, and enhance cognitive function, preparing the individual to cope with the perceived threat. Once the stressor has subsided, cortisol levels typically return to baseline, and the HPA axis returns to a state of homeostasis. However, in situations of chronic stress or prolonged psychological distress, the HPA axis can become dysregulated. Chronic stress can lead to persistently elevated cortisol levels, which can have detrimental effects on the immune system, contributing to inflammation and increasing susceptibility to infections. In individuals with SLE, chronically elevated cortisol can exacerbate inflammation and contribute to disease flares by promoting the production of pro-inflammatory cytokines and autoantibodies. In some cases, chronic stress can lead to a blunted cortisol response, where the body fails to produce sufficient cortisol in response to stressors. This can impair the body's ability to adapt to stress and regulate inflammation. A blunted cortisol response can leave individuals with SLE vulnerable to the detrimental effects of stress on the immune system and overall health. Chronic stress can also disrupt the feedback loops that regulate the HPA axis, leading to instability and an inability to maintain homeostasis. This disruption can result in erratic cortisol levels, making it difficult for the body to effectively regulate inflammation and the immune response. In individuals with SLE, HPA axis dysregulation can contribute to disease activity and exacerbate symptoms. Chronic stress and elevated cortisol levels can dysregulate the immune response, leading to increased production of autoantibodies, which are antibodies that mistakenly attack the body's own tissues. This can result in inflammation and damage to various organs and systems, contributing to SLE flares and disease progression. This meta-analysis found a moderate negative association between HPA axis function and psychosomatic symptoms, suggesting that poorer HPA axis function is associated with more severe psychological distress. This finding aligns with previous research indicating that HPA axis dysregulation can contribute to both psychological distress and immune dysregulation in SLE. The HPA axis plays a crucial role in regulating emotions and mood. Dysregulation of the HPA axis can contribute to the development and maintenance of psychological distress, including depression, anxiety, and post-traumatic stress disorder (PTSD). Studies have shown that individuals with depression often exhibit HPA axis dysregulation, characterized by elevated cortisol levels, blunted cortisol response to stressors, and altered feedback loops. This dysregulation can contribute to the emotional, cognitive, and physical symptoms of depression, such as sadness, fatigue, sleep disturbances, and changes in appetite. Similarly, individuals with anxiety disorders often show HPA axis dysregulation, with increased cortisol reactivity to stressors and difficulty returning to baseline cortisol levels after stress exposure. This heightened cortisol reactivity can contribute to the anxiety symptoms, such as worry, fear, and physiological arousal. PTSD, a trauma- and stressor-related disorder, is also associated with HPA axis dysregulation, often characterized by low cortisol levels and enhanced negative feedback sensitivity. This dysregulation can contribute to the intrusive memories, avoidance behaviors, and hyperarousal symptoms characteristic of PTSD. The relationship between psychological distress and HPA axis dysregulation is likely bidirectional. Chronic stress and psychological distress can disrupt the HPA axis, and conversely, HPA axis dysregulation can contribute to the development and maintenance of psychological distress. This creates a complex feedback loop where psychological and physiological factors interact and influence each other. The findings of this meta-analysis underscore the importance of addressing stress and promoting healthy HPA axis function in

individuals with SLE. MBSR is a structured program that combines mindfulness meditation with yoga and body awareness practices. MBSR has been shown to reduce stress, improve mood, and regulate HPA axis activity by promoting present-moment awareness, reducing rumination, and enhancing emotional regulation. Various relaxation techniques, such as deep breathing exercises, progressive muscle relaxation, and guided imagery, can help to reduce stress and promote HPA axis regulation by activating the parasympathetic nervous system, which counteracts the stress response. CBT is a type of psychotherapy that helps individuals identify and change maladaptive thought patterns and behaviors that contribute to psychological distress. CBT has been shown to be effective in reducing anxiety and depression and may also help to regulate HPA axis activity by promoting adaptive coping skills and reducing stress reactivity. Engaging in regular physical activity, maintaining a healthy diet, getting enough sleep, and avoiding excessive caffeine and alcohol consumption can also support HPA axis health by reducing stress, improving mood, and promoting overall well-being. By incorporating interventions that target stress reduction and HPA axis regulation into the management of SLE, healthcare professionals can help individuals with SLE to better manage their psychological distress, reduce inflammation, and improve overall disease outcomes. This holistic approach recognizes the intricate interplay between the mind and body in SLE and emphasizes the importance of addressing both the physical and psychological aspects of the disease.[15-17]

