Asthma: Biomedical and Psychobiological Perspectives

Thomas Ritz, PhD, Melissa A. Rosenkranz, PhD, Juan C. Celedón, MD, PhD, Paul W. Davenport, PhD, Ratko Djukanovic, MD, Jonathan M. Feldman, PhD, Paul Forsythe, PhD, Nizar N. Jajour, MD, Donata Vercelli, MD, Andreas von Leupoldt, PhD, and Rosalind J. Wright, MD, MPH

Abstract: Substantial knowledge about asthma has accumulated in past decades from biomedical and psychobiological research. This white paper reports on synergistic perspectives for these fields discussed at the first Annual Disease-A-Year Symposium of the American Psychosomatic Society. Progress has been made in identifying mechanical, cellular and molecular mechanisms of asthma and influences of psychosocial factors on development, pathophysiology, and management have been demonstrated. However, much remains to be learned about mechanisms of asthma development, in particular the role of genes and the microbiome, and their interaction with psychosocial factors. Additional psychobiological analysis of immunobiological pathways and pathophysiological features is also needed, as well as integration with asthma phenotypes. Although traditionally viewed as a peripheral disease of the airways, its effect on the central nervous system and cognition has begun to garner attention due to neuroscientific and technological advances. Brain-body interaction is also the focus of airway interoception research, with practical consequences for the management of overperception and underperception of airway obstruction. An integrative perspective on asthma recognizes societal factors that worsen and consolidate disparities in asthma outcomes and explores mechanisms of building resilience in patients from disadvantaged communities. Biomedical treatment with novel monoclonal antibodies promises a personalized medicine approach, while improvements to asthma management trainings have increased disease control and quality of life. Psychobiological and mind-body interventions, such as exercise, breathing training, cognitive behavioral therapy, or meditation techniques, require further exploration in large-scale multicenter trials. Close interdisciplinary collaboration will bring the field closer to the ideal of a holistic biopsychosocial treatment of asthma.

Key Words: asthma, etiology, pathophysiology, psychobiology, interoception, diversity, biopsychosocial treatment

Abbreviations: **IL** = interleukin, **T2** = type-2, **T1** = type 1, **Th2** = T-helper cell type 2, **Th17** = T-helper cell type 17 **PROMIS** = Patient-Reported Outcomes Measurement Information System, **fMRI** = functional magnetic resonance imaging **PET** = positron emission tomography, **RREP** = respiratory-related evoked potential, **CO_2** = carbon dioxide, **PCO_2** = partial pressure of carbon dioxide, **PEF** = peak expiratory flow, **ADHD** = attention deficit hyperactivity disorder, **ADRB2** = $ß_2$-adrenergic receptor gene, **ADCYAP1R1** = adenylate cyclase activating polypeptide 1 receptor 1 gene, **PLCB1** = phospholipase C beta 1 gene, **ICS** = inhaled corticosteroids, **IgE** = immunogobulin E, **INF-γ** = interferon gamma

(*Biopsychosoc Sci Med* 2025;87:428–444)

Received for publication December 22, 2024; accepted May 5, 2025.

From the Department of Psychology, Southern Methodist University, Dallas, Texas, (Ritz); Center for Healthy Minds, and Department of Psychiatry, University of Wisconsin-Madison, Madison, Wisconsin, (Rosenkranz); Department of Pediatrics, Division of Pulmonary Medicine, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh, Pittsburgh, Pennsylvania, (Celedón); Department of Physiological Sciences, University of Florida, Gainesville, Florida, (Davenport); Faculty of Medicine, Clinical and Experimental Sciences and Human Development and Health, University of Southampton, and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK (Djukanovic); Ferkauf Graduate School of Psychology, Yeshiva University, and Department of Pediatrics, Division of Academic General Pediatrics, Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, New York, New York, (Feldman); Department of Medicine, Division of Pulmonary Medicine, Alberta Respiratory Centre, University of Alberta, Edmonton, Canada (Forsythe); University of Wisconsin-Madison School of Medicine and Public Health, Pulmonary and Critical Care Division, Madison, Wisconsin, (Jajour); Department of Cellular and Molecular Medicine, Asthma and Airway Disease Research Center, BIO5 Institute, and Arizona Center for the Biology of Complex Diseases, University of Arizona, Tucson, Arizona, (Vercelli); Research Group Health Psychology, KU Leuven, Leuven, Belgium (von Leupoldt); Department of Environmental Medicine, Department of Public Health, and Institute for Exposomic Research, Icahn School of Medicine at Mount Sinai, New York, New York, (Wright).

T.R. and M.A.R. are sharing first-authorship of this report.

Article Editor: Suzanne C. Segerstrom

Address correspondence to Thomas Ritz, PhD, Department of Psychology, Southern Methodist University, P.O. Box 750442, Dallas, TX 75275 (E-mail: tritz@smu.edu); Melissa A. Rosenkranz, PhD, Center for Healthy Minds, University of Wisconsin-Madison, 625 W. Washington Avenue, Madison, WI 53703 (E-mail: melissa.rosenkranz@wisc.edu).

DOI: 10.1097/PSY.0000000000001410

INTRODUCTION

Asthma is a chronic respiratory disease that affects close to 270 million people worldwide.[1] In 2021, ~25 million people reported having current asthma in the United States, including ~4.7 million children and ~20.3

million adults.[2] Close to 10 people per day still die from asthma in the United States. As one of Franz Alexander's "Holy Seven" of psychosomatic disease, asthma has long been a focus of psychosomatic research,[3] while confounding medical and psychological scientists alike. Biomedical research has made strides in recent decades, highlighting roles of cellular and molecular pathways in the course of the disease.[4] At the same time, research from a psychobiological angle has identified major roles of behavioral and experiential factors in the etiology, pathophysiology, and management of asthma, with ongoing efforts to delineate mechanistic pathways that underlie such associations. Recent years have further shown substantial health disparities that are perpetuated by complex, multifactorial interactions of sociopolitical, psychological, and somatic factors. Psychosomatic intervention efforts have begun to address some of the psychological features that contribute to the pathophysiology of asthma, but require further development and rigorous testing of feasibility, efficacy, and underlying psychobiological mechanisms.

This executive summary of a white paper provides perspectives for an interdisciplinary research agenda on asthma. It follows the inaugural Disease-A-Year (DAY) symposium organized by the Society for Biopsychosocial Science and Medicine (SBSM, formerly American Psychosomatic Society) in November 2023. This symposium brought together biomedical and psychosomatic experts to review the state of current knowledge on asthma, with the goal to stimulate further cross-disciplinary dialogue and synthesis of ideas, and thereby develop an agenda for future collaborative research into this psychosomatic disease. The presented research priorities consider the latest evidence from basic and clinical research to inform a new generation of studies that ultimately benefit a biopsychosocial approach to treatment and management of asthma.

CLINICAL MANIFESTATION AND PATHOPHYSIOLOGY OF ASTHMA

Asthma is characterized by variable airway obstruction that is typically reversible, either spontaneously or with the use of an inhaled bronchodilator. It can manifest at any time in life, although it is more common during childhood, especially among people with allergies. Asthma can be intermittent with only mild disease, but can also be severe with significant morbidity and mortality, with more than 4,000 deaths a year in the United States and hundreds of thousands worldwide. Asthma diagnosis is suspected based on a combination of risk factors (presence of allergies, hay fever, and family history of asthma), episodic symptoms (cough, wheezing, shortness of breath, and chest tightness), identifiable triggers (Table 1), and pulmonary function tests including spirometry, airway hyperreactivity testing by bronchial challenge with inhalation of methacholine (or indirect stimuli such as exercise, histamine, dry powder manitol, cold or dry air), or bronchodilator reversibility testing (for diagnostic procedures[4,5]).

TABLE 1. Common Asthma Triggers

- Allergen exposure (e.g. ragweed, house dustmite, cat dander)
- Exercise
- Circadian variation (nighttime sleep)
- Psychosocial factors, stress, anxiety, depression
- Respiratory viral infections
- Occupational exposure, air pollution, smoking
- Medications (eg Aspirin)
- Nonadherence to antiasthma medication

Pathophysiology of Airway Inflammation, Obstruction, and Hyperresponsiveness

"Airway inflammation" is present in patients with asthma, especially when symptomatic. It manifests with infiltration and activation of leukocytes, release of active mediators, cytokines, enzymes and eosinophil granule proteins. These mediators lead to excessive smooth muscle contraction ("airway hyperresponsiveness"), causing airway obstruction, damage to the epithelium, exposure of the basement membrane, and recruitment of additional inflammatory cells to the airway. Mucus glands are also activated to generate more mucus, which contributes to airway luminal obstruction. Activation of fibroblasts results in collagen deposition and increased fibrosis, commonly in the sub-basement membrane area. Together with proliferation of airway smooth muscles and mucus glands, these structural changes are known as "airway remodeling," resulting in thickened airway walls and narrow lumens, a common manifestation in more severe asthma.

Distinctions of Subtypes of Asthma by Immune or Clinical Characteristics

The cardinal immune cell associated with airway inflammation in asthma is the eosinophil, which is recruited and activated by cytokines, mainly interleukin-5 (IL-5). The constellation of eosinophilic inflammation and expression of the cytokine family associated with allergy (ie, IL-4, IL-13, and IL-5) is known as Type-2 (T2) inflammation. By contrast, Type-1 (T1) inflammation is usually triggered by infections, marked by release of cytokines like interferon gamma, and meant to protect against pathogens.[6] These 2 distinct types have been distinguished in asthma, with important implications for the choice of therapy. Their definitions are part of a broader realization in recent years that asthma is a heterogeneous disease, characterized by different phenotypes distinguished by clinical signs or endotypes by pathobiological processes (Table 2). These different phenotypes have implications for the choice of biological precision therapies that have become more widely available.[7]

Pathophysiology of Asthma Exacerbations

The typical course of a severe exacerbation is shown in Figure 1. Exacerbations are often limited to early stages (moderate exacerbation[8]) with the right treatment. Patients' rising anxiety or panic can accelerate the course by hyperventilation, which leads to further airway obstruction, respiratory alkalosis, and respiratory muscle fatigue.[9,10]

TABLE 2. Common Asthma Phenotypes Defined by Typical Clinical Signs and Endotypes Defined by Pathobiological Processes[5,6]

Phenotypes
Allergic: childhood onset, family history of atopy, high eosinophils, responds to ICS
Nonallergic: lesser short-term response to ICS, sputum may be neutrophilic, eosinophilic, or paucigranulocytic (few inflammatory cells)
Cough variant/cough predominant: cough as only symptom, less variability of obstruction in daily life, reversibility by bronchodilator in later stages, responds to ICS
Late-onset: developed in adult life, often nonallergic, predominantly in women, reduced ICS response
Persistent airflow limitation: consequence of long-standing asthma, incomplete reversibility of obstruction, airway remodeling
Obesity-associated: due to obesity, less eosinophilic
Endotypes or molecular/physiological phenotypes
T2 high: eosinophilic inflammation, through T-helper cells type-2 and type-2 innate lymphoid cells, activating cytokines IL-4, IL-5, and IL-13
T2 low: neutrophilic inflammation, through T-helper cells type-1 T-helper cells type 17 activating cytokines INF-γ, IL-8, IL-1β, IL-17

DEVELOPMENT OF ASTHMA

Asthma is the most common chronic complex disease of childhood and is mechanistically positioned at the intersection of genetic, environmental and developmental factors.[11] Half of all cases of asthma manifest by age 3 years, 80% by age 8, making the early life period particularly relevant. Type-2 dominant immune responses (ie, atopy) are common during childhood, yet only a subset of atopic children develop asthma, while others are asymptomatic or affected with other conditions such as eczema or allergic rhinitis.

Genetic Factors in Asthma Development

Unbiased genetic analyses of asthma based on genome-wide association studies and whole genome sequencing have identified multiple variants and loci that are associated strongly and reproducibly with asthma phenotypes in large populations,[12] thereby providing testable hypotheses about asthma pathogenesis. Typically, asthma-associated variants are located in genes that regulate type-2 immune responses (those involved in allergic asthma) and in genes that modulate mucosal responses to respiratory viruses.[13] These findings are well aligned with epidemiologic data pointing to strong associations of asthma risk with type-2 allergic responses[14] and respiratory viral infections,[15] especially when the latter occur during the first 2 to 3 years of life, the time during which the lung develops.

