



STRESS, ANXIETY, AND DEPRESSION IN STOMATITIS PATHOGENESIS: A SYSTEMATIC REVIEW

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Literature Review

ABSTRACT

Introduction: Recurrent Aphthous Stomatitis (RAS) is a chronic inflammatory condition characterized by painful ulcers on the oral mucosa. Emerging evidence indicates that psychological factors, such as stress, anxiety, and depression, may play a role in its development. This review aims to examine the influence of these mental health factors on the onset and progression of RAS based on recent scientific literature. **Methods:** The exact mechanisms through which psychological stressors contribute to RAS remain poorly understood. To address this, a systematic review was conducted following PRISMA guidelines to consolidate current research findings. A thorough search was performed across PubMed, the Cochrane Library, and Google Scholar to identify original studies published within the past decade. The search terms used were: ("Recurrent Aphthous Stomatitis" OR "RAS") AND ("Stress" OR "Anxiety" OR "Depression") AND ("Psychological Factors" OR "Mental Health"). **Results:** Findings from the reviewed literature indicate a strong correlation between stress and both the initiation and recurrence of RAS. This association appears to be largely driven by the activation of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in increased cortisol levels and subsequent suppression of immune function. These physiological changes are believed to weaken mucosal defenses, thereby increasing vulnerability to ulcer formation. **Conclusions:** These insights underscore the importance of incorporating psychological interventions—particularly stress-reduction techniques—into the management of RAS to enhance patient well-being and reduce symptom burden.

INTRODUCTION

Recurrent Aphthous Stomatitis (RAS) is the most common form of recurrent oral ulceration, affecting up to 25% of the general population. It significantly impairs patients' quality of life due to pain, discomfort, and functional limitations such as difficulty in eating and speaking (Shinkre et al., 2024). Clinically, RAS presents as painful, round, or oval ulcers with a yellowish base surrounded by an erythematous halo, typically occurring on nonkeratinized oral mucosa such as the lips, cheeks, and tongue.

Despite its high prevalence, the exact etiology of RAS remains unclear. However, accumulating evidence suggests that psychological factors—including stress, anxiety, and depression—play a significant role in disease onset and exacerbation (Machanda, A et al., 2016; Vandana, S et al., 2019). Several studies have reported higher levels of perceived stress and depressive symptoms among individuals with RAS compared to healthy controls. Notably, dental students—who often experience high academic stress—have been shown to have a higher frequency of RAS, suggesting a direct link between psychosocial stress and disease activity (Woo, SB et al., 1996; Susanto, H et al., 2019).

While these findings suggest a possible association between psychological distress and RAS, the results remain inconsistent across studies. Some report a strong correlation between stress levels and RAS severity, while others find no significant relationship between anxiety or depression and lesion recurrence (Ganesa, A et al., 2024). Furthermore, the biological mechanisms underlying this connection are not yet fully understood, highlighting a critical gap in current knowledge.

Psychological stress activates the hypothalamic–pituitary–adrenal (HPA) axis, leading to elevated cortisol levels that suppress immune function and promote inflammatory responses (Razi, Afifa et al., 2021). This dysregulation may compromise mucosal integrity and increase susceptibility to oral ulceration. Similarly, both anxiety and depression have been associated with altered immune-inflammatory pathways, although the precise mechanisms linking them to RAS pathogenesis still require further investigation. Given the growing recognition of the mind–body connection in chronic diseases, understanding how psychological factors influence RAS development is crucial for improving patient management.

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Therefore, this review aims to analyze the role of stress, anxiety, and depression in the pathogenesis of RAS, focusing on recent research findings that explore the biological mechanisms involved. To guide this review, we address the following research questions on how psychological factors, particularly stress, anxiety, and depression, affect the frequency or severity of RAS, and what biological mechanisms link these psychological states to RAS.

MATERIALS AND METHODS

Study Design

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework to ensure a clear, transparent, and methodologically sound approach throughout the process. The main purpose of this review was to explore how psychological elements—particularly stress, anxiety, and depression—may contribute to the development of Recurrent Aphthous Stomatitis (RAS), with an emphasis on uncovering possible biological pathways that connect these psychological states to the condition.

Data Sources and Search Strategy

An extensive literature search was performed using PubMed, the Cochrane Library, and Google Scholar, targeting studies published between January 1, 2015, and March 31, 2025. To maximize both sensitivity and precision, the search strategy combined Medical Subject Headings (MeSH) terms with relevant free-text keywords, connected using Boolean operators. Key search strings included: ("Recurrent Aphthous Stomatitis" OR "RAS") AND ("Psychological Stress" OR "Stress"), ("Recurrent Aphthous Stomatitis" OR "RAS") AND ("Anxiety" OR "Depression"), as well as broader terms such as ("Mental Health" OR "Emotional Distress") used alongside oral ulceration-related keywords. All retrieved references were organized using Mendeley reference management software to remove duplicates and facilitate further screening.

