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# The Impact of Environmental Chronic and Toxic Stress on Asthma

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## Abstract

Several factors have been associated with the development of asthma and asthma-related morbidity and mortality. Exposures in the environment such as allergens and air pollutants have traditionally been linked to the risk of asthma and asthma outcomes. More recent literature has identified chronic psychosocial stress as an additional environmental exposure to consider in relation to asthma. Adverse childhood events (ACEs) and chronic and toxic stress have been associated with chronic diseases such as cardiovascular disease, cancer, and chronic obstructive pulmonary disease. Chronic stress has also been shown to result in biological changes such as expression of immunologic genes, changes in expression of the beta-adrenergic (*B2AR*) and the glucocorticoid receptor (*GR-α*) genes, cytokine regulation, and alterations in the hypothalamic pituitary axis and cortisol levels which all may affect asthma pathophysiology and therapeutic response among patients exposed to chronic stress. Recent research has revealed associations between ACEs and chronic and toxic stress and asthma risk in pre-conception to early childhood as well as morbidity and response to asthma treatments among pediatric and adult age groups. As some populations are more significantly impacted by asthma such as racial and ethnic minority groups, the influence of psychosocial stress has also been explored as a potential factor responsible for observed disparities in asthma prevalence and outcomes among these groups which also experience higher rates of psychosocial stress. Racial discrimination has specifically been shown to affect asthma-related outcomes among minority groups. Interventions to address the impact of chronic and toxic stress such as yoga and meditation have been shown to improve asthma outcome measures. Chronic and toxic stress is an important environmental exposure to further consider as we continue to explore the differences in underlying asthma pathophysiology leading to various disease phenotypes among patients and clinical/therapeutic response to interventions and treatments.

**Keywords** Asthma · Allergic disease · Chronic stress · Toxic stress · Adverse childhood events · Racial discrimination

## Introduction

Asthma is the most common childhood chronic illness in the USA and is a leading cause of health-related disability among adults [1]. Despite significant advancements in medicine and science, asthma remains a burden for many children and adults and some populations are disproportionately affected. Asthma is more prevalent among racial minority groups such as African-American and Hispanic populations vs. Caucasian children and adults. Recent data suggests that African-Americans are 20 % more likely to be diagnosed with asthma than non-Hispanic whites [1]. African-American and Hispanic populations have also been reported to have higher rates of emergency department visits and hospitalizations and are three times more likely to die from asthma than non-Hispanic whites [1]. Asthma is well described as a heterogeneous disease with several contributing factors including genetics and environmental exposure. Socioeconomic-related factors (e.g., family income, medical insurance type, parental educational level) have been associated with observed asthma-related disparities experienced by racial/ethnic minority groups. However, socioeconomic factors have not accounted for the entirety of gaps in asthma outcomes between racial groups [2, 3].

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Environmental exposures have been linked to morbidity/mortality in studies among patients with asthma. In a longitudinal study conducted among primarily African-American children, investigators observed an association between higher levels of ambient pollutants and poorer lung function [4]. Parker et al. conducted a study among almost 300 largely African-American households in Detroit, MI, with at least one child with asthma whereby interventions to reduce household environmental triggers such as pet dander, cockroach, and dust mites resulted in decreased medication use and improved pulmonary function [5]. However, there are also conflicting reports in regard to the impact of traditional environmental interventions (e.g., allergen reduction) on asthma outcomes in highly impacted communities [6]. It is necessary to consider additional factors that patients may experience in their environment when investigating and designing interventions to improve asthma-related health outcomes among highly affected populations such as African-American and Hispanic children and adults.

Recently, psychosocial chronic stress (e.g., violence in your neighborhood) and toxic stress (e.g., sexual abuse) have been described in relation to risk of chronic disease and disease morbidity and mortality, including asthma [7–9]. Psychosocial chronic and toxic stress is a novel but important concept to explore in thinking about "environmental" exposures that impact disease risk, morbidity, and response to interventions.

