



Perspective

Stress and asthma

Physiological manifestations and clinical implications

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Persistent or long-term, stress and stress correlates (eg, maternal and childhood anxiety) in early life have been associated with increased risk for new-onset respiratory disorders including episodic wheezing and asthma. These findings are not limited to early life, with major negative stressful events in childhood and adolescence prospectively associated with new active asthma diagnosed in adulthood.¹ In addition, although these findings highlight the incidence of new asthma, stressors, both acute and chronic, are also implicated in exacerbations among patients with asthma. Complex interactions among stressors, individualized coping mechanisms, and environmental risk factors (eg, outdoor air pollution and cigarette smoking) are likely to result in lasting physiological changes that influence subsequent disease risk. One hypothesis is that short-term stress can enhance and chronic stress can depress delayed hypersensitivity reactions. This risk is magnified if an individual has multiple chronic stressors.

Persistent psychological stress accentuates the magnitude of inflammatory responses to various environmental triggers. These triggers include living in greater proximity to traffic, environmental tobacco smoke, and indoor allergens. As a response to these triggers, normal homeostatic functions of key physiological systems are disrupted; both hormonal and endocrine abnormalities in addition to autonomic imbalance may result in long-term adverse health consequences. Current evidence suggests that these triggers may also partially mediate and confound the relationship between stress and asthma. It is also important to note that these chronic stressors facilitate childhood asthma exacerbations in the context of the social environment, with neighborhood and social factors closely related to asthma outcomes through both behavioral and biological pathways.

Throughout childhood, and adolescence, many shifts are observed in neuroendocrine function, with a dramatic change in reactivity exhibited by the hypothalamic-pituitary-adrenal axis in response to stressors. These types of responses are observed for both acute and more chronic stressors, although the evidence indicates more transient effects among the former. For example, youth with asthma and greater chronic family stress indicate greater in vitro stimulated production of cytokines implicated in asthma, including interleukin (IL)-5 and IL-13, and in vivo mobilization and activation of eosinophils.² Examination-related stress potentiates IL-5 production and eosinophil mobilization in sputum after an airway challenge among university students with asthma.³ Naturalistic clinical assessments are not as common. In a small sample of adults with asthma, everyday stressors, assessed across a 10-day period using preprogrammed watches, were linked to the participants' peak expiratory flow rate and asthma symptoms.⁴

A few studies have also evaluated the role of genetic or epigenetic mechanisms on stress-related asthma. For example, 1 study found that exposure to violence is associated with methylation of a CpG site in the promoter of ADCYAP1R1 and that such methylation is associated with asthma in Puerto Rican children (adjusted odds ratio per each 1% increment in methylation, 1.3; 95% confidence interval, 1.0–1.6; $P = .03$).⁵

Finally, stress can increase asthma morbidity by reducing response to inhaled corticosteroids and inhaled β_2 -agonists. Short-term and long-term stress have both been associated with reduced expression of genes encoding the glucocorticoid receptor (by 5.5-fold) and the β_2 adrenergic receptors (by 9.5-fold) in leukocytes of children with asthma (adjusted $P < .05$ in both instances).⁶

As the evidence base has increased, it is important to note the difficulty in a single standardized approach in assessing the stress-asthma association, with differences in populations, study designs, stress measures used, timing, chronicity of exposures and outcomes, and possible interactions. It is also noteworthy to point out some differences in subpopulations. For example, women may report more persistent stressful life events than men, consistent with other reports that girls are more likely to report cumulative

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stress.⁷ However, stronger associations with incident asthma have been observed among men.¹ It is unclear whether this difference in sex in response to stress translates into differential susceptibility for the prevalence or development of the disease. Marked differences by sex emerge in adolescence in physiological response systems that include corticolimbic circuitries, the hypothalamic-pituitary-adrenal axis, and the autonomic nervous system.⁸ In the analyses of data from the Asthma Coalition on Community, Environment, and Social Stress birth cohort in Boston, Massachusetts, there was a clear dose-response relationship between both increasing prenatal and postnatal maternal stress and the higher odds of childhood asthma among boys, whereas only the trend in postnatal stress was associated with asthma in girls.⁹ Clearly, both social and physiological factors may contribute to the difference in asthma risk by sex.

From a research perspective, the continuing development of rapid novel indicators or biomarkers of long-term stress is imperative (eg, hair cortisol gene expression). Continued epidemiologic research evaluating the mediators of early life stressors could also help us understand the extent that adherence, continuing life events, exposures, and coping strategies might play in attenuating or exacerbating the effects of stressors on asthma.

Given the evidence above, it is perhaps surprising that clinical assessments of stress levels are not routinely incorporated into patient examinations. A variety of quick means of measuring stress have been noted, such as self-reported questionnaires and event checklists. These tools may not always provide high-quality data, and thus, may not properly capture true events with sufficient sensitivity. In contrast, more resource-intensive interviews may provide in-depth information that is needed for a robust assessment. Different tools may also assess symptom perceptions, such as the visual analog scale, a psychometric response scale for subjective characteristics or attitudes (eTable 1). This is important given the subjective appraisals of stress and varying dimensions such as duration, intensity, and valence (ie, something considered negative). A recent cross-sectional study provided evidence that visual analog scale assessment of breathing perception could be a useful tool to measure symptom severity when compared with lung function measurement in a large cohort of children with a clinical diagnosis of asthma.¹⁰ Assessment of comorbid emotional disorders

could be useful in managing patients with asthma and understanding the role that other conditions play in an interplay with asthma. Finally, a comprehensive understanding of resilience, as has been espoused in other fields (eg, multiple sclerosis), may provide a more holistic opportunity for patient well-being. The role of disability-specific, biological, psychological, and social factors can be integrated in a more intensive fashion, incorporating both direct biological measures (eg, high-throughput systems-wide approaches that include epigenomics or microbiomes) and key elements of emotional health such as self-efficacy, physical dependence, and social support.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.anai.2020.07.022>.

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Supplementary Data

eTable 1
Examples of Clinical Stress Assessments

Measure	Brief description
Cohen's Perceived Stress Scale ¹	This is a frequently used 10-item measure that assesses subjective stress experiences by asking participants about how stressful they feel their life is in general.
Visual analog scale ²	This scale is particularly well-suited to assess perceived psychological stress in a clinical setting
Kessler's Psychological Distress Scale ³	This is a 10-item questionnaire intended to yield a global measure of distress based on questions about anxiety and depressive symptoms that a person has experienced in the most recent 4-week period.
The Child Stress Disorders Checklist ⁴	The Child Stress Disorders Checklist is an observer-report measure designed for use as a screening instrument for traumatic stress symptoms in children. It measures symptoms of acute stress disorder and posttraumatic stress disorder.
Pediatric Emotional Distress Scale ⁵	This 21-item parent-report measure was designed to rapidly assess and screen for elevated symptomatology in children after exposure to a stressful or traumatic event.

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