Influence of the Environment in Asthma Development

While these findings highlight important genetic components of asthma pathogenesis, asthma is also an environmental disease. This was made clear by the demonstration of dramatic increases in asthma incidence over the last few decades,[16] a finding that could only be explained by major changes in the environment. These studies ignited much new research which led to the formulation of what became known as the hygiene hypothesis[17]—the concept that individuals who grow up in a microbe-rich environment, such as traditional dairy farms, develop strong protection against asthma, allergies and severe respiratory viral infections.[18] The initial European epidemiologic findings supporting the hygiene hypothesis[19,20] were replicated in a myriad of studies world-wide[21] and were decisively extended by work in the Amish and Hutterite U.S. farming populations,[22] which share genetic ancestry and multiple lifestyle-related risk factors for asthma but differ in their approach to farming, which remains traditional among the Amish but is modern and highly mechanized among the Hutterites.[23] Microbial load, measured as endotoxin levels in house dust, was 6-fold higher, while prevalence of asthma was 5-fold lower, among the Amish compared with the Hutterites.[22] Moreover, and critically, inhalation of Amish but not Hutterite farm dust was sufficient to protect mice from allergic asthma through processes that require innate immunity, providing a mechanistic framework to understand the critical role of environmental microbial exposures in asthma protection.[24]

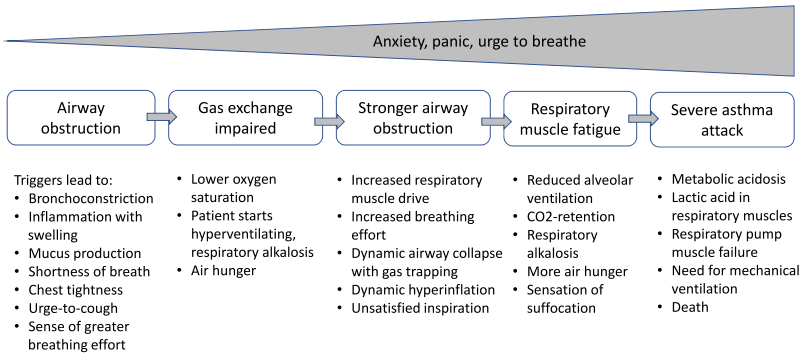

FIGURE 1. Time course of a severe asthma exacerbation. Less severe or "moderate exacerbations" are limited to earlier stages with the right treatment. A moderate exacerbation is defined by a "deterioration in symptoms, deterioration in lung function, and increased rescue bronchodilator use" that "should last for 2 days or more, but not be severe enough to warrant systemic corticosteroid use and/or hospitalization."[8]

Copyright © 2025 Society for Biopsychosocial Science and Medicine

Role of the Microbiome in Asthma Development

Of note, later studies, again in European farmers, showed that a microbe-rich environment promotes the maturation of the gut microbiome in the first year of life,[24] the time at which microbiome and immune system are most effectively shaped by environmental exposures and influence one another's development. Indeed, a cutting-edge working model proposes that *in utero* and early life trajectories of microbiome and immune maturation differ in participants who will or will not develop asthma during childhood,[25,26] with delayed immune and microbiome development found early on in children who will later be diagnosed with asthma. Taken together, these results show how inextricably genes, environment and development interact to shape the asthma trajectory. They highlight promising avenues that can inform efforts at early intervention to not just manage existing asthma through behavioral and psychobiological pathways, but to prevent the development of asthma at an early age.

The Gut Microbiome in Asthma

There is now good evidence of an association between the composition of airway and gut microbiomes and asthma development, severity, and symptomatology.[27] In the lungs, certain bacterial species have been implicated in triggering inflammatory responses leading to asthma exacerbations.[28,29] Most evidence linking commensal organisms to asthma is associated with the gut microbiota, showing that reduced gut microbial diversity and/or paucity of select bacterial genera during infancy is associated with an increased risk of asthma later in life.[30–32] Transfer of human neonatal gut microbiome associated with allergy development into pregnant germ-free mice confers susceptibility to allergic airway inflammation to their offspring, while addition of putative protective bacterial genera reversed the susceptibility.[29,32] More research is needed on asthma-relevant microbial pathways in other bodily tissues, in particular the lung, nasal, and oral compartments as part of a continuous airway.

Gut-lung Axis in Asthma

The influence of gut microbes on asthma development and severity relies on the "gut-lung axis," a major component of which is the common mucosal immune system. In that, activated lymphocytes migrate from one mucosal site to another,[33] in particular through mesenteric lymph nodes, where the microbe-associated dendritic cells then influence the development of T cells, B cells and regulatory T cells (Treg). The latter normally confer protective effects by maintaining immune tolerance to self-antigens, preventing autoimmune/autoinflammatory disease[34] and mediating down-regulation of the allergic airway responses.[35] However, gut microbial composition can also lead to reduced Treg development and/or promotion of pro-inflammatory Th2 or Th17 cells that may predispose one to asthma development or increased disease severity.[36,37] Beyond the common mucosal immune system, it has been suggested that gut microbe-derived metabolites, such as short chain fatty acids,[38,39] or even components of the commensal bacteria, in the form of bacterial microvesicles,[40] could directly enter the circulation and influence the immune environment of the lung. Psychobiological influences on these processes through the autonomic, endocrine, and immune system pathways remain largely unexplored.

Gut Microbiota and the Gut-brain Axis in Asthma

There is increasing awareness of the influence of gut microbes on brain function, mood, and behavior. The mechanisms underlying communication between gut microbes and the brain have yet to be delineated in detail but broadly involve engagement of nervous, immune and endocrine signaling pathways, with the vagus nerve appearing to play a central role in linking these systems.[41] Extensive preclinical evidence indicates that disruption of the gut microbiota, for example, through exposure to clinically relevant doses of antibiotic, or exposure to specific commensal organisms, can alter brain chemistry and behaviors associated with depression, anxiety, and social bonding.[41–45] Correspondingly, studies in humans have identified altered gut microbiota composition in individuals with mood disorders, while consumption of certain organisms, such as lactobacilli, has been demonstrated to attenuate stress responses.[41,46,47] Thus, the disrupted gut microbiota associated with asthma may modulate brain function, predisposing one to enhanced stress perception and/or mood disorders. Importantly, this microbiota-gut-brain axis is bidirectional and psychological perturbations such as chronic social stress can shift gut microbial composition, with associated changes in the immune system.[48] Correspondingly, stress associated with asthma may influence gut microbiota composition that, in turn, perpetuates a pro-inflammatory immune environment.

Perspectives on Psychobiologically Relevant Microbiome Research in Asthma

Overall, research is uncovering a complex system of multidirectional relationships between commensal microbes, the immune system and the mind.[41,49] In asthma, both immune and psychological dysregulation associated with the disorder may influence microbiome composition, while, in turn, functionally significant disruption of the microbiome, whatever the instigating factor, may maintain and reinforce the detrimental relationship between chronic airway inflammation and mental health. More research is needed into the response of the human brain to specific functional changes in the gut microbiota. In general, we require a greater mechanistic understanding of microbe-host interactions in humans to allow for the development of knowledge-based approaches to therapeutic modulation of the microbiota. There has been very limited research into the significance of a microbiota-lung-brain axis. Our understanding of the lung as a sensory organ is limited, we need to know more about how microbes engage the sensory systems of the lung, how this influences the brain and the degree to which microbiota-lung-brain communication might be altered in asthma.

Prenatal and Postnatal Exposure to Psychosocial Stress

Starting very early in pregnancy, stress can play a role that persists across the entire lifespan. Beyond genetics and environmental exposure, one of the modifiable risk factors is psychosocial stress. This factor starts in the womb and continues throughout a sensitive period in infancy. In addition to individual-level factors such as race, ethnicity, or socioeconomic status, neighborhood or community-level risk factors also require consideration.[50]

Longitudinal Pregnancy Cohort Designs

Studies following mothers during prenatal and postnatal periods have shown psychosocial risk factors for development of respiratory diseases. Thus, for both prenatal and postnatal periods, the number of negative life events in the family is linked to financial, legal, neighborhood and personal safety in the past 6 months. Further, the number of these events has been shown to increase the risk of wheeze in children up to the age of 3 years.[51] Interestingly, sex differences exist where boys show more of a susceptibility in the prenatal period, whereas girls show greater susceptibility postnatally.[52,53] Interactions of stress with other environmental or community factors, which have been observed for air pollution,[54] require further study.

Resiliency

Factors that may help buffer risk also deserve attention. For example, early life adversity has been associated with flatter diurnal cortisol slopes in 6-month-old infants.[55] Greater maternal sensitivity at that stage can buffer the association between these cortisol abnormalities and wheezing in the first years of life, which was selectively observed in boys. In addition to demonstrating the importance of early life psychosocial environment, these findings should motivate greater attention to sex effects in asthma development and protective factors that build resilience.

PSYCHOBIOLOGY OF MANIFEST ASTHMA

The role of psychological factors in asthma symptoms and exacerbations appears to be firmly established after decades of experimental, observational, and clinical research. Consequently, recent clinical guidelines have included stress and emotions as triggers of asthma.[4,56–58] Similarly, the elevated prevalence of psychological disorders in asthma, in particular anxiety and depression, is now well-recognized,[59,60] although psychological triggers can predict asthma outcomes beyond these comorbidities.[61] Increasingly, stress and mental health are also identified as risk factors for asthma onset.[62–64] Further study of interactions between triggers or risk factors of asthma is needed, in particular synergistic effects of psychological factors with other prominent triggers of asthma exacerbations, such as air pollution[65–67] or respiratory infections.[68,69]

Psychobiological Pathways to Pathophysiological Features of Asthma

Much remains to be learned about differential effects of psychosocial stimuli and challenges on asthma pathophysiology, as even basic psychobiology research continues to uncover physiological correlates of emotional states, acute and chronic stress, burnout, as well as various psychological disorders. More integrative studies that combine central and peripheral autonomic nervous systems, with endocrine and immune pathways as they interact and contribute to asthma pathophysiology are needed.

Acute Stress Effects on the Airways

A more complex understanding of these mechanisms is necessary to, for example, reconcile the effects of acute stress on the airways. Airway smooth muscles contract with stimulation of muscarinic receptors by the parasympathetic (vagal) system and relax with stimulation of beta-adrenergic receptors on the muscle surface, mostly by circulating catecholamines[70] (the latter mechanism is exploited by common short-acting beta-adrenergic inhalers). Therefore, theoretically, stress-induced sympathetic activation should be bronchodilatory and thus beneficial. Paradoxically, experimental research has shown that negative emotions have bronchoconstrictive effects.[71,72] There is evidence from cholinergic blockade with ipratropium bromide that central vagal excitation is driving bronchoconstriction induced by aversive picture and film material in the laboratory.[73] Similarly, earlier work using experimental suggestions of bronchoconstriction has shown that cholinergic blockade eliminates their constrictive effects.[71] However, whereas these laboratory paradigms require passive endurance, evidence from stress-induction by tasks that require more active coping is so far inconclusive, potentially due to sympathetic activation counteracting vagally induced bronchoconstriction.[74] Anti-inflammatory effects of steroid hormones can also be expected to be beneficial, and brief laboratory induction of psychosocial stress has shown that exhaled nitric oxide (as a proxy for airway inflammation) can be reduced by cortisol mobilization.[75] A better understanding of the precise neural, molecular, genetic, and epigenetic signaling pathways underlying these effects is essential to developing a more comprehensive treatment arsenal.[76,77]

Chronic Stress Effect on the Airways

Chronic stress and depression are known to elevate cortisol levels. Although anti-inflammatory effects of cortisol could be expected to alleviate asthmatic airway inflammation, psychosocial stress has been shown to exacerbate airway inflammation[78–80] in asthma. Studies have highlighted the role of early childhood adversity in asthma.[81] These effects could be mediated by the hypothalamic-pituitary-adrenal axis, in that elevated levels or flatter cortisol slopes are observed initially, but blunted cortisol activity favoring inflammation is observed in later adolescence and adulthood.[82] Low levels of endogenous cortisol[75,83] and reduced cortisol responsiveness to stress[84] have been observed in children and adults with asthma, a finding that seems to extend to atopy in general.[85,86] Reduced cortisol mobilization has been linked to lower spirometric lung function[83] or higher exhaled nitric

oxide.[75,87,88] Comorbid depression[89,90] and anxiety disorders[60] in asthma may also contribute to inflammation, but more research is needed. The allostatic load of chronic stress and persistent psychopathology, their impact on the efficacy of pharmacological asthma treatments, and their association with the variable nature of asthma exacerbations require detailed longitudinal study protocols.

