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Interplay of psychological factors and bronchial asthma: a comprehensive review

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Abstract

Bronchial asthma, a chronic condition marked by persistent inflammation and bronchial obstruction, affects over 334 million people globally. Although extensive research has been conducted on its biological and environmental causes, the impact of psychiatric disorders such as stress and anxiety on asthma is less understood, despite their significant association with the condition. Stress can exacerbate asthma by weakening the body's response to medications and is associated with a higher prevalence of anxiety and depressive disorders among asthmatics. A bidirectional relationship exists between asthma and psychiatric disorders, influenced by genetic and environmental factors. The interplay between asthma and psychological states involves psychophysiological mediation, medication noncompliance, exposure to triggers, and symptom misperception. Non-pharmacological interventions, including cognitive behavioral therapy, relaxation therapy, breathing exercises, and yoga, show promise in reducing the asthma burden. Combined efforts between mental health specialists and allergists can improve symptom control, quality of life, and overall functioning in asthma patients, thereby decreasing morbidity and mortality.

Key words: stress, depression, psychiatric disorders, asthma, neurophenotype.

Introduction

Bronchial asthma is a chronic and multidimensional condition, now affecting more than 334 million people worldwide. It involves persistent inflammation of the respiratory tract, bronchial obstruction, and recurrent episodes of breathlessness differing in severity in different patients. Interactions between genetic predisposition and environmental factors are majorly responsible for the development of this condition [1]. Its diagnosis is based on typical respiratory symptoms like wheezing, shortness of breath, coughing or chest tightness, along with evidence of variable airflow obstruction detected through spirometry testing. Although there has been intensive research on biological and environmental causes of asthma, the influence of psychiatric disorders such as stress, anxiety on the functioning of asthma patients is not thoroughly understood [2]. Asthma and psychological states may mutually reinforce each other through direct psychophysiological mediation, noncompliance with medication regimens, exposure to asthma triggers, and inaccurate perception of asthma symptoms [2,3]. Chronic asthma can be a persistent source of stress throughout life, acting as a trigger for asthma attacks, this ongoing stress affects individuals physically, emotionally, and socially, underscoring the importance of stress management in maintaining control over the disease [4]. Research also indicates that patients with long-standing asthma experience less psychological distress compared to those with recent onset asthma, highlighting the significance of learning effective coping mechanisms to manage the illness effectively [5]. Asthma education initiatives containing information on trigger avoidance, medicine, and the physiology of the condition may reduce the morbidity associated with the disease. Additional psychological approaches that show promise as supplements to medical care include yoga, hypnosis, stress management, training in symptom perception, and several forms of monitoring [6].

Stress can worsen asthma by weakening the body's response to medications like inhaled corticosteroids and b2-agonists. The genes that encode the glucocorticoid receptor have been shown to have decreased activity in response to both short- and long-term stress [7].

One of the important predictors of psychological problems in asthmatics is poor quality of life (QOL) in addition to physical symptoms like coughing, wheezing, and even lung malfunction. In studies, stressful situations caused exacerbations in about 20–35% of asthma patients [8]. Compared to healthy controls, asthma patients had comparatively higher levels of psychopathology, that has been associated to low self-esteem, depression, and non- specific bodily aches, phobias, and introversion [9]. Exposure to physiological stress during childhood and adulthood is strongly linked to asthma attacks and poor outcomes. This correlation is closely connected to living conditions, including lower socioeconomic status and issues in home and neighbourhood environments [10]. Though, in this review, we need to elucidate the psychological factors and their mechanisms contributing to the burden of asthma.

Search strategy

A study of the most recent literature was conducted utilizing electronic databases between January 2006 and September 2023 in order to identify publications that were suitable for inclusion.