Eligibility Criteria

To maintain relevance and scientific integrity, clearly defined inclusion and exclusion criteria were established a priori. Only original research articles—including observational studies and controlled clinical trials—that investigated the relationship between RAS and psychological factors such as stress, anxiety, and depression were considered. Priority was given to studies that also examined potential immunological or physiological mechanisms. Included articles were required to have been published between 2015 and 2025 and to have employed validated tools for measuring psychological status, such as the Perceived Stress Scale (PSS) or Hospital Anxiety and Depression Scale (HADS). Studies excluded from the review included case reports, editorials, narrative reviews, and those focusing exclusively on clinical features or treatment

modalities of RAS without addressing its psychological or pathophysiological aspects. Furthermore, studies not written in English or lacking sufficient detail were also excluded.

Study Selection Process

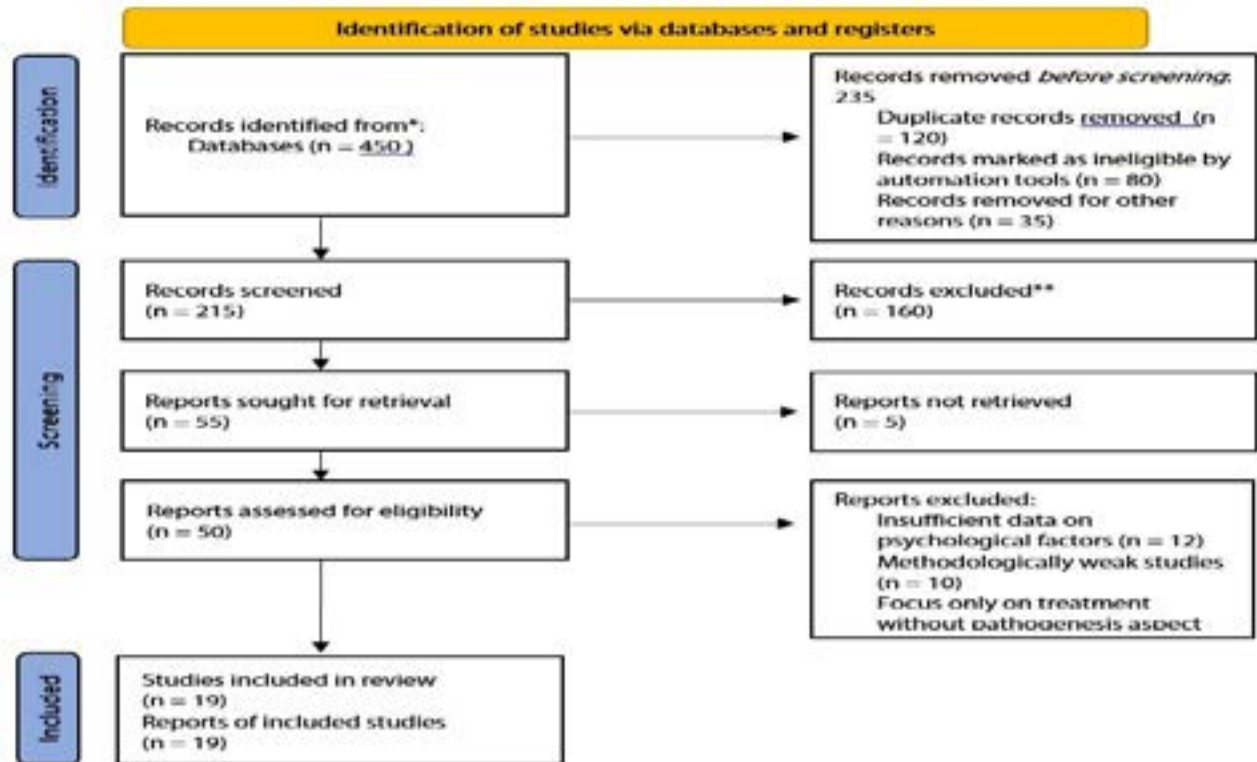
The identification of relevant studies followed a structured, three-stage screening process. In the initial stage, two independent reviewers separately evaluated all study titles based on the predefined eligibility criteria, eliminating those deemed irrelevant. In the second stage, abstracts of potentially relevant articles were assessed by both reviewers to determine whether they met the inclusion criteria. Articles with unclear relevance were retained for full-text evaluation. In the final stage, the full texts of selected studies were reviewed independently by both evaluators. Any disagreements regarding study inclusion were resolved through discussion, and, if necessary, a third reviewer was consulted to reach a consensus.