Further Study of Relevant Biological Variables

Psychobiological mechanisms that mediate the impact of various psychosocial factors are far from fully elucidated. Among the key pathophysiological features of asthma, only mechanical lung function and airway inflammation have been studied in much depth,[71,74,78] whereas effects on mucus production and airway remodeling are virtually unexplored. Examination of the immune and inflammatory processes has also been almost exclusively limited to systemic (ie, circulating) biomarkers. Exceedingly little research has examined psychologically driven changes in the airway milieu. In the little work that has been done, stress paradigms combined with measures of induced sputum or bronchoalveolar lavage have demonstrated alterations in the canonical immune pathway of allergic asthma, the Th2 response, by stimulated airway cytokines[78] or gene expression changes associated with a Th17 inflammatory response in the airways.[79,80,91] The descending effects of psychological stimuli on epithelial cells, pulmonary neuroendocrine function, mucus production, and other immune signaling pathways are completely opaque and require directed research efforts. The development of noninvasive indices of such processes that can be implemented in biopsychosocial studies requires more in-depth collaboration of psychobiologically-oriented scientists with medical specialists, biophysicists, and biomedical engineers.

Psychobiology of Asthma Phenotypes and Endotypes

It is now well-established that only a subgroup of asthma patients is susceptible to psychological triggers. Laboratory studies, field observations, and patients' self-reports converge on an estimated 25% of affected cases,[71,72,92] although patient populations identified by these methods only partly overlap. The extent to which these features coincide with distinct asthma phenotypes and endotypes identified more recently in medical research[93,94] remains unknown. It has been recognized for some time that asthma is not exclusively an allergic process,[95–97] a fact that is also reflected in patients' tendencies to independently perceive allergic versus nonallergic precipitating factors of their asthma symptoms.[61,92]

Thus, psychobiological research is now presented with the new challenge of considering phenotypic and endotypic variations. There is probably no one-size-fits-all approach to biopsychosocial disease characterization for a heterogeneous disease such as asthma, except for the most generic lifestyle and disease management recommendations. It is likely that the neglect of distinguishing endotypic (or molecular/physiological phenotypic[94]) features has been a barrier for important mechanistic psychobiological insights. Endotyping according to proposed criteria[98] will require a broader range of data sources, including markers from blood, sputum, and challenge tests.[6] Of particular interest are endotypes of low type-2 cytokine activation and neutrophilic inflammation as observed in severe asthma, comorbid obesity, and smoking,[6,99] given the apparent public health burden and the paucity of psychobiology research for these conditions.

Similarly, medical research should include, at a minimum, scales that allow basic psychological characterization of patients such as Patient-Reported Outcomes Measurement Information System (PROMIS) measures,[100] to identify potential phenotypes characterized by psychosocial features. It is quite possible that such research can help identify a broader range of phenotypes that incorporate biopsychosocial characteristics and expand our knowledge on asthma endotypes with thus far unrecognized psychobiological mechanisms, offering new opportunities for additional refinement of personalized management efforts.

Extrapulmonary Features of Asthma: The Role of the Brain

The past two decades have seen the conceptualization of asthma as a disease confined to the airways erode. This is partially due to the recognition that triggers outside the airway play important roles in asthma pathophysiology. This dawning has been aided by neuroimaging research that shows that the brain is both impacted by, and influences the trajectory of disease expression in asthma.[101] Both fMRI and PET brain imaging have been used to show differential processing of cognitive and emotional information, depending on airway status,[34,102,103] and that neural responses to psychological stimuli have measurable and clinically relevant relationships with airway mechanics and inflammation.[79,80,104,105] This domain of research opens a new frontier of previously unexplored extrapulmonary treatment targets.

Consequences for Cognition, Health and Disease Management, and Daily Life Functioning

Indeed, it is becoming clear that the psychobiological impact on the trajectory of asthma is also not limited to stress and emotion. Emerging data suggest that brain structure[80,106,107] and chemistry (eg, hippocampus[108]) are compromised by asthma pathophysiology, and the potential consequences of these changes for learning, memory, behavior and, by extension, disease management, are currently unclear. Meta-analytic data do corroborate the deterioration of cognitive function, and executive function in particular, in asthma patients.[109] Thus, future research should include measures of cognitive function, as well as their interaction with stress and emotion, to investigations of psychobiological contributions to asthma. Further, association of these cognitive and emotional phenomena with various lifestyle factors, such as physical activity, sleep, and nutrition, and disease management factors such as

medication treatment and adherence, as well as the possible role of these factors as instigators or mediators of beneficial or detrimental asthma outcomes requires attention. Linking these psychobiological findings with daily life functionality of patients will lead to more ecologically valid insights that facilitate translation into individually-tailored interventions to meet the notable gaps in disease management that currently exist.

INTEROCEPTION OF ASTHMA

Dyspnea and the Problem of Deficient Perception of Airflow Limitation

Dyspnea is an aversive symptom that is perceived as breathlessness, difficulty of breathing, or shortness of breath in asthma and many other diseases.[5,110] The ability to recognize airflow limitation and interpret resulting asthma symptoms such as dyspnea is central to effective asthma management and control. Recent recommendations for controller and as-needed medication use[111] rely on accurate perception of airflow limitation to trigger timely use. Patients who underperceive may be less likely to follow these recommendations and worsen control of their asthma. Underperception has been linked to increased asthma morbidity and elevated risk for near-fatal and fatal asthma exacerbations,[112,113] as it may result in a lack of appropriate health care or undertreatment. Conversely, over-perception of airflow limitation may lead to overuse of rescue medications and iatrogenic adverse effects (eg, tachycardia and tremors), excessive avoidance of activities, overuse of health care resources, and worse physician ratings of asthma control.[114,115] A resulting discordance between patient's and physician's perception of asthma control[116,117] is linked to poor asthma control and lack of pulmonary function testing.[117,118] Despite the long-standing recognition of this problem, there is a paucity of knowledge about causes and mechanisms of overperception and underperception of airflow obstruction in asthma.

Central Nervous System Processes in Respiratory Interoception

The perception of dyspnea is a highly complex brain integration process of myriad physiological signals, their neural gating and subsequent cortical processes with various psychological (eg, emotions, cognitions, predictions) and social/environmental factors. While much of the sensory input from respiration and the airways is not consciously perceived, a stimulus that elicits a change in ventilation allows for conscious awareness.[119] Research suggests that this is based on a neural gate, which allows information to move from the brainstem-pontine regions to cognitive higher brain regions[119–122] and activates a respiratory motivation system with two parallel cortical activation pathways, discriminatory (sensory) and affective.[119,123] Both pathways project to executive regions where modality-specific recognition and discrimination occurs.[119,124,125] Modality-specific behavioral respiratory motor compensation can then be elicited, specific to the modality of breathing change that occurred, for example, an asthma exacerbation. More research is needed on modality-specific and multimodal executive mechanisms of cognition, discrimination, and decision that will lead to behavior compensation and their association with concrete asthma management behaviors.

Respiratory Interoceptors

Myriad inputs from respiratory interoceptors, providing information about airflow, volume, pressure, pumping force and chemical sensation, are involved in this process.[119] These afferents feed into the CNS through two primary tracks, either through spinal nerves into the spinal cord or through cranial nerves into the brainstem. If an error signal "opens" the gate, the interoceptor clusters project into the discriminative and affective pathways where multiple modalities of breathing can be differentiated into specific sensations such as air hunger, hyperinflation, effort of breathing, the urge to breathe, chest tightness and respiratory defensive reflexes (Urge-to-Cough).

Mechanical Load Testing

Added resistive loads that elicit obstructed breathing have been used to study thresholds of dyspnea perception. In the electroencephalogram, they elicit respiratory-related evoked potentials (RREPs) as indicators of conscious cortical processing. Paired presentations of such loads, including transient inspiratory occlusions, demonstrate gating by a dampened response to the second load.[121,122,126,127] There is evidence that affective states, such as anxiety, reduce the efficiency of the gate[128–130] and thus can contribute to symptoms, but both physical location of the gate and cognitive and affective processes that may modulate it require more attention.

Underperception of mechanical loads (higher detection threshold, reduced discriminative ability) has been observed in children with life-threatening asthma,[131] together with a lack of RREPs,[132] suggesting a lack of somatosensory cortical activation with increased breathing effort. This will delay their awareness of, and consequently ability to respond to, an asthma exacerbation. A more comprehensive testing of patient populations and subpopulations defined by phenotypes or endotypes would be needed to gain insight into prevalence and mechanistic pathways underlying such perceptual abnormalities.

The asthmatic respiratory interoceptive experience on the sensory side can be specific to stages of an exacerbation (Fig. 1). The role of mitigating and aggravating psychological factors at various stages requires more research.

Integration of Respiratory Interoception With Affect and Cognition

The brain is continuously monitoring respiratory interoceptive signals and integrates them with the affective state of the individual (eg, anxiety, depression), and with cognitive processes (eg, direction of attention, making predictions, catastrophizing thoughts) based on contextual

information (eg, environmental stimuli, social support).[133,134] The perception of dyspnea is, therefore, a personal experience and the net result of a highly complex integration process of various physiological signals (see above) with various other psychosocial factors and environmental signals within the brain.[110,135]

Interactions between dyspnea, cognitive and affective processes have frequently been reported.[115,133,136,137] For example, high levels of negative affect (eg, anxiety, depression) and disease-specific catastrophizing are commonly associated with greater dyspnea reports in adult and pediatric patients with asthma.[115,138–142] Moreover, maladaptive behaviors (eg, reduced sociality, hypervigilance) and implicit (learned) associations[143–146] have been shown to contribute to increased dyspnea experiences, typically in the absence of ventilatory changes.

Neuroimaging of Respiratory Interoception With Affect and Cognition

In healthy volunteers, studies with functional magnetic resonance imaging (fMRI), positron emission tomography or electroencephalography with experimentally induced dyspnea by CO_2 inhalation or resistive loaded breathing show that dyspnea is commonly associated with activations in two major networks, sensorimotor and cognitive-affective brain areas.[123,147–149] The former includes areas such as the sensory cortex, (pre) motor cortex, supplementary motor area and cerebellum, typically involved in the processing of sensory (ie, intensity of dyspnea) and qualitative aspects (ie, work/effort of breathing vs air hunger vs chest tightness) of perceived dyspnea. The latter include areas such as the insula, amygdala, anterior cingulate cortex, periaqueductal gray, hippocampus and prefrontal cortex, which are known to be involved in several affective, cognitive and self-regulatory processes. There is also a high degree of overlap between regions responsive to dyspnea and airway inflammation,[102,103] suggesting their general role in airway interoceptive processes and their contributions to the cognitive-affective aspects of asthma (ie, unpleasantness of dyspnea)[150] However, much remains to be learned about the neural implementation of affect, cognition, and dyspnea interactions, both in health and disease.

As brain imaging studies have begun to identify asthma-related alterations in brain responses to emotion and stress and their relation to asthma-specific pathophysiology, considerable overlap is observed with brain areas that respond to dyspnea induced by manipulations of affect or expectations of dyspnea induced by experimental cues in individuals without asthma.[151–153] However, too few studies have examined interactions between dyspnea and cognitive and affective processing in asthma,[154] limiting our understanding of potential disease-specific alterations in these brain networks.

Whether such brain responses causally underlie overperception and underperception of dyspnea in asthma patients, process the dyspnea-cognition/affect interactions or are a consequence of the disease, requires thoughtfully designed future studies. Such studies should, in addition, examine interactions with several other potentially contributing factors (eg, inflammation, activity levels, medication use) and associations with important health outcomes in asthma. Future multidisciplinary research programs should examine the predictive value of central nervous system markers of dyspnea for the early identification of asthma patients at risk for underperception/overperception of dyspnea, as well as for the individualized selection and/or subsequent evaluation of specific asthma treatments, including interoception trainings.

Perception of Airflow Limitation in Naturalistic Settings

A widely used methodology in naturalistic settings involves asking participants to guess their peak expiratory flow (PEF) and assess correspondence with their actual PEF.[155,156] In naturalistic settings, the resulting accuracy measure is associated with self-reported asthma symptoms,[157] also across a 1-year period,[158] whereas accuracy with resistive load detection does not show this association.[157,158] Several characteristics can influence the ability to perceive airflow limitation, such as lower cognitive function scores,[155] poverty, younger age in children,[159] lower attentional abilities[160] and ADHD symptoms in children.[161,162] Puerto Rican and Dominican children with asthma are less accurate and more likely to overperceive airflow limitation than non-Latino white children.[155] Anxiety symptoms in children[156] and depressive symptoms in older adults[163] are linked to over-perception. Older adults with asthma are at risk for underperception,[164] and asthma beliefs mediate the relationship between underperception and under-reporting of asthma symptoms.[165] Therefore, asthma beliefs and perception of lung function might be important modifiable targets for interventions.