The sources of information used to gather information were electronic databases including Google Scholar, MEDLINE/PubMed, Cochrane Library, and Web of Science. Our search primarily focused on key terms to be studied such as “asthma,” “psychological disorders,” “stress”, “depression” “anxiety and “association,” which were combined with Boolean operators (AND, OR) to identify relevant studies and sources.

Psychosocial factors in the development of bronchial asthma

The word "psychosomatic" implies that mood and emotions have an impact on the illnesses. Psychological factors such as subjective perception of symptoms, alexithymia, and levels of depression and anxiety play significant roles in the experience and management of asthma, affecting both cognitive and emotional dimensions of the condition as shown in Figure 1 [11]. Alexithymia is a condition that affects the ability to recognize sensations, symptoms, judgments, thoughts, and emotions and that can also be associated with respiratory allergies. Patients may underestimate their chance of experiencing an asthma exacerbation if they have problems identifying the frequency and severity of their symptoms. Furthermore, there is a correlation between higher alexithymia scores and a higher reporting of asthma symptoms as well as a decreased pulmonary function as shown by %FEV1/FVC . Higher TAS-20 scores (Toronto Alexithymia Scale) (indicating higher alexithymia) are often correlated with inadequate symptom perception in asthma and psychiatric conditions. Under-perception increases the risk of exacerbations due to delayed treatment. Thus, can lead to lower degree of symptom perception

Over-perception leads to unnecessary medication use and heightened anxiety that can cause higher degree of symptom perception [12].

Psychological stressors can affect adolescents on an individual, familial, and societal level. Examples of these stressors include poverty, exposure to violence, racism, and prejudice [13]. Multiple studies have linked psychosocial stressors, including acute, severe, or chronic stress to higher asthma prevalence and worse asthma outcomes in children and adults. Furthermore, these factors are strongly correlated with living conditions, such as a lower socioeconomic status and problems in the home and neighbourhood [11,13].

The initial symptoms of asthma are unpredictable, brought on by either allergic predictors or non-allergic precursors such as stressful events, shifts in the weather and strong emotions. These symptoms activate specific brain regions related to emotions and socialization. Thus, it is

important to address the signs and symptoms as soon as possible to lessen the number of exacerbations [14].

The psychological impact of living with the fear of asthma exacerbations plays a significant role in the mental health challenges experienced by individuals with asthma. In certain individuals, the fear of having an asthma attack can be stressful and raise their risk of developing anxiety and mood disorders [15]. Early onset of asthma has been often found linked to the experiences of emotional trauma in childhood. This can cause long-term changes in the body's stress response, increasing the risk of asthma. Tendency of people towards negative emotions has also been associated with higher risk of developing asthma, which is also called neuroticism [16]. Psychological distress can result in behaviors that worsen asthma, like smoking, poor diet, and insufficient exercise. These behaviors can intensify asthma symptoms and negatively impact overall health. However, sedentary lifestyles and lack of physical activity are modifiable traits in individuals with asthma [17,18].

Shared underlying mechanisms of asthma and psychiatric illnesses

Asthma is an inflammatory disorder of lower airways characterized by airway hyperresponsiveness due to increased secretion of type 2 cytokines (IL-4, IL-5, and IL-13) [19]. The direct factors linking asthma and mental disorders are still unclear. However, cytokines that modulate inflammatory responses may be shared by both asthma and depression. It is found that remission from depression is associated with improved asthma symptoms. People with mental illnesses have elevated levels of inflammatory cytokines and associated receptors in the peripheral blood, cerebrospinal fluid [20]. According to recent research, depression may be an inflammatory condition since individuals with depression release more interleukin (IL)- 1β, IL-6, and tumor necrosis factor (TNF)-α. Depressed subjects have significantly increased concentrations of certain cytokines (e.g., IL-4, IL-1, IL-6, and TNF-α) compared to the control group [21]. There are instances where signals associated with inflammation can get through the blood-brain barrier, causing cytokines to affect and control the neurological system. The ratio of IFN-γ/IL-4 concentration is measured, and a decreased ratio suggests a transition towards inflammatory response mediated by Th-2-like cells. IL-4 is a Th2 cytokine and IFN-γ is Th1 cytokine. This imbalance in the Th1/Th2 ratio can lead to further allergic reactions, including asthma [22]. As in a study by Takemori Y et al, it was found that psychological stress was inversely correlated with the salivary IFN-γ to IL-4 ratio according to K10 grading system. It determines stress-induced alteration of the Th1/ Th2 balance of cytokine production in saliva [23]. This explains the abnormal cytokine expression seen in both depressed and asthmatic patients and as a result, chronic inflammation in allergic processes probably acts as a