## Adverse Childhood Experiences and Chronic and Toxic Stress

Adverse childhood events (ACEs) were first described in the literature in 1998. Felitti et al., in a landmark investigation, described the impact of these ACEs, described as negative childhood experiences such as emotional/physical/sexual abuse, mental illness in household, maternal abuse, parental separation/divorce, and emotional or physical neglect, on chronic disease outcomes later in adulthood. This cross-sectional study, conducted among a largely Caucasian (79%) adult cohort ($n = 8506$) with higher education (43% with a college degree), aimed to determine the impact of negative experiences during childhood on health outcomes later in adulthood. Approximately 50% of study participants reported that they had experienced one or more ACE categories, and the number of ACEs experienced increased likelihood of having a chronic disease such as chronic obstructive pulmonary disease, cancer, ischemic heart disease or stroke, or diabetes [9]. This pioneering work has led to subsequent studies and replication of these findings in other populations in addition to exploring other aspects of psychosocial stress described as "chronic" and/or "toxic" stressors. Toxic stress has been described as "severe, prolonged, or repetitive adversity with a lack of the necessary nurturance or support of a caregiver to prevent an abnormal stress response" [7, 10, 11].

Investigators have further expanded the work of Felitti et al. among a more socioeconomically and racially diverse population. The investigators have included the evaluation of community level stressors that children may experience chronically. These other domains of stress exposure include living in an unsafe neighborhood, witnessing community violence, bullying, having been in foster care, and experiencing racism. In this study, the investigators found that these community-level adversities were commonly experienced among this population (63.4% experienced at least one of the "Expanded ACEs") [12]. Other investigators have also investigated expanded domains of chronic and toxic stress to include financial (e.g., decrease in income), legal (e.g., someone getting arrested), career (e.g., getting laid off), relationship (e.g., getting divorced), medical (e.g., flare up of chronic illness), and authority/institutional stressors (e.g., trouble with superiors at work) [13]. These stressors were even more commonplace, and investigators revealed that these Expanded ACEs among parents were related to asthma morbidity in their child [14].

Therefore, the originally described ACEs in addition to chronic and toxic stressors that children and adults may experience daily or very frequently (e.g., violence in the neighborhood, racism, and financial stress) are relevant environmental stress exposures that may modify susceptibility for disease, disease burden, and outcomes and may be especially relevant for asthma (Fig. 1).

## Impact of ACEs and Chronic and Toxic Stress on Asthma

Many investigators have hypothesized that experiences of chronic and toxic stress have impact on asthma morbidity and outcomes especially among communities that experience high asthma prevalence and morbidity (Table 1). Psychosocial stress has been described by some as a "social pollutant" that when "*breathed* into the body, disrupts biological systems overlapping with those altered by physical pollutants and toxicants" [31].

Even starting in conception, stress exposure has been associated with asthma risk and outcomes. A study conducted by Reyes et al. assessed the association between psychological distress in pregnant mothers and risk of future wheeze in the child. The study was conducted among a cohort of African-American and Dominican women with low income in New York City. They found that high levels of stress experienced by mothers during the prenatal period, as measured by the Psychiatric Epidemiology Research Instrument-Demoralization (PERI-D) scale, was associated with increased risk of child wheeze at 5 years of age (odds ratio