ASTHMA DISPARITIES

Asthma disproportionately affects people living below the poverty level and historically marginalized racial and ethnic groups. In the United States, structural determinants such as government policies, socioeconomic status, and racism lead to an uneven distribution of social determinants of health across racial or ethnic groups, causing disproportionate exposure to environmental (eg, tobacco use, air pollution, occupational hazards), lifestyle (eg, unhealthy dietary patterns and obesity) and psychosocial (eg, violence, lack of health insurance) risk factors for asthma and asthma morbidity in marginalized groups.[166] Thus, governmental policies that advance "environmental justice" by dismantling structural racism and promoting equal access to adequate housing and education, outdoor spaces, safe working conditions, healthy foodstuff, gun control, health care, and "clean air" would have the greatest impact on asthma disparities in the United States.

Exposure to Violence and Chronic Stress in Disadvantaged Populations: Response to Medication Treatment

Exposure to violence and chronic (prenatal and postnatal) stress have been implicated as risk factors for

asthma and worse asthma outcomes across the lifespan, particularly in disadvantaged and marginalized populations.[167,168] Chronic stress related to violence could increase asthma risk through direct effects (eg, inducing functional abnormalities in the hypothalamic-pituitary-axis or altering immune responses) and indirect effects (eg, leading to obesity through unhealthy dietary habits), as well as by interacting with other risk factors such as outdoor pollutants. A potential mechanism for the violence-stress-asthma link is reduced response to treatment. In Puerto Ricans who also suffer from high prevalence of psychosocial stress and mental illness,[169–172] asthma and high violence-related distress is associated with lower response to short-acting inhaled β2-agonists possibly due to increased secretion of catecholamines leading to down-regulation of the β2-adrenergic receptor gene (*ADRB2*).[172,173] Reduced lung function growth despite treatment with low-dose inhaled corticosteroids[174] in youth exposed to violence-related distress over time may also indicate elevated corticosteroid resistance. More research is needed on response to pharmacological treatment in asthma patients exposed to the stress of adverse life conditions.

Violence-related Distress and Atopy: Pathways of Epigenetic Regulation

High exposure to violence has been associated with persistent or new-onset asthma with biomarkers of high Th2 immunity (IgE, blood eosinophil counts) in children.[175,176] Only recently, epigenetic regulation of stress-related genes has garnered attention as a possible key to atopy development. For example, DNA methylation of the promoter of a candidate gene for childhood anxiety (*ADCYAP1R1*) was associated with both violence exposure and asthma in Puerto Rican children.[170] An epigenome-wide association study suggested that violence-related distress may lead to atopic asthma through abnormal epigenetic regulation of nasal (airway) epithelial function in this and other populations. Here, the *PLCB1* gene is of particular interest, as it has been linked to depression and, separately, with bronchodilator response and treatment resistance in children with asthma.[177] While preliminary, these results encourage more research on violence-related distress and asthma phenotypes (eg, atopic and nonatopic) and endotypes (eg, Th2-high and Th17-high asthma) in high-risk populations.

Resilience to Disadvantage and Adversity in Asthma

Though disadvantage, discrimination, and adversity are very real risk factors in asthma, they are not deterministic. Plenty of children who face adverse circumstances do not develop asthma or other health problems. The ability to predict who will be resilient to serious adversity, in terms of asthma development and progression, would inform both novel therapeutic approaches and policy recommendations, as well as provide new insights into the psychobiological mechanisms of asthma. Current research has identified factors that contribute to resilience at individual (eg, coping skills), family (eg, sensitive caregiving[55]) and community levels. The ability to adapt oneself to adverse environments, through emotion regulation and cognitive reframing, while simultaneously maintaining hope, finding meaning, and seeking opportunities for growth and agency—an orientation referred to as "shift and persist" has been shown to be a particularly effective at buffering the immune, endocrine, and autonomic dysregulation through which adversity contributes to asthma pathophysiology.[178,179] Here, we find another ripe area for future research: the development and evaluation of interventions that foster a "shift and persist" orientation.

ASTHMA TREATMENT

Pharmacological Treatment

Earlier asthma treatments focused on relieving breathlessness with inhaled nonspecific bronchodilators, eventually expanding to more selective β^2 adrenergic drugs, anticholinergics and corticosteroids.[180] Combined β-adrenergic agonists and inhaled corticosteroids (ICS) are now widely used, enabling effective control of both bronchoconstriction and inflammation. Despite the success of these treatments, between 5% and 10% of patients have asthma that is resistant to inhaled drugs and require systemic corticosteroids.[181] Long-term systemic corticosteroid use is associated with a variety of serious adverse effects, necessitating an alternative treatment for steroid-resistant asthma, catalyzing the era of biological treatment.[182] This has culminated in the development and approval of several monoclonal antibodies (mAb), including omalizumab, which neutralizes IgE,[182] anti-IL-5 mAb mepolizumab,[183,184] anti-IL-5 receptor mAb benralizumab[185], shared receptor subunit IL-4R alpha mAb dupilumab, which blocks both Il-4 and IL-13,[186] and a mAb against thymic stromal lymphopoietin,[187] a cytokine that is upstream of the other cytokines in the complex cascade of pro-inflammatory mechanisms. These therapeutic approaches are guided by underlying pathobiology, rather than purely clinical criteria, and are far more effective at preventing exacerbations, also igniting the clinical biomarker era in asthma and the concept of "treatable traits."[188,189] However, there are, as yet, no biomarkers that can predict which of these would be the most effective in the individual patient. Thus, there is an unmet need for (probably a combination of) biomarkers that can help select the most likely effective biologic.

Most recently, asthma experts have started to stratify responses to biologics into good and super responses, with clinical remission (freedom from exacerbation and oral corticosteroids, showing good symptom control and lung function) being the final ambition.[190–192] This coincides with increasing interest in comorbidities that are common in asthma, more so in severe forms, including gastro-esophageal reflux, chronic sinusitis, obesity, obstructive apnea,[193,194] and psychological disorders.[195] Solutions to such clinical complexity will require a much more holistic approach to asthma treatment than is

currently the standard of care, bringing together services that are able to "zoom into" the conditions of their specialties in a way that provides complex, but effective and affordable, solutions for complex problems. A personalized approach to treatment of asthma also includes flexible adjustments of medication depending on the level of symptom control. The best approach to that has been subject of much debate and is constantly under review by international guidelines and respiratory societies. Thus, reduction in the dose of ICS is recommended if patients remain well-controlled for a longer period. Simple clinical biomarkers, such as exhaled nitric oxide and blood eosinophil counts, can guide treatment and help avoid the need for systemic corticosteroids, even when the symptoms seem to make them inevitable.[196]

Behavioral and Biobehavioral Treatment

While pharmacological interventions have significantly improved asthma outcomes and quality of life for patients, asthma remains poorly managed in 30% to 50% of patients with moderate to severe asthma.[197] Thus, there is an urgent need for innovation in treatment approaches as existing reviews highlight the role of psychosocial factors in risk for asthma exacerbation.[198–200] Such interventions may serve as adjunct treatments that enhance effects of existing pharmacological management plans.

Behavioral Support of Asthma Treatment

Behavioral interventions that have focused on supporting pharmacological treatment directly, such as self-management plans with regular health care professional review, are now evidence-based and endorsed by guidelines[4,201] and should be part of an integrated asthma care plan. However, additional efforts are needed in designing efficacious medication adherence interventions, as patients' follow-through with prescribed medication regimens remains stubbornly low.[202] Digital technologies have the potential to generate much-needed progress in this area.[203,204]

Biobehaviorally Oriented Interventions

Biobehavioral interventions that are also expected to impact pathophysiology of asthma directly by reducing airway obstruction and inflammation, require further scrutiny in larger trials. Breathing trainings that educate patients to systematically alter breathing patterns and ventilation, such as the Buteyko training[205] or biofeedback-supported trainings to elevate PCO_2 levels,[206] are among the more promising interventions, which, by virtue of addressing hyperventilation as a bronchoconstrictor, may also impact anxious psychopathology.[207] Perspectives also arise from interventions that are based on physical activity. Despite the tendency of intense or longer-lasting exercise to induce symptoms of asthma in a sizeable number of patients, benefits of physical exercise on fitness and asthma control are well-established.[208,209] Additional treatment modalities that leverage the bronchodilatory and bronchoprotective effects of physical activity deserve further exploration.[210]

Training of Interoception

To target overperception or underperception of airway constriction, advantages and limitations of perception trainings, such as systematic presentation of added resistive loads,[211] need to undergo further evaluation. Although findings are encouraging, there is also evidence that not all patients benefit equally, especially when oversensitivity to asthma symptoms exists at the outset.[212] Thus, as in many applications, a one-size-fits-all approach is not recommended here. Other perception training approaches, through longitudinal self-monitoring of airflow obstructions with hand-help spirometers, that is contrasted with patients' estimations of their obstructions, also hold promise in educating both children and older patients.[159,213] The full benefit of these interventions on asthma control and exacerbations has yet to be explored.

Psychotherapy Techniques

Concrete steps to mitigate psychological factors in asthma are still missing, beyond the most generic recommendations to refer patients to psychotherapy or counseling. However, there are encouraging signals that cognitive behavioral therapy tailored to adults or children with asthma can improve anxiety, asthma control, and quality of life.[214,215] Still, more work is needed to devise and test individual strategies (eg, expressive or suggestive techniques) to manage problematic feeling states such as depressed mood, anger/irritability, or fatigue, which are commonly expressed in patients during routine care.[216]

Mind-body Interventions

While a small literature reporting the efficacy of mind-body interventions in respiratory disease does exist,[217–220] much more work in this domain is needed. Most studies focus on psychological outcomes, such as quality of life or perceived stress, with little emphasis on clinical or biological outcomes. In addition, existing meditation studies are often small and lack rigor. This is an area ripe for future investigation with carefully designed trials of sufficient size to evaluate predictors of response. Personalization of treatments may be key to greater success rates in this area. Preliminary evidence is emerging from a smaller trial that patient populations with specific psychological challenges (such as depression) and residual airway inflammation despite maintenance medication are most likely to show benefits in asthma control following mindfulness training.[221] Larger and more comprehensive evaluations of response predictors, including comorbidities and phenotypes, are needed.

Improving Access to Mind-body Interventions

Despite the potential promise of mind-body interventions to complement pharmacological treatments in asthma, barriers to accessing these interventions exist. In the United States, complementary medicine interventions are not routinely covered by health insuranceand out-of-pocket expenses can be high. Further, these interventions

are often time-consuming, limiting their feasibility for many. For these reasons, many low-cost digital and/or mobile mind-body interventions are gaining traction. Indeed, smartphone-delivered, app-based mindfulness interventions in asthma, can show reasonable uptake and high feasibility across an impressively broad age range.[222] This approach can also improve quality of life, asthma control, and some features of mental health, in particular anxiety and depression, but more research is needed regarding long-term effects of digitally supported meditation interventions.

Community-level Interventions

More radical attempts to modify risk factors for underserved populations have involved housing subsidies or relocation of children to more advantaged communities. The "Moving to Opportunity" housing voucher experiment has remained disappointing for asthma outcomes and even showed reduced mental health and asthma control in boys.[223,224] In contrast, governmental rental assistance for low-income families in public and multi-family housing reduced emergency department use for children with asthma.[225] Another housing mobility program in Baltimore showed that providing vouchers and assistance for moving to low-poverty neighborhoods resulted in reductions of recent asthma symptoms and exacerbations in children and adolescents. Improved psychosocial factors related to social cohesion, stress, and safety mediated the largest percentage of improvement in asthma outcomes[226] due to this program, indicating an opportunity to work on such factors in less economically taxing programs also.