"bridge" linking both conditions.

Stress alone does not alter immune functions to the extent that it causes asthmatic symptoms. Rather, stress appears to increase the inflammatory response of the airways in response to external stimuli, leading to an increase in the frequency, length, and severity of asthma attacks in individuals. Still, research has also shown that stress can have a direct impact on immunological responses as shown in Figure 2, the neuroendocrine, autonomic, and immune systems, as well as the epigenetic regulation of gene expression [24]. Acute stress can activate the sympathetic and adrenomedullary nervous systems as well as the hypothalamic-pituitary-adrenocortical (HPA) axis, creating an imbalance and increasing blood levels of neurotransmitters, which can have bronchodilator and anti-inflammatory effects. However, prolonged or chronic stress can lead to the downregulation of effector receptors, causing an imbalance between glucocorticoids and catecholamines [25]. This imbalance creates a pro-inflammatory environment with a hyporesponsive HPA axis and a diminished response to treatments like short-acting bronchodilators. Consequently, chronic stress can amplify airway inflammation in response to environmental and infectious triggers, resulting in asthma exacerbations.

Psychological stress triggers type 17 T helper (Th17) immune responses, including an increase in neutrophils in people with asthma, which contributes to glucocorticoid-resistant refractory asthma [26,27]. These findings imply that neural activation in specific brain regions in response to psychological stimuli can lead to immune responses, potentially worsening asthma severity.

Mental health and bronchial asthma: a bidirectional association

Although the chronology of onset for mental disorders and asthma may vary from person to person, there may be shared pathways between mental illnesses and asthma, such as hereditary factors, inflammation and glucocorticoids, that can increase the risk for both conditions. Additionally, each illness could raise the risk of the other through various underlying mechanisms [28,29]. According to Xiaoqin Liu et al.'s research, there is a complex and reciprocal association between mental diseases and asthma. This study uses a Danish database of over 5 million persons, including over 300,000 with asthma and over 300,000 with psychiatric problems, to investigate the association between asthma and other mental health and conditions. The results of this investigation suggest that mental health issues are linked to a higher chance of acquiring asthma in the future, and vice versa. The degree of increased risk was dependent on the type of mental disorder, which disorder was diagnosed first, and the time elapsed since the prior disorder [30]. Epidemiological research frequently indicates that anxiety, depression, substance use disorders, suicide, and schizophrenia often coexist with bronchial asthma. Females exhibited slightly stronger associations of psychiatric

disorders along with asthma. Mental illnesses and asthma typically manifest at different ages, with mental illnesses usually appearing later in life. In studies where asthma was the first disorder rather than the second, stronger correlations were discovered [31].

Hyperventilation and rapid breathing are common features of panic episodes, and in susceptible people, these factors can precipitate asthma attacks. While psychiatric disorders do not directly cause asthma, they can greatly affect its onset, severity, and management [32]. Furthermore, there are a few explanations for the co-occurrence of mental health problems and asthma. Firstly, overusing anti-asthma drugs may cause or worsen symptoms of sadness and anxiety. Some anti-asthma drugs, such as systemic or inhaled corticosteroids, may have anxiogenic qualities. Second, there are environmental risk factors like smoking and air pollution, psychosocial risk factors like stress, and genetic variables that are shared by mental disorders and asthma [33]. One recent review compiled observational studies on the relation between asthma and suicide-related practices, including ideation, attempts, and completion. There are evidences from many studies that patients with asthma have a 1.4 to 3.5 times higher risk of engaging in suicide-related behavior compared to those without asthma [34].