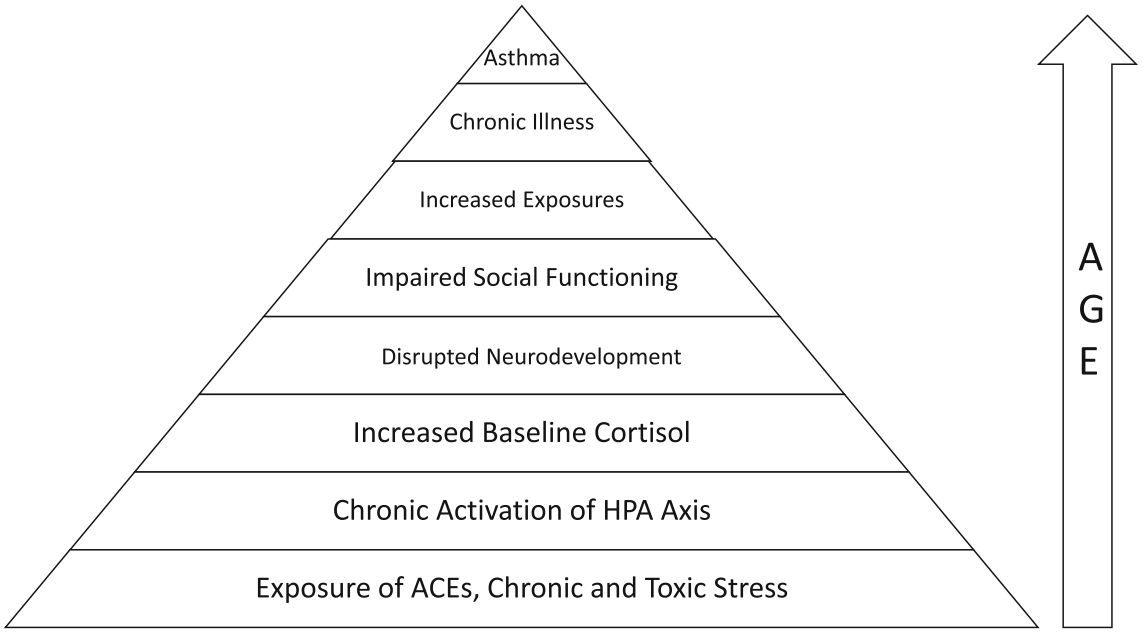


**Fig. 1** Paradigm of the impact of ACEs (adverse childhood events) and chronic and toxic stress through the age continuum resulting in alterations in biology, neurodevelopment, social functioning, and risk for disease

1.6; 95% confidence interval 1.24–2.06) [32]. Along the life continuum, a cross-sectional study was conducted which demonstrated that parental/guardian report of ACE exposure in the home was associated with increased risk of asthma among African-American, Caucasian, and Hispanic children. In this study, it was found that children exposed to at least one ACE had a 28% increased odds of asthma compared with those with no ACE exposure. The study also demonstrated a dose-effect with correlation between increased ACE exposure and a parallel increase in asthma risk. Their study also revealed a disproportionately higher risk of asthma among Hispanic children in relation to ACE exposure. Among Hispanic children exposed to four or more ACEs, there was a 4.46 odds of asthma compared to no ACE exposure in contrast to 1.19 and 1.60 odds in non-Hispanic White and non-Hispanic Black children respectively who experience the same number of ACEs. These data also suggest that racial/ethnic and cultural differences may alter the impact of stress on disease outcomes [33].

Community-level stress exposures have additionally been associated with asthma. In a study conducted among over 2000 children in Chicago, investigators found that medium and high levels of community violence (e.g., child witnessing someone being shoved, kicked, or punched) were associated with increased risk of having an asthma diagnosis in comparison to children with low violence exposure [34]. This study highlights the importance of considering in-home environmental stressors along with outside stressors when considering the impact of psychosocial stress on asthma. Studies have also revealed the potential of compounding effects of environmental stressors and traditional environmental exposure. A novel study by Islam et al. aimed to determine the effect of household stress and traffic-related pollutants on children with asthma in exploration of the interaction between traditional environmental pollutants and stress as a pollutant. They studied parents and children in Southern California and evaluated household psychosocial stress and pollutant exposure (e.g., nitric oxide, nitrogen dioxide, total oxides of nitrogen). They observed that pollutant effects on lung function were significantly larger among children from high-stress households in comparison to those from low-stress households after correcting for socioeconomic factors. Children who experienced high stress in their household had lower FEV1 and FVC in relation to increased environmental nitric oxide exposure [35]. This study suggests that high stress exposure may modify the biological response to air pollutants, a known factor in asthma pathogenesis, making some more vulnerable to air pollutants as a function of stress exposure. Therefore, a multiplicity of factors must be considered when addressing environmental "triggers" for asthma.

Housing-related exposures such as pet dander, rodents, and household insects are commonly considered in regard to respiratory health. However, one study has explored the concept of housing stability as a potential stress-related factor that likely leads to increased psychological stress exposure and allergen/environmental exposures. Investigators studied the association between parent reported housing-related stressors (e.g., did you miss rent or mortgage payment because you could not pay; did you lose your housing?) and asthma-related health outcomes that suggest poor asthma health (e.g., exercise intolerance, unplanned medical visits). They found that children who experienced high housing-related