Need for Rigorous Multicenter Trials

Overall, initial indications suggest that behavioral and mind-body interventions may be able to improve asthma outcomes and meet some of the unmet needs in this population. However, it is important to emphasize the paucity of work in this area and the urgent need for clinically-oriented, rigorous research in this domain. This includes conceptualization and testing of concrete mechanistic models that tie psychological and behavioral manipulations of interventions to psychological and pathophysiological outcomes. Funding for larger multidisciplinary multicenter trials is needed to put the incremental gain these interventions promise to achieve to the test in a more representative sample of the population of asthma patients. In that, differential suitability according to phenotypes and endotypes of asthma should be explored. Beyond addressing asthma control deficits over and above pharmacological treatment, they may be a critical factor that supports the goal of reducing treatment intensity once full control is achieved.[227]

CONCLUSION

Substantial progress has been made in diagnosis and pharmacological treatment of asthma in recent decades. Hand in hand with this progress, the empirical study of psychobiological aspects of asthma has gained momentum in psychosomatic medicine. Yet, concrete improvements in patients' asthma control and quality of life have often lagged behind these developments. Empirical consolidation of findings by replications, implementation trials, and translation into impactful interventions has all too often been neglected in psychobiological research. At the same time, in the spirit of a biopsychosocial model of illness,[228] the realization is growing in the biomedical field that inclusion of psychosocial, behavioral, and lifestyle perspectives is essential for further progress in both primary prevention and diagnosis and management of asthma. Multidisciplinary teamwork involving medical and psychological subdisciplines is advisable in both basic, clinical, and treatment research and patient care. While perspectives for future research have been articulated for individual areas, major priorities requiring collaborations of fields and disciplines are:

- Primary prevention of asthma: Substantial investment of efforts is required to create perinatal and early childhood environments that interfere with early priming of the immune system that favors atopy and asthma development. This includes identification and targeting of microbial pathways.
- Autonomic, endocrine, and immune pathways of asthma exacerbations require further elucidation, with the goal of identifying treatable psychobiological traits.
- Psychobiological exploration of asthma requires reference to phenotypes and endotypes, while biomedical treatment should increasingly incorporate psychological assessment in clinical evaluation of biologics. Exploration of possible convergence of both fields on common treatable pathways will be of interest. Dimensional versus typological conceptualizations of asthma patient subpopulations require additional scrutiny.
- The interactions of asthma and its medical treatment with the brain, and with the perceptual, motor, affective, and cognitive functions, require further mechanistic studies.
- Further development of creative interventions that consider racial, ethnic, and cultural diversity and target known community risk factors and poverty are needed to create an equitable approach to asthma management. This includes interventions that enhance resilience factors.
- The pathophysiological and biopsychosocial determinants of overperception and underperception of airway obstruction and biases in asthma perception require further elucidation.
- While there is a further need to develop biomarkers that support personalized treatments, additional systematic consideration of psychosocial factors will require the development of complex, multidimensional algorithms that guide treatment decisions.
- Adherence to medication remains a challenge, and more efforts are needed to determine predictors and barriers, and devise novel intervention tools.
- Rigorous multicenter clinical efficacy and effectiveness trials of behavioral, biobehavioral, and mind-body

interventions are needed. These should be accompanied by a detailed monitoring of medication needs.

This report has highlighted progress in individual areas of medical and psychobiological research on asthma, showcasing an increasing interdisciplinarity and synergy of agendas with the ultimate goal of improving the ability of health care professionals and patients to improve management of this chronic inflammatory disease.

Source of Funding and Conflicts of Interest: N.N.J. has received consulting fees from GSK and Astra Zeneca (each is < $5000) regarding investigative treatments for asthma. J.C.C. has received research materials from Merck (inhaled steroids) to provide medications free of charge to participants in NIH-funded studies, outside of this submitted work. Also, supported by grants HL152475, HL168539, and HL158295 from the U.S. NIH. R.D. declares ownership of shares and consultancy with Synairgen plc, consultancy for ALK Abello, GlaxoSmithKline, ZenasBio and Celltrion. T.R. was partially supported by the American Psychosomatic Society (APS, now Society for Biopsychosocial Science and Medicine, SBSM), National Heart Lung and Blood Institute (R01 HL142775), and National Center for Complementary and Integrative Health (R33 AT012022). M.R. was partially supported by the National Institute on Aging (RF1 AG082215). P.F. is the AstraZeneca (Canada) Chair in Asthma and Obstructive Lung Disease. D.V. was funded by P01AI148104, U19AI125357 from the U.S. NIH and by a research grant provided by OM Pharma SA to The University of Arizona. A.v.L. was supported by grants from the Research Foundation Flanders (FWO), Belgium (G004624N, G0C1921N), by an infrastructure grant from the FWO and the Research Fund KU Leuven, Belgium (I011320N; AKUL/19/06), and by a project grant of the Research Fund KU Leuven, Belgium (C16/23/002). For the remaining authors none were declared.

REFERENCES

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1204–22; [published correction appears in Lancet. 2020;396(10262):1562. doi:10.1016/S0140-6736(20)32226-1]
2. Centers for Disease Control and Prevention (CDC). Asthma Data, Statistics, and Surveillance. Accessed April 19, 2024. https://www.cdc.gov/asthma/asthma_data
3. Weiner HM. *Psychobiology and Human Disease*. New York, NY: Elsevier; 1977.
4. National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program (NHLBI/NAEPP). Expert panel report: Guidelines for the diagnosis and management of asthma. Full report 2007. NIH Publication No. 07-4051. National Institutes of Health, Bethesda, MD, 2007.
5. Global Initiative for Asthma (GINA) (2024). GINA Report, Global Strategy for Asthma Management and Prevention. Accessed November 15, 2024. http://www.ginasthma.org/
6. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: moving toward precision medicine. *J Allergy Clin Immunol*. 2019;144:1–12.
7. Buhl R, Bel E, Bourdin A, Dávila I, Douglass JA, FitzGerald JM, et al. Effective management of severe asthma with biologic medications in adult patients: a literature review and international expert opinion. *J Allergy Clin Immunol Pract*. 2022;10:422–432.
8. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009;180:59–99.
9. Juan G, Calverley P, Talamo C, Schnader J, Roussos C. Effect of carbon dioxide on diaphragmatic function in human beings. *N Engl J Med*. 1984;310:874–879.
10. van den Elshout FJ, van Herwaarden CL, Folgering HT. Effects of hypercapnia and hypocapnia on respiratory resistance in normal and asthmatic subjects. *Thorax*. 1991;46:28–32.
11. Vercelli D. From Amish farm dust to bacterial lysates: the long and winding road to protection from allergic disease. *Semin Immunol*. 2023;68:101779.
12. Pividori M, Schoettler N, Nicolae DL, Ober C, Im HK. Shared and distinct genetic risk factors for childhood-onset and adult-onset asthma: genome-wide and transcriptome-wide studies. *Lancet Respir Med*. 2019;7:509–522.
13. Vercelli D, Bleecker ER. Strength in numbers: the quest for asthma genes. *J Allergy Clin Immunol*. 2019;144:413–415.
14. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med*. 1989;320:271–277.
15. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med*. 2008;178:667–672.
16. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med*. 2002;347:911–920.
17. von Mutius E, Smits HH. Primary prevention of asthma: from risk and protective factors to targeted strategies for prevention. *Lancet*. 2020;396:854–866.
18. von Mutius E. The "Hygiene Hypothesis" and the lessons learnt from farm studies. *Front Immunol*. 2021;12:635522.
19. Ege MJ, Mayer M, Normand AC, Genuneit J, Cookson WOCM, Braun-Fahrländer C, et al. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med*. 2011;364:701–709.
20. Braun-Fahrländer C, Riedler J, Herz U, Eder W, Waser M, Grize L, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med*. 2002;347:869–877.
21. von Mutius E, Vercelli D. Farm living: effects on childhood asthma and allergy. *Nat Rev Immunol*. 2010;10:861–868; [published correction appears in Nat Rev Immunol. 2019 Sep;19(9):594]. doi:10.1038/s41577-019-0199-3
22. Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE, et al. Innate immunity and asthma risk in Amish and Hutterite farm children. *N Engl J Med*. 2016;375:411–421.
23. Ober C, Sperling AI, von Mutius E, Vercelli D. Immune development and environment: lessons from Amish and Hutterite children. *Curr Opin Immunol*. 2017;48:51–60.
24. Depner M, Taft DH, Kirjavainen PV, Kalanetra KM, Karvonen AM, Peschel S, et al. Maturation of the gut microbiome during the first year of life contributes to the protective farm effect on childhood asthma. *Nat Med*. 2020;26:1766–1775.
25. Vercelli D. Microbiota and human allergic diseases: the company we keep. *Curr Opin Immunol*. 2021;72:215–220.
26. Lynch SV, Vercelli D. Microbiota, epigenetics, and trained immunity. Convergent drivers and mediators of the asthma trajectory from pregnancy to childhood. *Am J Respir Crit Care Med*. 2021;203:802–808.
27. Smulders T, Van Der Schee MP, Maitland-Van Der Zee AH, Dikkers FG, Van Drunen CM. Influence of the gut and airway microbiome on asthma development and disease. *Pediatr Allergy Immunol*. 2024;35:e14095.
28. Rahman Fink N, Chawes BL, Thorsen J, Stokholm J, Krogfelt KA, Schjorring S, et al. Neonates colonized with pathogenic bacteria in the airways have a low-grade systemic inflammation. *Allergy*. 2018;73:2150–2159.
29. Sunde RB, Thorsen J, Kim M, Schoos AM, Stokholm J, Bonnelykke K, et al. Bacterial colonisation of the airway in