Poorly managed asthma is associated with a higher frequency of emergency department (ED) visits, resulting in a greater burden on healthcare resources. Mislabelling of symptoms can lead to needless treatment progression in either disorder.

In a study by A ten BRINKE et al., a comparative analysis of healthcare use in severe asthma patients with versus without psychiatric illnesses was conducted in 2001. It was found that patients with severe asthma who also had psychiatric conditions were nearly 11 times more likely to experience two or more asthma exacerbations and nearly 5 times more likely to require two or more hospitalizations in the past year compared to those without psychiatric disorders. Additionally, a total of 71% of the cases required two or more emergency department visits, in contrast to 31% of the non-cases. [35]. According to a large administrative claims-based analysis of children with asthma, children with anxiety or depression had 1.2 to 1.8 times the rates of asthma-related ED visits compared to children without these mental health conditions [36].

The Global Initiative for Asthma (GINA) guidelines emphasize the importance of managing stress and psychological factors in asthma care. Patients should be assessed and counselled on modifiable risk factors and triggers, including stress, anxiety, and depression. Asthma patients can benefit from montelukast, although caution is required due to the possibility of neuropsychiatric adverse effects. Close observation, patient education, and shared decision-making can all help reduce risks and provide the best possible results [37].

Neurophenotype in asthma

Asthma is most effectively categorized by clinical presentations (known as phenotypes) or by the mechanisms underlying the disease (referred to as endotypes). Beyond the pathological, cellular and molecular immune processes that characterize the known phenotypes, there is evidence that neural processes, especially those related to emotion, play a role in regulating airway inflammation and the clinical severity of asthma [38]. Psychological stress can amplify the Th2-dominant immune response during asthma exacerbations. The interaction between stress and the worsening of the Th2 type immune response through μ-opioid receptor (MOR) dependent sensitivity to signals in asthma suggests the presence of a "neuropsychiatry phenotype" within the pathophysiology of allergies [39,40].

Asthma's neural phenotype consists of structural and functional alterations in certain brain regions, abnormal cellular and molecular immunological responses, and external indications of neurological or psychological illness [41]. It describes the pattern of symptom expression triggered by the interplay between brain functions and the immunological response, which controls inflammation.

In the brain, the substance NPY (neuropeptide) plays a role in regulating eating behavior, secretion of neuroendocrine hormones, and responses to anxiety and stress. It has been suggested as a significant controller of inflammation, primarily by interacting with the NPY-Y1 receptor found in various immune cells that promote allergic airway inflammation. Nociceptin and its receptor are present in both central and peripheral nervous systems, where they participate in pain perception, mood disorders, anxiety, memory control, appetite, and immune system regulation [42]. They are crucially involved in the development of airway inflammation, heightened responsiveness, and bronchoconstriction [43].

Genetic correlation of asthma and psychiatric disorders

A genetic predisposition significantly influences the likelihood of developing asthma. Both mental health issues and asthma are highly heritable characteristics. Globally, parallel pandemic patterns in mental health problems and asthma suggested that these two diseases share genetic and environmental components [34]. On the other hand, not much is known about the common genetic components that link mental health issues and asthma.

Comprehensive genome-wide cross-trait studies have revealed shared genetics and potential causative links between asthma and three mental health problems, primarily MAD, ANX, and ADHD (attention deficit hyperactivity disorder, anxiety, and major depressive disorder) [44]. Their similar genetic makeup suggests that they may have novel biological activities in common. Research indicates that environmental factors may have a greater role in explaining the phenotypic association between ADHD and asthma in children than significant genetic

influences. According to previous research, there is a genetic association between a hereditary predisposition to ADHD (most of which are in children) and a genetic susceptibility to adult-onset asthma. Depression is found to be highly polygenic, with approximately 11,700 variants accounting for 90% of its SNP-heritability [45].