Critical Appraisal and Quality Assessment

For randomized controlled trials, the risk of bias was evaluated using the Cochrane Risk of Bias Assessment Tool, which examines domains such as randomization method, blinding procedures, allocation concealment, and potential for selective outcome reporting. Each study was rated according to these parameters, and only those achieving a predefined quality benchmark were considered suitable for inclusion in the final synthesis. Two independent reviewers carried out the assessments, and any inconsistencies in their evaluations were addressed through mutual discussion to reach a consensus.

Quality Assurance in the Review Process

Throughout the review process, rigorous measures were applied to ensure methodological integrity and minimize bias. These included clearly defined inclusion and exclusion criteria, dual independent screening and data extraction by two reviewers, and a formal consensus-building approach to resolve disagreements. When necessary, a third reviewer provided an impartial evaluation to ensure the resolution of persistent discrepancies. All decisions and justifications were documented systematically to support transparency, consistency, and replicability.

Figure 1. PRISMA flow diagram

Data Extraction

A structured data extraction tool was created to gather key information from each selected study. Two independent reviewers extracted the data, which was then cross-verified for accuracy. Extracted items included study characteristics (author, year, country, and design), participant demographics (sample size, age range, and diagnostic criteria), psychological evaluation tools (e.g., PSS or HADS), clinical RAS outcomes (frequency, severity, and duration of lesions), and potential biological or immunological pathways linking psychological states to RAS. Any inconsistencies in data interpretation were resolved through discussion, with additional input from

a third reviewer when required, ensuring that the final synthesis was accurate and comprehensive.

Data Analysis Technique

Findings from the studies that met the inclusion criteria were analyzed narratively using a thematic approach to identify key patterns in the psychological effects on RAS. For comparable quantitative data, a meta-analysis was performed to calculate the overall effect sizes of stress, anxiety, and depression on RAS incidence. The meta-analysis results were presented as forest plots for clearer interpretation.

RESULTS

A systematic review of nineteen ([Levinsky, Y et al 2022](#)) studies was conducted to explore the relationship between psychological factors—particularly stress, anxiety, and depression—and the pathogenesis of Recurrent Aphthous Stomatitis (RAS). These studies included a range of research designs, from cross-sectional surveys assessing psychological stress levels in various populations to randomized controlled trials evaluating therapeutic interventions for RAS. The selected studies involved diverse participant groups, including dental students, university students, office workers, and patients with recurrent ulcers, allowing for a comprehensive analysis of how psychological stress may influence the onset, frequency, and severity of RAS.

Table 1. Summary of included studies by theme and sub-theme

Theme	Subtheme	Key findings
Psychological Factors and RAS Association	Stress and Ras	All studies found a statistically significant association between stress levels and the occurrence or frequency of RAS ($p < 0.05$). Exam-related stress was particularly linked to RAS episodes.
	Anxiety and RAS	High prevalence of anxiety among RAS patients. Significant correlation between anxiety and RAS severity and pain perception ($p = 0.04\text{--}0.05$).

Theme	Subtheme	Key findings
Psychological Factors and RAS Association	Depression and RAS	Stronger link in OLP patients; moderate correlation between depression scores and inflammation. Also reported higher depression in RAS patients.
Biomarkers and Physiological Mechanisms	Cortisol and HPA Axis	Elevated salivary cortisol and DHEA levels in RAS patients. One study found no difference in cortisol but noted negative correlation with anxiety.
Interventional Approaches for RAS Management	Mucoadhesive formulations	Caffeic acid and other topical agents significantly reduced pain and lesion size. No added benefit from laser therapy.
	Anti-inflammatory therapies	Caffeic acid and other topical agents significantly reduced pain and lesion size. No added benefit from laser therapy.
	Immunomodulatory interventions	Topical penicillin and TGO gel showed faster healing times and pain relief compared to placebo.
Special Populations and Contextual Triggers	Academic stress in students	High prevalence of RAS among dental and medical students. Stress during exams was identified as a key trigger.
	Pandemic-related stress	Increased RAS incidence during the pandemic; emotional stress triggered PFAPA flares in children ($P = 0.017$).

The findings from this review consistently suggest a significant association between psychological stress and the occurrence of RAS, with several studies reporting higher stress levels among individuals experiencing recurrent oral ulcers. While some studies found no direct correlation between cortisol levels and RAS, others identified potential biomarkers such as elevated salivary cortisol and dehydroepiandrosterone (DHEA) in RAS patients. Anxiety and depression were also frequently linked to increased RAS severity and pain perception. Despite methodological variations across studies, the evidence supports the hypothesis that psychological factors play a role in RAS pathogenesis, likely through immune modulation and activation of the hypothalamic–pituitary–adrenal (HPA) axis. These results underscore the importance of integrating psychological assessment and management into the clinical care of patients with RAS.