neonates and risk of asthma and allergy until age 18 years. *Eur Respir J*. 2024;63:2300471.
30. Galeana-Cadena D, Gomez-Garcia IA, Lopez-Salinas KG, Irineo-Moreno V, Jimenez-Juarez F, Tapia-Garcia AR, et al. Winds of change a tale of: asthma and microbiome. *Front Microbiol*. 2023;14: 1295215.
31. Kahhaleh FG, Barrientos G, Conrad ML. The gut-lung axis and asthma susceptibility in early life. *Acta Physiol (Oxf)*. 2024;240: e14092.
32. Arrieta MC, Stiemsma LT, Dimitriu PA, Thorson L, Russell S, Yurist-Doutsch S, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med*. 2015;7: 307ra152.
33. Clancy Am R. The common mucosal system fifty years on: From cell traffic in the rabbit to immune resilience to SARS-CoV-2 infection by shifting risk within normal and disease populations. *Vaccines (Basel)*. 2023;11:1251.
34. Plitas G, Rudensky AY. Regulatory T cells: differentiation and function. *Cancer Immunol Res*. 2016;4:721–725.
35. Karimi K, Inman MD, Bienenstock J, Forsythe P. Lactobacillus reuteri-induced regulatory T cells protect against an allergic airway response in mice. *Am J Respir Crit Care Med*. 2009;179:186–193.
36. Adami AJ, Bracken SJ, Guernsey LA, Rafti E, Maas KR, Graf J, et al. Early-life antibiotics attenuate regulatory T cell generation and increase the severity of murine house dust mite-induced asthma. *Pediatr Res*. 2018;84:426–434.
37. Di Gangi A, Di Cicco ME, Comberiati P, Peroni DG. Go with your gut: the shaping of T-cell response by gut microbiota in allergic asthma. *Front Immunol*. 2020;11:1485.
38. Cait A, Hughes MR, Antignano F, Cait J, Dimitriu PA, Maas KR, et al. Microbiome-driven allergic lung inflammation is ameliorated by short-chain fatty acids. *Mucosal Immunol*. 2018;11:785–795.
39. Losol P, Wolska M, Wypych TP, Yao L, O'Mahony L, Sokolowska M. A cross talk between microbial metabolites and host immunity: its relevance for allergic diseases. *Clin Transl Allergy*. 2024;14:e12339.
40. Fujita Y, Kadota T, Araya J, Ochiya T, Kuwano K. Extracellular vesicles: new players in lung immunity. *Am J Respir Cell Mol Biol*. 2018;58:560–565.
41. Forsythe P, Kunze W, Bienenstock J. Moody microbes or fecal phrenology: what do we know about the microbiota-gut-brain axis? *BMC Med*. 2016;14:58.
42. Kayyal M, Javkar T, Firoz Mian M, Binyamin D, Koren O, McVey Neufeld KA, et al. Sex dependent effects of post-natal penicillin on brain, behavior and immune regulation are prevented by concurrent probiotic treatment. *Sci Rep*. 2020;10:10318.
43. Leclercq S, Mian FM, Stanisz AM, Bindels LB, Cambier E, Ben-Amram H, et al. Low-dose penicillin in early life induces long-term changes in murine gut microbiota, brain cytokines and behavior. *Nat Commun*. 2017;8:15062.
44. Neuman H, Forsythe P, Uzan A, Avni O, Koren O. Antibiotics in early life: dysbiosis and the damage done. *FEMS Microbiol Rev*. 2018;42:489–499.
45. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci U S A*. 2011;108: 16050–16055.
46. Arbabi F, Shapoury R, Haghi F, Zeighami H, Pirzeh R. Investigating the bacterial profiles of Lactobacillus, Bifidobacterium, Actinobacteria, Fusobacterium, Firmicutes, and Bacteroides in stool samples from patients with severe depression and healthy individuals. *Psychoneuroendocrinology*. 2024;170:107090.
47. Pirbaglou M, Katz J, de Souza RJ, Stearns JC, Motamed M, Ritvo P. Probiotic supplementation can positively affect anxiety and depressive symptoms: a systematic review of randomized controlled trials. *Nutr Res*. 2016;36:889–898.
48. Bharwani A, Mian MF, Foster JA, Surette MG, Bienenstock J, Forsythe P. Structural & functional consequences of chronic psychosocial stress on the microbiome & host. *Psychoneuroendocrinology*. 2016;63:217–227.
49. Liu Y, Sanderson D, Mian MF, McVey Neufeld KA, Forsythe P. Loss of vagal integrity disrupts immune components of the microbiota-gut-brain axis and inhibits the effect of Lactobacillus rhamnosus on behavior and the corticosterone stress response. *Neuropharmacology*. 2021;195:108682.
50. Sternthal MJ, Jun HJ, Earls F, Wright RJ. Community violence and urban childhood asthma: a multilevel analysis. *Eur Respir J*. 2010;36:1400–1409.
51. Chiu YH, Coull BA, Cohen S, Wooley A, Wright RJ. Prenatal and postnatal maternal stress and wheeze in urban children: effect of maternal sensitization. *Am J Respir Crit Care Med*. 2012;186: 147–154.
52. Rosa MJ, Just AC, Tamayo Y, Ortiz M, Schnaas L, Svensson K, et al. Prenatal and postnatal stress and wheeze in Mexican children: sex-specific differences. *Ann Allergy Asthma Immunol*. 2016;116: 306–12.e1.
53. Pape K, Cowell W, Sejbaek CS, Andersson NW, Svanes C, Kolstad HA, et al. Adverse childhood experiences and asthma: trajectories in a national cohort. *Thorax*. 2021;76:547–553.
54. Chiu YH, Coull BA, Sternthal MJ, Kloog I, Schwartz J, Cohen S, et al. Effects of prenatal community violence and ambient air pollution on childhood wheeze in an urban population. *J Allergy Clin Immunol*. 2014;133:713–22.e4.
55. Frost A, Bosquet Enlow M, Malin AJ, Bernard K, Wright RJ. Early adverse experiences and repeated wheezing from 6 to 30 months of age: Investigating the roles of hypothalamicpituitary-adrenal axis functioning, child sex, and caregiving sensitivity. *Child Dev*. 2021;92:e1260–e1274.
56. BTS/SIGN British Guideline on the Management of Asthma (2019). Accessed November 14, 2024. https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/
57. Deutsche Gesellschaft für Arbeitsmedizin und Umweltmedizin e. V. Deutsche Gesellschaft für Rehabilitationswissenschaften e.V.und Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V., et al. Guideline for the Diagnosis and Treatment of Asthma - Guideline of the German Respiratory Society and the German Atemwegsliga in Cooperation with the Paediatric Respiratory Society and the Austrian Society of Pneumology [published correction appears in Pneumologie. 2017 Dec;71(12):e2. doi:10.1055/s-0044-100881. Taube, R C [corrected to Taube, C]] [published correction appears in Pneumologie. 2017 Dec;71(12):e3. doi:10.1055/a-0790-0021.]. Pneumologie. 2017;71:849–919.
58. Nakamura Y, Tamaoki J, Nagase H, Yamaguchi M, Horiguchi T, Hozawa S, et al. Japanese guidelines for adult asthma 2020. *Allergol Int*. 2020;69:519–548.
59. Trojan TD, Khan DA, Defina LF, Akpotaire O, Goodwin RD, Brown ES. Asthma and depression: the Cooper Center Longitudinal Study. *Ann Allergy Asthma Immunol*. 2014;112:432–436.
60. Ye G, Baldwin DS, Hou R. Anxiety in asthma: a systematic review and meta-analysis. *Psychol Med*. 2021;51:11–20.
61. Ritz T, Wittchen HU, Klotsche J, Mühlig S, Riedel O, sap-NEEDs study group. Asthma trigger reports are associated with low quality of life, exacerbations, and emergency treatments. *Ann Am Thorac Soc*. 2016;13:204–211.
62. Choi HG, Kim JH, Park JY, Hwang YI, Jang SH, Jung KS. Association between asthma and depression: a national cohort study. *J Allergy Clin Immunol Pract*. 2019;7:1239–45.e1.
63. Gao YH, Zhao HS, Zhang FR, Gao Y, Shen P, Chen RC, et al. The relationship between depression and asthma: a meta-analysis of prospective studies. *PLoS One*. 2015;10:e0132424.
64. Hasler G, Gergen PJ, Kleinbaum DG, Ajdacic V, Gamma A, Eich D, et al. Asthma and panic in young adults: a 20-year prospective community study. *Am J Respir Crit Care Med*. 2005;171: 1224–1230.
65. Chen E, Schreier HM, Strunk RC, Brauer M. Chronic trafficrelated air pollution and stress interact to predict biologic and clinical outcomes in asthma. *Environ Health Perspect*. 2008;116:970–975.
66. Clougherty JE, Levy JI, Kubzansky LD, Ryan PB, Suglia SF, Canner MJ, et al. Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. *Environ Health Perspect*. 2007;115:1140–1146.

67. Rancière F, Bougas N, Viola M, Momas I. Early exposure to traffic-related air pollution, respiratory symptoms at 4 years of age, and potential effect modification by parental allergy, stressful family events, and sex: a prospective follow-up study of the PARIS birth cohort. *Environ Health Perspect*. 2017;125:737–745.
68. Trueba AF, Ritz T. Stress, asthma, and respiratory infections: pathways involving airway immunology and microbial endocrinology. *Brain Behav Immun*. 2013;29:11–27.
69. Wright RJ, Cohen RT, Cohen S. The impact of stress on the development and expression of atopy. *Curr Opin Allergy Clin Immunol*. 2005;5:23–29.
70. Barnes PJ. Neural control of human airways in health and disease. *Am Rev Respir Dis*. 1986;134:1289–1314.
71. Isenberg SA, Lehrer PM, Hochron S. The effects of suggestion and emotional arousal on pulmonary function in asthma: a review and a hypothesis regarding vagal mediation. *Psychosom Med*. 1992;54: 192–216.
72. Ritz T. Airway responsiveness to psychological processes in asthma and health. *Front Physiol*. 2012;3:343.
73. Ritz T, Kullowatz A, Goldman MD, Smigh HJ, Kanniess F, Dahme B, et al. Airway response to emotional stimuli in asthma: the role of the cholinergic pathway. *J Appl Physiol*. 2010;108: 1542–1549.
74. Plourde A, Lavoie KL, Raddatz C, Bacon SL. Effects of acute psychological stress induced in laboratory on physiological responses in asthma populations: a systematic review. *Respir Med*. 2017;127:21–32.
75. Ritz T, Ayala ES, Trueba AF, Vance CD, Auchus RJ. Acute stressinduced increases in exhaled nitric oxide in asthma and their association with endogenous cortisol. *Am J Respir Crit Care Med*. 2011;183:26–30.
76. Rosenberg SL, Miller GE, Brehm JM, Celedón JC. Stress and asthma: novel insights on genetic, epigenetic, and immunologic mechanisms. *J Allergy Clin Immunol*. 2014;134:1009–1015.
77. Wright RJ. Epidemiology of stress and asthma: from constricting communities and fragile families to epigenetics. *Immunol Allergy Clin North Am*. 2011;31:19–39.
78. Liu LY, Coe CL, Swenson CA, Kelly EA, Kita H, Busse WW. School examinations enhance airway inflammation to antigen challenge. *Am J Respir Crit Care Med*. 2002;165:1062–1067.
79. Rosenkranz MA, Esnault S, Christian BT, Crisafi G, Gresham LK, Higgins AT, et al. Mind-body interactions in the regulation of airway inflammation in asthma: A PET study of acute and chronic stress. *Brain Behav Immun*. doi:10.1016/j.bbi.2016.03.024
80. Rosenkranz MA, Esnault S, Gresham L, Davidson RJ, Christian BT, Jarjour NN, et al. Role of amygdala in stress-induced upregulation of airway IL-1 signaling in asthma. *Biol Psychol*. 2022;167:108226.
81. Lietzén R, Suominen S, Sillanmäki L, Virtanen P, Virtanen M, Vahtera J. Multiple adverse childhood experiences and asthma onset in adulthood: role of adulthood risk factors as mediators. *J Psychosom Res*. 2021;143:110388.
82. Hakamata Y, Suzuki Y, Kobashikawa H, Hori H. Neurobiology of early life adversity: a systematic review of meta-analyses towards an integrative account of its neurobiological trajectories to mental disorders. *Front Neuroendocrinol*. 2022;65:100994.
83. Landstra AM, Postma DS, Boezen HM, van Aalderen WM. Role of serum cortisol levels in children with asthma. *Am J Respir Crit Care Med*. 2002;165:708–712.
84. Buske-Kirschbaum A, von Auer K, Krieger S, Weis S, Rauh W, Hellhammer D. Blunted cortisol responses to psychosocial stress in asthmatic children: a general feature of atopic disease? *Psychosom Med*. 2003;65:806–810.
85. Buske-Kirschbaum A, Jobst S, Wustmans A, Kirschbaum C, Rauh W, Hellhammer D. Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. *Psychosom Med*. 1997; 59:419–426.
86. Buske-Kirschbaum A, Ebrecht M, Hellhammer DH. Blunted HPA axis responsiveness to stress in atopic patients is associated with the acuity and severeness of allergic inflammation. *Brain Behav Immun*. 2010;24:1347–1353.
87. Ritz T, Trueba AF, Liu J, Auchus RJ, Rosenfield D. Exhaled nitric oxide decreases during academic examination stress in asthma. *Ann Am Thorac Soc*. 2015;12:1638–1645.
88. Kroll JL, Brown ES, Ritz T. Cortisol awakening response and fractional exhaled nitric oxide in asthma. *Clin Exp Allergy*. 2019;49: 1150–1153.
89. Miller BD, Wood BL, Lim J, Ballow M, Hsu C. Depressed children with asthma evidence increased airway resistance: "vagal bias" as a mechanism? *J Allergy Clin Immunol*. 2009;124:66–73.e1-10.
90. Shanahan L, Copeland WE, Worthman CM, Angold A, Costello EJ. Children with both asthma and depression are at risk for heightened inflammation. *J Pediatr*. 2013;163:1443–1447.
91. Dill-McFarland KA, Altman MC, Esnault S, Jarjour NN, Busse WW, Rosenkranz MA. Molecular pathways underlying lung-brain axis signaling in asthma: Relevance for psychopathology and neuroinflammation. *J Allergy Clin Immunol*. 2024;153:111–121.
92. Ritz T, Steptoe A, Bobb C, Harris AH, Edwards M. The asthma trigger inventory: validation of a questionnaire for perceived triggers of asthma. *Psychosom Med*. 2006;68:956–965.
93. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. *Lancet*. 2008;372:1107–1119.
94. Gauthier M, Ray A, Wenzel SE. Evolving concepts of asthma. *Am J Respir Crit Care Med*. 2015;192:660–668.
95. Knudsen TB, Thomsen SF, Nolte H, Backer V. A population-based clinical study of allergic and non-allergic asthma. *J Asthma*. 2009; 46:91–94.
96. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax*. 1999;54:268–272.
97. Rackemann FM. Intrinsic asthma. *J Nerv Ment Dis*. 1947;106:497.
98. Lötvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, et al. Asthma endotypes: A new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol*. 2011;127:355–360.
99. Althoff MD, Gaietto K, Holguin F, Forno E. Obesity-related asthma: a pathobiology-based overview of existing and emerging treatment approaches. *Am J Respir Crit Care Med*. 2024;210: 1186–1200.
100. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol*. 2010;63: 1179–1194.
101. Kroll JL, Ritz T. Asthma, the central nervous system, and neurocognition: current findings, potential mechanisms, and treatment implications. *Neurosci Biobehav Rev*. 2023;146:105063.
102. Rosenkranz MA, Busse WW, Johnstone T, Swenson CA, Crisafi GM, Jackson MM, et al. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. *Proc Natl Acad Scie U S A*. 2005;102:13319–13324.
103. Rosenkranz MA, Busse WW, Sheridan JF, Crisafi GM, Davidson RJ. Are there neurophenotypes for asthma? Functional brain imaging of the interaction between emotion and inflammation in asthma. *PLoS One*. 2012;7:e40921.
104. Laubacher C, Kral TRA, Imhoff-Smith T, Klaus DR, Goldman RI, Sachs J, et al. Resting state functional connectivity changes following mindfulness-based stress reduction predict improvements in disease control for patients with asthma. *Brain Behav Immun*. 2024;115:480–493.
105. Ritz T, Kroll JL, Patel SV, Chen JR, Yezhuvath US, Aslan S, et al. Central nervous system signatures of affect in asthma: associations with emotion-induced bronchoconstriction, airway inflammation, and asthma control. *J Appl Physiol (1985)*. 2019; 126:1725–1736.
106. Ritz T, Kroll JL, Aslan S, Janssens T, Khan DA, Pinkham AE, et al. Subcortical gray matter volumes in asthma: associations with asthma duration, control, and anxiety. *Brain Imaging Behav*. 2020; 14:2341–2350.
107. von Leupoldt A, Brassen S, Baumann HJ, Klose H, Büchel C. Structural brain changes related to disease duration in patients with asthma. *PLoS One*. 2011;6:e23739.