Hormonal influence in triggering asthma exacerbations during psychological stress

Stress hormones, such as glucocorticoids, adrenaline, and norepinephrine, are released during central nervous system activation and are implicated in the immunological changes linked to psychological stress-induced asthma exacerbations [46]. The HPA axis is a well-established pathway through which external psychological factors trigger a peripheral stress response. Key components such as corticotrophin-releasing hormone (CRH) and arginine vasopressin from the hypothalamic paraventricular nucleus (PVN), along with α-melanocyte-stimulating hormone, β-endorphin (β-END), and adrenocorticotropic hormone (ACTH) released from the pituitary gland, significantly influence the brain's stress response by acting as neurotransmitters at the onset of the HPA axis signal transduction [25]. These elements are strongly associated with the severity of allergic inflammatory responses. Neuroendocrine hormones such as prolactin, cortisol, and ACTH were shown to be considerably greater in stressed asthma patients compared to non-stressed ones [47,48].

Non-pharmacological modalities for reduction of burden in bronchial asthma

In clinical practice, stress is often overlooked as a possible trigger for exacerbations or uncontrolled asthma. When treating asthma, behavioral therapy such as stress management programs and cognitive-behavioral therapy (CBT), can be a useful addition. It improves asthma control, reduce the frequency of exacerbations, and improve quality of life. Early referral recognition can improve the patient's general health and avoid exacerbations [49].

However, a patient can refer to a behavioural therapist for identification of such disorders in following conditions:

- When physical and environmental problems are addressed yet asthma remains uncontrolled.
- When patients exhibit signs of despair, anxiety, or stress.
- When there is evidence of significant life stresses or inadequate coping strategies. There are various non pharmacological modalities which can be considered crucial for preventing disease progression and enhancing quality of life in asthmatic patients with psychiatric illnesses. Some of them are:

1. *Cognitive Behavioural Therapy (CBT):* A type of verbal therapy called cognitive behavioral

therapy (CBT) analyses how a person views themselves and other people in addition to how their behavior affects their emotions and ideas. Positive cognitive and behavioral changes are the goals of cognitive behavioral therapy (CBT). It helps to provide optimal thinking and perceptive approaches along with enhancement in coping mechanisms and tries to identify and rectify cognitive distortions. It may enhance the quality of life and asthma control in adults with asthma, but there is limited evidence regarding other significant outcomes [50].

2. *Relaxation therapy:* Relaxation therapies encompass meditation, progressive relaxation (systematically creating tension and relaxation in different body parts), autogenic training (focusing on bodily sensations and mentally controlling them), and hypnosis (deep relaxation induced by mental imagery) [51].
3. *Breathing exercises*: In Papworth technique of breathing exercise, patients are instructed to use their diaphragmatic muscles for breathing rather than improper auxiliary muscles of respiration and to breathe through their nose rather than mouth [52,53].
4. *Yoga*: Yoga integrates physical postures, or "asanas," with meditation techniques and controlled breathing, or "pranayama," with the goal of harmonizing the body, spirit, and mind. The repetitive breathing and muscle relaxation exercises in yoga may potentially improve lung function in children with asthma, particularly during their lung development [54].

Conclusions

Effective management of both asthma and mental health conditions requires a comprehensive approach that addresses both physical and psychological factors. Poor adherence to treatment regimens can result from psychological problems related to asthma, such as stress and anxiety. Having both psychiatric problems and asthma can result in increased functional disability, a worse quality of life, and more frequent doctor visits and hospitalizations. Asthma and mental health conditions can both benefit from psychological interventions like cognitive-behavioral therapy (CBT). These approaches can lessen stress and increase treatment adherence.