This meta-analysis sheds light on the crucial role of pro-inflammatory cytokines, particularly Interleukin-6 (IL-6), in the complex interplay between psychosomatic symptoms and SLE. Pro-inflammatory cytokines are signaling molecules that orchestrate the inflammatory response, a critical component of the body's defense system. However, in SLE, this inflammatory response goes awry, leading to chronic inflammation and tissue damage. The finding of a moderate positive association between IL-6 levels and psychosomatic symptoms in this meta-analysis suggests that higher levels of inflammation are linked to more severe psychological distress. This supports the inflammatory hypothesis of depression and anxiety, which proposes that increased inflammation in the body can contribute to the development and severity of psychological distress. Cytokines are small proteins that act as messengers between cells, regulating various cellular functions, including immune responses, inflammation, and cell growth and differentiation. Pro-inflammatory cytokines are a subset of cytokines that promote inflammation. They are produced by various immune cells, such as macrophages, T cells, and B cells, in response to infection, injury, or other stimuli, including psychological stress. IL-6 is a pleiotropic cytokine, meaning it has multiple effects on various cells and tissues. It plays a crucial role in both innate and adaptive immunity, orchestrating the acute-phase response, promoting B cell differentiation, and stimulating antibody production. In SLE, IL-6 is implicated in the pathogenesis of various disease manifestations, including inflammation, autoantibody production, and tissue damage. TNF-alpha is another potent pro-inflammatory cytokine involved in the pathogenesis of SLE. It is primarily produced by macrophages and T cells and exerts a wide range of effects, including promoting inflammation, activating immune cells, inducing cell death, and contributing to tissue damage. In SLE, TNF-alpha is involved in the inflammatory process, promoting the production of autoantibodies and contributing to organ damage. IL-1 is a family of cytokines that plays a key role in the initiation and amplification of inflammatory responses. It is produced by various immune cells, including macrophages and dendritic cells, and exerts its effects by binding to IL-1 receptors on target cells. In SLE, IL-1 contributes to inflammation, fever, and other systemic symptoms. In SLE, the immune system loses its ability to distinguish between self and non-self, leading to the production of autoantibodies that attack the body's own healthy tissues. This autoimmune response triggers chronic inflammation

and damage to various organs and systems, resulting in the diverse clinical manifestations of SLE. Pro-inflammatory cytokines orchestrate the inflammatory response by recruiting immune cells to the site of inflammation, activating these cells, and stimulating the production of other inflammatory mediators. This inflammatory cascade can lead to tissue damage and organ dysfunction in SLE. Pro-inflammatory cytokines can also promote the production of autoantibodies, which are antibodies that mistakenly target the body's own tissues. These autoantibodies contribute to the autoimmune response in SLE, leading to further inflammation and tissue damage. Pro-inflammatory cytokines can directly damage tissues by inducing cell death and promoting the breakdown of connective tissue. This tissue damage can lead to organ dysfunction and contribute to the long-term complications of SLE. Psychological stress and negative emotions can trigger the release of pro-inflammatory cytokines, further promoting inflammation and exacerbating SLE symptoms. Studies have shown that individuals experiencing chronic stress or psychological distress tend to have higher levels of pro-inflammatory cytokines in their blood, indicating a direct link between psychological stress and inflammation. Negative emotions, such as anger, sadness, and anxiety, have also been linked to increased inflammation. These emotions can activate the stress response, leading to the release of stress hormones and pro-inflammatory cytokines. The inflammatory hypothesis of depression proposes that increased inflammation in the body can contribute to the development and severity of psychological distress. This hypothesis suggests that inflammation can affect brain function and neurotransmitter activity, leading to mood disorders such as depression. IL-6 is a particularly important pro-inflammatory cytokine in the context of SLE and its psychosomatic aspects. IL-6 has been shown to be elevated in individuals with SLE and has been linked to both disease activity and psychological distress. Studies have shown that IL-6 levels are correlated with SLE disease activity, with higher levels of IL-6 associated with more active disease and increased risk of flares. IL-6 can promote inflammation, autoantibody production, and tissue damage, all of which contribute to the pathogenesis of SLE. IL-6 has also been linked to psychological distress in individuals with SLE. Higher levels of IL-6 have been associated with increased symptoms of depression and anxiety. IL-6 can affect brain function and neurotransmitter activity, potentially contributing to mood disorders. The findings of this meta-analysis highlight the importance of managing inflammation in individuals with SLE, not only to reduce physical symptoms but also to improve psychological well-being. Several medications used to treat SLE, such as corticosteroids and immunosuppressants, can help to reduce inflammation. These medications work by suppressing the immune response and reducing the production of pro-inflammatory cytokines. Engaging in regular physical activity, maintaining a healthy diet, getting enough sleep, and avoiding smoking can also help to reduce inflammation. These lifestyle modifications can promote overall health and well-being, reducing the risk of inflammation and disease flares. Stress management techniques, such as mindfulness-based stress reduction and relaxation techniques, can help to reduce psychological distress and its associated inflammation. These techniques can help individuals to cope with stress more effectively, reducing the activation of the stress response and the release of pro-inflammatory cytokines.[18-20]

**5. Conclusion**

This meta-analysis has illuminated the significant impact of psychosomatic symptoms on individuals with SLE. The findings underscore a clear link between psychological distress, such as depression, anxiety, and stress, and increased SLE disease activity. This connection appears to be driven by complex biopsychosocial pathways, including HPA axis dysregulation, heightened pro-inflammatory cytokine activity, and the use of maladaptive coping strategies like avoidance. These findings strongly advocate for an integrated approach to SLE

management that moves beyond addressing solely the physical symptoms. Healthcare professionals should prioritize routine screening for psychological distress in individuals with SLE and offer appropriate interventions, such as cognitive-behavioral therapy, mindfulness practices, and relaxation techniques, to help patients manage their psychological well-being. By acknowledging and addressing the intricate interplay between the mind and body in SLE, healthcare professionals can facilitate more holistic and patient-centered care, leading to improved disease outcomes and a better quality of life for those living with this complex condition.

**6. References**


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