108. Kroll JL, Steele AM, Pinkham AE, Choi C, Khan DA, Patel SV, et al. Hippocampal metabolites in asthma and their implications for cognitive function. *Neuroimage Clin*. 2018;19:213–221.
109. Irani F, Barbone JM, Beausoleil J, Gerald L. Is asthma associated with cognitive impairments? A meta-analytic review. *J Clin Exp Neuropsychol*. 2017;39:965–978.
110. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al. An official American Thoracic Society statement: Update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*. 2012;185:435–452; T.
111. Sobieraj DM, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, et al. Association of inhaled corticosteroids and longacting β-Agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. *JAMA*. 2018;319:1485–1496.
112. Kikuchi Y, Okabe S, Tamura G. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. *N Eng J Med*. 1994;330:1329–1334.
113. Magadle R, Berar-Yanay N, Weiner P. The risk of hospitalization and near-fatal and fatal asthma in relation to the perception of dyspnea. *Chest*. 2002;121:329–333.
114. Barnes PJ, Szefler SJ, Reddel HK, Chipps BE. Symptoms and perception of airway obstruction in asthmatic patients: clinical implications for use of reliever medications. *J Allergy Clin Immunol*. 2019;144:1180–1186.
115. Janssens T, Verleden G, De Peuter S, Van Diest I, Van den Bergh O. Inaccurate perception of asthma symptoms: a cognitive-affective framework and implications for asthma treatment. *Clin Psychol Rev*. 2009;29:317–327.
116. Fuhlbrigge A, Marvel J, Electricwala B, Siddall J, Scott M, Middleton-Dalby C, et al. Physician–patient concordance in the assessment of asthma control. *J Allergy Clin Immunol: In Practice*. 2021;9:3080–3088.
117. Crespo-Lessmann A, Plaza V, González-Barcala FJ, Fernández-Sánchez T, Sastre J. Concordance of opinions between patients and physicians and their relationship with symptomatic control and future risk in patients with moderate-severe asthma. *BMJ Open Respir Res*. 2017;4:e000189.
118. Matsunaga K, Hamada K, Oishi K, Yano M, Yamaji Y, Hirano T. Factors associated with physician-patient discordance in the perception of asthma control. *J Allergy Clin Immunol: In Practice*. 2019;7:2634–2641.
119. Chan PS, Lee LY, Davenport PW. Neural mechanisms of respiratory interoception. *Auton Neurosci*. 2024;253:103181.
120. Davenport PW, Chan PS, Zhang W, Chou YL. Detection threshold for inspiratory resistive loads and respiratory-related evoked potentials. *J Appli Physiol*. 2006;102:276–285.
121. Chan PS, Cheng CH, Wu YT, Wu CW, Liu HA, Shaw FZ, et al. Cortical and subcortical neural correlates for respiratory sensation in response to transient inspiratory occlusions in humans. *Front Physiol - Respir Physiol*. 2018;9:1804.
122. Chan PS, Cheng CH, Wu YT, Wu CW, Hsu AL, Liu CY, et al. Neural substrates of respiratory sensory gating: a human fMRI study. *Biol Psychol*. 2022;169:108277.
123. Davenport PW, Vovk A. Cortical and subcortical central neural pathways in dyspnea. *Respir Physiol Neurobiol*. 2009;167:72–86.
124. Burt JS, Davenport MP, Welch J, Davenport PW. fNIRS analysis of rostral prefrontal cortex activity and perception of inspiratory loads. *Respir Physiol Neurobiol*. 2023;316:104113.
125. Rassam P, de Mori T, Van Hollebeke M, Rozenberg D, Davenport PW, Vallis LA, et al. Cognitive interference of respiratory versus limb muscle dual tasking in healthy adults. *ERJ Open Res, 2024 IN PRESS, ERJOR-00169-2024R1, 2024*. 2024;1000169–2024.
126. Davenport PW, Freidman WA, Thompson FJ, Franzen O. Respiratory related cortical evoked potentials in humans. *J Appl Physiol*. 1986;60:1843–1848.
127. Chan PY, Davenport PW. Respiratory related evoked potential measures of respiratory sensory gating. *J Appl Physiol*. 2008;105:1106–1113.
128. von Leupoldt A, Chan PY, Bradley MM, Lang PJ, Davenport PW. The impact of anxiety on the neural processing of respiratory sensations. *Neuroimage*. 2011;55:247–252.
129. Chan PY, von Leupoldt A, Bradley MM, Lang PJ, Davenport PW. The effect of anxiety on respiratory sensory gating measured by respiratory-related evoked potentials. *Biol Psychol*. 2012;91:185–189.
130. Chan PY, Cheng CH, Hsu SC, Liu CY, Davenport PW, von Leupoldt A. Respiratory sensory gating measured by respiratoryrelated evoked potentials in generalized anxiety disorder. *Front Psychol*. 2015;6:957.
131. Kifle Y, Seng V, Davenport PW. Magnitude estimation of inspiratory resistive loads in children with life-threatening asthma. *Am J Respir Crit Care Med*. 1997;156:1530–1535.
132. Davenport PW, Cruz M, Stecenko A, Kifle Y. Respiratory related evoked potentials in children with life-threatening asthma. *Am J Respir Crit Care Med*. 2000;161:1830–1835.
133. Hayen A, Herigstad M, Pattinson KTS. Understanding dyspnea as a complex individual experience. *Maturitas*. 2023;76:45–50.
134. Laviolette L, Laveneziana P, Research ERS. Seminar Faculty. Dyspnoea: a multidimensional and multidisciplinary approach. *Eur Respir J*. 2014;43:1750–1762.
135. Similowski T. Treat the lungs, fool the brain and appease the mind: Towards holistic care of patients who suffer from chronic respiratory diseases. *Eur Respir J*. 2018;51:1800316.
136. von Leupoldt A, van den Bergh O, Davenport PW. Anxiety, depression and panic, In: Mahler DA, O'Donnell D. eds. *Dyspnea: Mechanisms, measurement and management*, 3rd edn.. CRC Press; 2014:129–143.
137. von Leupoldt A, Dahme B. Psychological aspects in the perception of dyspnea in obstructive pulmonary diseases. *Respir Med*. 2007;101:411–422.
138. De Peuter S, Lemaigre V, Van Diest I, Van den Bergh O. Illnessspecific catastrophic thinking and overperception in asthma. *Health Psychol*. 2008;27:93–99.
139. Janson C, Björnsson E, Hetta J, Boman G. Anxiety and depression in relation to respiratory symptoms and asthma. *Am J Respir Crit Care Med*. 1994;149(4 Pt 1):930–934.
140. von Leupoldt A, Denutte Y. Affective traits, states, and breathlessness. *Curr Opin Support Palliat Care*. 2020;14:182–189.
141. Rietveld S, Everaerd W, van Beest I. Excessive breathlessness through emotional imagery in asthma. *Behav Res Ther*. 2000;38:1005–1014.
142. von Leupoldt A, Dahme B. The impact of emotions on symptom perception in patients with asthma and healthy controls. *Psychophysiology*. 2013;50:1–4.
143. Herzog M, Sucec J, Van Diest I, Van den Bergh O, von Leupoldt A. The presence of others reduces dyspnea and cortical neural processing of respiratory sensations. *Biol Psychol*. 2019;140:48–54.
144. Herzog M, Sucec J, Vukovic M, Van Diest I, Van den Bergh O, von Leupoldt A. Experimental social rejection increases dyspnoea perception and neural processing of respiratory sensations in healthy subjects. *Eur Respir J*. 2019;53:1801409.
145. von Leupoldt A, Seemann N, Gugleva T, Dahme B. Attentional distraction reduces the affective but not the sensory dimension of perceived dyspnea. *Respir Med*. 2007;101:839–844.
146. de Peuter SD, Put C, Lemaigre V, Demedts M, Verleden G, Van den Bergh O. Context-evoked overperception in asthma. *Psychol Health*. 2007;22:737–748.
147. Evans KC. Cortico-limbic circuitry and the airways: insights from functional neuroimaging of respiratory afferents and efferents. *Biol Psychol*. 2010;84:13–25.
148. Herigstad M, Hayen A, Wiech K, Pattinson KT. Dyspnoea and the brain. *Respir Med*. 2011;105:809–817.
149. von Leupoldt A, Dahme B. Cortical substrates for the perception of dyspnea. *Chest*. 2005;128:345–354.
150. von Leupoldt A, Sommer T, Kegat S, Baumann HJ, Klose H, Dahme B, et al. The unpleasantness of perceived dyspnea is processed in the anterior insula and amygdala. *Am J Respir Crit Care Med*. 2008;177:1026–1032.
151. Faull OK, Jenkinson M, Ezra M, Pattinson KTs. Conditioned respiratory threat in the subdivisions of the human periaqueductal gray. *eLife*. 2016;5:e12047.