Therapeutic strategies to manage asthma exacerbations induced by psychological stress are still needed. To better evaluate and treat patients with asthma and mood disorders, a deeper understanding of the clinical, psychological, cellular, and molecular connections between these conditions is necessary. There are multiple proposed research domains to look into “Lung-Brain” axis where immune crosstalk is to be explored and along with assessment of epigenetic modulations various phenotypes can be evaluated. Collaboration between mental health professionals and allergists could lead to improved symptom management, enhanced quality of life, better overall functioning, and ultimately reduced mortality.

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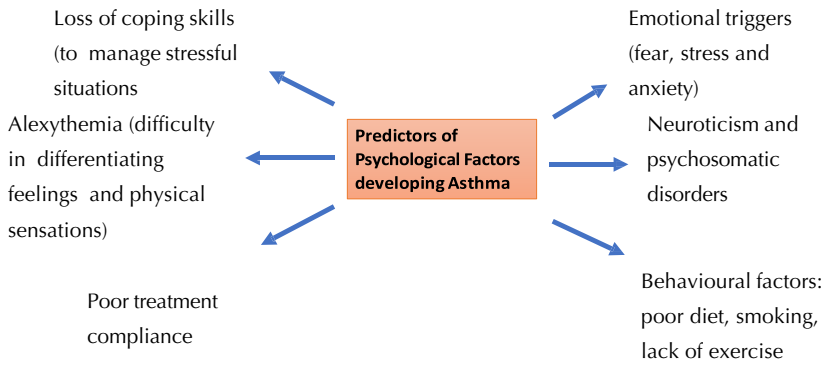

Figure 1. Psychological factors developing asthma symptoms.

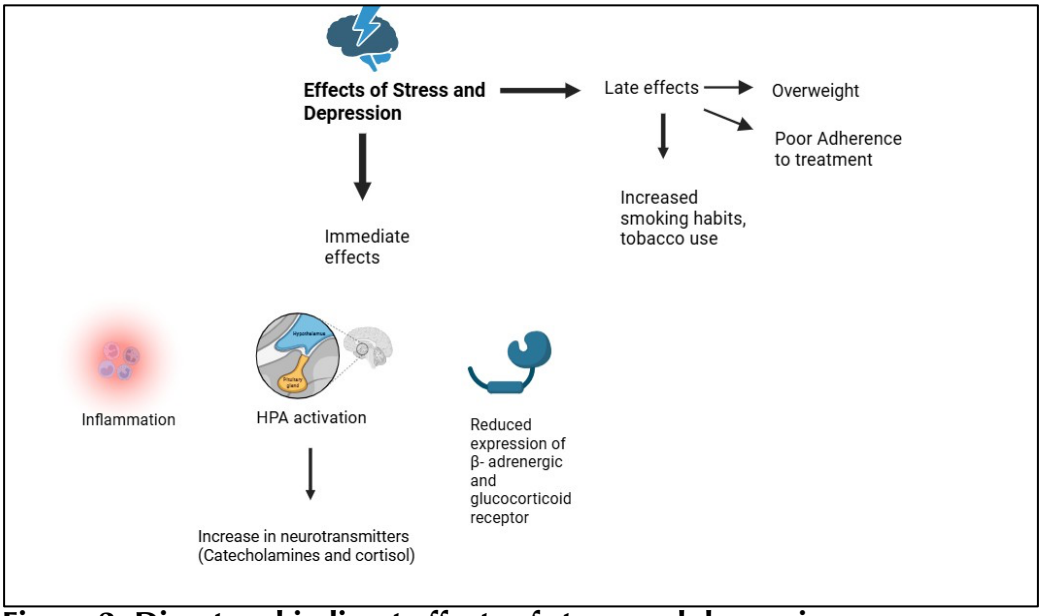

Figure 2. Direct and indirect effects of stress and depression.