DISCUSSION

The findings of this systematic review provide strong evidence supporting the role of psychological stress in the pathogenesis of Recurrent Aphthous Stomatitis (RAS). Across multiple observational studies involving diverse populations—including students, office workers, and patients—stress was consistently identified as a significant contributing factor to the onset and exacerbation of RAS (Karthikeyan, et al., 2016; Nadendla, LK et al., 2015). These results align with existing literature that highlights the impact of psychological distress on immune regulation and mucosal integrity (Zhou, H et al., 2023; Abiko, Y., et al., 2021). The consistent association between high-stress environments (e.g., academic pressure or pandemic-related anxiety) and increased RAS frequency further reinforces the hypothesis that emotional stress may act as a trigger for ulcer development (Sajewicz-Radtke, U et al., 2023; Valle, A et al., 2013).

Several of the included studies also explored the potential biological mechanisms underlying this relationship. Many reported elevated levels of salivary cortisol and dehydroepiandrosterone (DHEA) among

RAS patients, suggesting activation of the hypothalamic–pituitary–adrenal (HPA) axis under psychological stress (Manczkyn, B et al., 2019; Szymczak-Paluch, M et al., 2023). This hormonal response is known to modulate immune function, potentially leading to local immunosuppression and increased susceptibility to oral ulcers (Dhopte, A et al, 2018; Najafi, S et al., 2018). While one study found no significant difference in cortisol levels between RAS patients and controls, it reported a moderate negative correlation between cortisol and anxiety, indicating complex interactions between stress biomarkers and psychological states that warrant further investigation (Machanda, A et al., 2016; Praitmbodo, NT et al., 2019).

In addition to stress, anxiety and depression were frequently linked to RAS severity and pain perception. Studies using standardized tools such as the Depression Anxiety Stress Scales (DASS-21) and Hospital Anxiety and Depression Scale (HADS) consistently showed a higher prevalence of these psychological conditions among individuals with RAS compared to healthy controls (Susanto, H et al., 2019; Nur'aeny, N et al., 2020). Moreover, several studies observed a direct correlation between the intensity of RAS symptoms and the degree

of psychological distress (Osipowicz, K et al., 2024). These findings suggest that emotional health should be considered not only as a potential contributor to disease onset but also as a factor influencing clinical outcomes and patient-reported symptom burden.

The therapeutic implications of these findings are also noteworthy. Among the interventional studies reviewed, those targeting both physical and psychological aspects of RAS demonstrated improved outcomes. For instance, mucoadhesive formulations containing anti-inflammatory agents reduced pain and accelerated healing (Paudel, D et al., 2022), while psychological interventions and stress management strategies could potentially complement pharmacological treatments (Osipowicz, K et al., 2024). These results highlight the importance of a multidisciplinary approach in managing RAS, integrating oral care with mental health support to improve overall patient well-being.

Limitations

Despite the thoroughness of the methodology, certain limitations should be noted. Most of the included studies employed cross-sectional designs, limiting causal inference. Considerable variability in populations, measurement tools, and outcome definitions also restricted direct comparisons across studies. Furthermore, publication bias cannot be ruled out, as positive results are more likely to be published than null findings. Finally, reliance on self-reported psychological assessments in many studies may have introduced subjective biases and recall inaccuracies.

CONCLUSIONS

In summary, this review suggests that psychological stress is the most significant contributor to the pathogenesis of Recurrent Aphthous Stomatitis (RAS), whereas the roles of anxiety and depression appear less consistent. As such, stress-reduction approaches, including mindfulness practices and Cognitive Behavioral Therapy (CBT), may serve as valuable complementary treatments for individuals suffering from RAS. Further investigation is needed to clarify how anxiety and depression influence disease progression. Additionally, future studies focusing on measurable stress biomarkers—such as salivary cortisol—could enhance the development of targeted preventive and therapeutic interventions.

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AUTHORS' CONTRIBUTIONS

All authors were actively involved in the conceptualization and design of this systematic review. EK conducted the initial database searches, screened the literature, and extracted relevant data. EA and NH independently assessed study eligibility and performed quality evaluations. Data interpretation and thematic synthesis were carried out collaboratively by all authors. The manuscript was primarily drafted by BDC, with substantial critical input and revisions from RSA and RN. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for its content.

CONFLICT OF INTEREST

The authors declare no competing interests related to the content of this manuscript. There are no financial or personal relationships that could inappropriately influence the findings or interpretations presented in this review. All authors have read and approved the final version of the manuscript and confirm the absence of any potential conflicts of interest.

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