152. Harrison OK, Köchli L, Marino S, Luechinger R, Hennel F, Brand K, et al. Interoception of breathing and its relationship with anxiety. *Neuron*. 2021;109(4080–93):e8.
153. Stoeckel MC, Esser RW, Gamer M, Büchel C, von Leupoldt A. Dyspnea catastrophizing and neural activations during the anticipation and perception of dyspnea. *Psychophysiology*. 2018;55:10.
154. Harrison OK, Marlow L, Finnegan SL, Ainsworth B, Pattinson KTs. Dissociating breathlessness symptoms from mood in asthma. *Biol Psychol*. 2021;165:108193.
155. Fritz GK, McQuaid EL, Kopel SJ, Seifer R, Klein RB, Mitchell DK, et al. Ethnic differences in perception of lung function: a factor in pediatric asthma disparities? *Am J Respir Crit Care Med*. 2010; 182:12–18.
156. Feldman JM, Steinberg D, Kutner H, Eisenberg N, Hottinger K, Sidora-Arcoleo K, et al. Perception of pulmonary function and asthma control: the differential role of child versus caregiver anxiety and depression. *J Pediatr Psychol*. 2013;38:1091–1100.
157. Fritz GK, Adams SK, McQuaid EL, Klein R, Kopel S, Nassau J, et al. Symptom perception in pediatric asthma: resistive loading and in vivo assessment compared. *Chest*. 2007;132:884–889.
158. Feldman JM, McQuaid EL, Klein RB, Kopel S, Nassau JK, Mitchell DK, et al. Symptom perception and functional morbidity across a 1-year follow-up in pediatric asthma. *Pediatr Pulmonol*. 2007;42:339–347.
159. Feldman JM, Kutner H, Matte L, Lupkin M, Steinberg D, Sidora-Arcoleo K, et al. Prediction of peak flow values followed by feedback improves perception of lung function and adherence to inhaled corticosteroids in children with asthma. *Thorax*. 2012;67: 1040–1045.
160. Koinis–Mitchell D, McQuaid EL, Seifer R, Kopel SJ, Nassau JH, Klein R, et al. Symptom perception in children with asthma: cognitive and psychological factors. *Health Psychol*. 2009;28:226.
161. Fruchter N, Arcoleo K, Rastogi D, Serebrisky D, Warman K, Feldman JM. Attention-deficit hyperactivity disorder symptoms, underperception of respiratory compromise, and illness representations in Black and Latino children with asthma. *J Pediatr Psychol*. 2023;48:896–906.
162. Davenport KL, Julius SM, Davenport PW. Perception of inspiratory resistive (R) loads in asthmatic children with attention deficit disorder. *Clin Med Insights Circ Respir Pulm Med*. 2007;1: CCRPM–S351.
163. Feldman JM, Becker J, Arora A, DeLeon J, Torres-Hernandez T, Greenfield N, et al. Depressive symptoms and overperception of airflow obstruction in older adults with asthma. *Psychosom Med*. 2021;83:787–794.
164. Battaglia S, Sandrini MC, Catalano F, Arcoleo G, Giardini G, Vergani C, et al. Effects of aging on sensation of dyspnea and health-related quality of life in elderly asthmatics. *Aging Clin Exp Res*. 2005;17:287–292.
165. Feldman JM, Arcoleo K, Greenfield N, Styke S, Becker J, Jariwala S, et al. Under-perception of airflow limitation, self-efficacy, and beliefs in older adults with asthma. *J Psychosom Res*. 2023;170: 111353.
166. Forno E, Ortega V, Celedón JC. Asthma and chronic obstructive pulmonary disease. *Clin Chest Med*. 2023;44:519–530.
167. van de Loo KF, van Gelder MM, Roukema J, Roeleveld N, Merkus PJ, Verhaak CM. Prenatal maternal psychological stress and childhood asthma and wheezing: a meta-analysis. *Eur Respir J*. 2016;47:133–146.
168. Landeo-Gutierrez J, Forno E, Miller GE, Celedon JC. Exposure to violence, psychosocial stress, and asthma. *Am J Respir Crit Care Med*. 2020;201:917–922.
169. Lange NE, Bunyavanich S, Silberg JL, Canino G, Rosner BA, Celedón JC. Parental psychosocial stress and asthma morbidity in Puerto Rican twins. *J Allergy Clin Immunol*. 2011;127:734–40.e407.
170. Chen W, Boutaoui N, Brehm JM, Han YY, Schmitz C, Cressley A, et al. ADCYAP1R1 and asthma in Puerto Rican children. *Am J Respir Crit Care Med*. 2013;187:584–588.
171. Ramratnam SK, Han YY, Rosas-Salazar C, Forno E, Brehm JM, Rosser F, et al. Exposure to violence and asthma among children in Puerto Rico. *Respir Med*. 2015;109:975–981.
172. Brehm JM, Ramratnam SK, Tse SM, Croteau-Chonka DC, Pino-Yanes M, Rosas-Salazar C, et al. Stress and bronchodilator response in children with asthma. *Am J Respir Crit Care Med*. 2015;192:47–56.
173. Miller GE, Chen E. Life stress and diminished expression of genes encoding glucocorticoid receptor and beta2-adrenergic receptor in children with asthma. *Proc Natl Acad Sci U S A*. 2006;103: 5496–5501.
174. Gaietto K, Han Y, Forno E, Bacharier L, Phipatanakul W, Guilbert T, et al. Violence-related distress and lung function in two longitudinal studies of youth. *Eur Respir J*. 2022;59:2102329.
175. Gaietto K, Han YY, Forno E, Acosta-Pérez E, Marsland A, Miller GE, et al. Exposure to violence and asthma in Puerto Rican youth with high Th2 immunity. *Pediatr Pulmonol*. 2023;58:2289–2297.
176. Han YY, Celedón JC. The effects of violence and related stress on asthma. *Ann Allergy Asthma Immunol*. 2024;133:630–640.
177. Yan Q, Forno E, Cardenas A, Qi C, Han YY, Acosta-Pérez E, et al. Exposure to violence, chronic stress, nasal DNA methylation, atopic asthma in children. *Pediatr Pulmonol*. 2021;56:1896–1905.
178. Chen E, Jiang T, Chen MA, Chiu RY, Miller GE. Resilience in children with chronic illness: tests of the shift-and-persist and skindeep resilience theories. *Dev Psychopathol*. 2023;35:2264–2274.
179. Lam PH, Miller GE, Chiang JJ, Levine CS, Le V, Shalowitz MU, et al. One size does not fit all: links between shift-and-persist and asthma in youth are moderated by perceived social status and experience of unfair treatment. *Dev Psychopathol*. 2018;30: 1699–1714.
180. Chu EK, Drazen JM. Asthma: one hundred years of treatment and onward. *Am J Respir Crit Care Med*. 2005;171:1202–1208.
181. Hekking PW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol*. 2015;135:896–902.
182. Milgrom H, Fick RB Jr, Su JQ, Reimann JD, Bush RK, Watrous ML, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 Study Group. *N Engl J Med*. 1999;341: 1966–1973.
183. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med*. 2009;360:985–993.
184. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med*. 2009;360:973–984.
185. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β(2)-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388: 2115–2127.
186. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013;368:2455–2466.
187. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med*. 2021;384:1800–1809.
188. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J*. 2016;47:410–419.
189. McDonald VM, Clark VL, Cordova-Rivera L, Wark PAB, Baines KJ, Gibson PG. Targeting treatable traits in severe asthma: a randomised controlled trial. *Eur Respir J*. 2020;55:1901509.
190. Portacci A, Dragonieri S, Carpagnano GE. Super-responders to biologic treatment in type 2-high severe asthma: passing fad or a meaningful phenotype? *J Allergy Clin Immunol Pract*. 2023;11:1417–1420.
191. Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, et al. An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol*. 2020;145: 757–765.
192. Upham JW, Le Lievre C, Jackson DJ, Masoli M, Wechsler ME, Price DB, et al. Defining a severe asthma super-responder: findings from a Delphi process. *J Allergy Clin Immunol Pract*. 2021;9: 3997–4004.

193. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: Clinical impact and management. *Respirology*. 2017;22:651–661.
194. ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. *Respir J*. 2005;26:812–818.
195. Ji Z, López-de-Andrés A, Jiménez-García R, Maestre-Miquel C, Zamorano-León JJ, Scarano-Pereira JP, et al. Mental health in patients with asthma: a population-based case-control study. *Respir Med*. 2022;193:106758.
196. Heaney LG, Busby J, Hanratty CE, Djukanovic R, Woodcock A, Walker SM, et al. Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial. *Lancet Respir Med*. 2021;9: 57–68; [published correction appears in Lancet Respir Med. 2021: e18. doi:10.1016/S2213-2600(20)30601- 9.].
197. Czira A, Turner M, Martin A, Hinds D, Birch H, Gardiner F, et al. A systematic literature review of burden of illness in adults with uncontrolled moderate/severe asthma. *Respir Med*. 2022;191:106670.
198. Ritz T, Meuret AE, Trueba AF, Fritzsche A, von Leupoldt A. Psychosocial factors and behavioral medicine interventions in asthma. *J Consult Clin Psychol*. 2013;81:231–250.
199. Rosenkranz MA, Davidson RJ. Affective neural circuitry and mind-body influences in asthma. *Neuroimage*. 2009;47:972–980.
200. Stanescu S, Kirby SE, Thomas M, Yardley L, Ainsworth B. A systematic review of psychological, physical health factors, and quality of life in adult asthma. *NPJ Prim Care Respir Med*. 2019;29:37.
201. Hodkinson A, Bower P, Grigoroglou C, Zghebi SS, Pinnock H, Kontopantelis E, et al. Self-management interventions to reduce healthcare use and improve quality of life among patients with asthma: systematic review and network meta-analysis. *Brit Med J*. 2020;370:m2521; published correction appears in BMJ. 2023 Jul 27;382:p1743. doi:10.1136/ bmj.p1743
202. Hardtstock F, Maywald U, Timmermann H, Unmüßig V, Müller S, Wilke T, et al. Extent of non-adherence and non-persistence in asthma patients: analysis of a large claims data set. *J Asthma*. 2022; 59:829–839.
203. Chan A, De Simoni A, Wileman V, Holliday L, Newby C, Chisari C, et al. Digital interventions to improve adherence to maintenance medication in asthma. *Cochrane Database Syst Rev*. 2022;6: CD013030.
204. Doshi H, Hsia B, Shahani J, Mowrey W, Jariwala SP. Impact of technology-based interventions on patient-reported outcomes in asthma: a systematic review. *J Allergy Clin Immunol Pract*. 2021;9: 2336–2341.
205. Kadam S, Prem V, Ughreja RA. Effect of breathing re-training on end-tidal carbon-di-oxide in patients with asthma: a systematic review and meta-analysis. *J Asthma*. 2023;60:1493–1502.
206. Ritz T, Rosenfield D, Steele AM, Millard MW, Meuret AE. Controlling asthma by training of Capnometry-Assisted Hypoventilation (CATCH) vs slow breathing: a randomized controlled trial. *Chest*. 2014;146:1237–1247.
207. Meuret AE, Rosenfield D, Millard MM, Ritz T. Biofeedback training to increase P co2 in asthma with elevated anxiety: a onestop treatment of both conditions? *Psychosom Med*. 2023;85:440–448.
208. Hansen ESH, Pitzner-Fabricius A, Toennesen LL, Rasmusen HK, Hostrup M, Hellsten Y, et al. Effect of aerobic exercise training on asthma in adults: a systematic review and meta-analysis. *Eur Respir J*. 2020;56:2000146.
209. McLoughlin RF, Clark VL, Urroz PD, Gibson PG, McDonald VM. Increasing physical activity in severe asthma: a systematic review and meta-analysis. *Eur Respir J*. 2022;60:2200546.
210. Dickinson J, Amirav I, Hostrup M. Nonpharmacologic strategies to manage exercise-induced bronchoconstriction. *Immunol Allergy Clin North Am*. 2018;38:245–258.
211. Harver A, Kotses H, Ersek J, Humphries CT, Ashe WS Jr, Black HR II. Effects of feedback on the perception of inspiratory resistance in children with persistent asthma: a signal detection approach. *Psychosom Med*. 2013;75:729–736.
212. Janssens T, Harver A. Effects of symptom perception interventions on trigger identification and quality of life in children with asthma. *Pulm Med*. 2015;2015:825137.
213. Feldman JM, Ankam J, Barry M, Fruchter N, Becker J, Jariwala S, et al. A Pilot Randomized controlled trial of an intervention to improve perception of lung function in older adults with asthma. *Am J Respir Crit Care Med*. 2023;207:487–490.
214. Kew KM, Nashed M, Dulay V, Yorke J. Cognitive behavioural therapy (CBT) for adults and adolescents with asthma. *Cochrane Database Syst Rev*. 2016;9:CD011818.
215. Pateraki E, Morris PG. Effectiveness of cognitive behavioural therapy in reducing anxiety in adults and children with asthma: a systematic review. *J Asthma*. 2018;55:532–554.
216. Salsman ML, Nordberg HO, Wittchen HU, Klotsche J, Mühlig S, Riedel O, et al. Extrapulmonary symptoms of patients with asthma treated in specialist pulmonary care. *J Psychosom Res*. 2021;148: 110538.
217. Lack S, Brown R, Kinser PA. An integrative review of yoga and mindfulness-based approaches for children and adolescents with asthma. *J Pediatr Nurs*. 2020;52:76–81.
218. Heredia-Rizo AM, Martinez-Calderon J, Piña-Pozo F, González-García P, García-Muñoz C. Effectiveness of mind-body exercises in chronic respiratory diseases: an overview of systematic reviews with meta-analyses. *Disabil Rehabil*. 2024;46:2496–2511.
219. Paudyal P, Jones C, Grindey C, Dawood R, Smith H. Meditation for asthma: systematic review and meta-analysis. *J Asthma*. 2018; 55:771–778.
220. Yang ZY, Zhong HB, Mao C, Yuan JQ, Huang YF, Wu XY, et al. Yoga for asthma. *Cochrane Database Syst Rev*. 2016;4:CD010346.
221. Higgins ET, Davidson RJ, Busse WW, Klaus DR, Bednarek GT, Goldman RI, et al. Clinically relevant effects of mindfulness-based stress reduction in individuals with asthma. *Brain Behav Immun Health*. 2022;25:100509.
222. Ainsworth B, Stanescu S, Stuart B, Russell D, Liddiard M, Djukanovic R, et al. A feasibility trial of a digital mindfulness-based intervention to improve asthma-related quality of life for primary care patients with asthma. *J Behav Med*. 2022;45:133–147.
223. Sanbonmatsu L Katz LF Ludwig J Gennetian LA Duncan GJ Kessler RC et al Moving to Opportunity for Fair Housing Demonstration Program - Final Impacts Evaluation. U.S. Department of Housing and Urban Development Office of Policy Development & Research, November 2011. Accessed November 14, 2024. https://www.huduser.gov/portal/publications/pubasst/MTOFHD.html
224. Schmidt NM, Lincoln AK, Nguyen QC, Acevedo-Garcia D, Osypuk TL. Examining mediators of housing mobility on adolescent asthma: results from a housing voucher experiment. *Soc Sci Med*. 2014;107:136–144.
225. Boudreaux M, Fenelon A, Slopen N, Newman SJ. Association of childhood asthma with federal rental assistance. *JAMA Pediatr*. 2020;174:592–598.
226. Pollack CE, Roberts LC, Peng RD, Cimbolic P, Judy D, Balcer-Whaley S, et al. Association of a housing mobility program with childhood asthma symptoms and exacerbations. *JAMA*. 2023;329: 1671–1681.
227. Saito N, Kamata A, Itoga M, Tamaki M, Kayaba H, Ritz T. Assessment of biological, psychological and adherence factors in the prediction of step-down treatment for patients with well-controlled asthma. *Clin Exp Allergy*. 2017;47:467–478.
228. Engel GL. The need for a new medical model: a challenge for biomedicine. *Science*. 1977;196:129–136.