**Table 1** Association between ACEs and chronic and toxic stress. Selected publications

| Aim/objective of the study | Outcome age group | Reported r/ethnic demographics | Conclusion | Reference |
|---|---|---|---|---|
| To determine if within-day variability in stress is associated with increased asthma symptomatology | Adolescents | Hispanic cohort; other race demographics not reported | Experiences of stress associated with increased shortness of breath, self-report of wheezing | [21] |
| To determine the interaction effect of community violence exposure, protective factors, and asthma morbidity | Children | 96% African-American | Higher caregiver community violence exposure predicted increased asthma health care utilization | [22] |
| To examine differences in asthma outcomes by levels of child reported neighborhood and family stress | Children | 55.3% Latino<br>22.1% Black/African-American<br>22.6% non-Latino White | Increased neighborhood and family stress was associated with poorly controlled asthma | [23] |
| To determine if a cumulative risk index including psychosocial stress exposures is associated with asthma morbidity | Children | 40% Black<br>51% Anglo<br>8% multicultural<br>1% others | Higher cumulative risk index was associated with increased asthma related functional limitation, hospitalizations, and ED visits | [24] |
| To determine the association between maternal experiences of intimate partner violence and housing disarray/instability and asthma diagnosis | Children | 54% Black<br>27% Hispanic | Chronic intimate partner violence associated with increased odds of asthma which was compounded by housing disarray/instability | [25] |
| To determine the association between ACE exposure and asthma and chronic obstructive pulmonary disease in women | Adults | 26% White<br>13% Hawaiian<br>16% Filipino<br>26% Japanese | For every increase in ACE exposure the likelihood of asthma diagnosis increased by 7% | [26] |
| To determine the relationship between ACE exposure and asthma prevalence in 10 US States | Adult | 81% non-Hispanic White<br>6% non-Hispanic Black<br>3% Hispanic<br>9% others | Increased childhood adversity was associated with asthma prevalence in adults | [27] |
| To determine the association between prenatal stress and occurrence of atopic dermatitis, food allergy, wheezing, recurrent respiratory tract infections | Children | Polish cohort, race/ethnicity not reported | Association between perceived maternal stress exposure and risk of infant wheezing in first year of life | [28] |
| To determine the relationship between whether women's experiences of common adverse experiences during pregnancy was associated with the risk of developing atopic disease in the child | Children | Australian cohort, race/ethnicity not reported | Prevalence of asthma at age 14 years in the child was associated with increased prenatal stress exposure | [29] |
| To determine if there is a synergistic effect between psychosocial and socioeconomic stress and air pollution on childhood asthma | Children | Chinese cohort, race/ethnicity not reported | Parental stress was associated with childhood asthma diagnosis. Childhood asthma was only associated with increased air pollution exposure among those with high parental stress. | [30] |
| To determine the association between ACEs and adult health and impact of socioeconomic status | Adult | 45% White<br>44% Black<br>4% Asian/Pacific Islander<br>4% Multiracial<br>4% Hispanic | High Conventional ACEs increases the odds ratio for asthma | [25] |

stress had higher risks and rates of exercise intolerance, asthma-related night time awakenings, and unplanned medical visits for asthma [36]. Poor stability in housing may result in lack of access to medications and/or medications which may be lost during a move or left behind, present a barrier in accessing their health care provider or care at all, and may lead to patients living in inadequate housing and put them at risk of allergen and other toxic exposures. Beyond these factors, housing instability puts a significant psychosocial burden on patients and families. Therefore, housing instability may be uniquely relevant among those with asthma as both a psychosocial stressor and risk factor for traditional environmental trigger exposure.

Although urban and racial minority populations are reported to have high levels of chronic and toxic stressors that appear to impact asthma, other racial/ethnic groups have also

demonstrated an association between chronic/toxic stress and asthma. For example, in a study conducted among a population in Scotland, it was observed that high chronic stress was associated with risk of asthma attacks [37]. A study among Dutch children also found that parental stress was associated with higher airway inflammation in children with asthma [38]. The impact of ACEs, toxic stress, and chronic stress on asthma has been universally demonstrated among several populations; however, specific population-related factors (e.g., income level, educational background, access to interventions to address stress and disease, race) may make some more vulnerable to the effects on disease and outcomes.

## Biological Changes of Chronic Stress

Although ACEs, chronic stress, and toxic stress have been associated with risk and outcomes of various diseases, what is the biological plausibility for this association, especially as it would relate to asthma? For example, telomere length, which shortens with age and may be a marker for aging, has also been associated with stress exposure in a dose-response fashion [39]. However, it is currently unclear as to how telomere length might be associated with asthma.

Psychosocial stressors have been shown to affect biological responses that may result in alterations in the susceptibility to infections and systemic illness. A study conducted by Breen et al. evaluated expression of gene networks utilizing whole-transcriptome RNA-Seq gene expression in a cohort of Marines ($n = 188$) aimed to determine the effects of pre- and post-conflict zone exposure on gene expression. They observed that distinct groups of co-regulated genes demonstrated increased expression among those who developed post-traumatic stress disorder (PTSD). These gene groups included those related to innate immune response and interferon signaling. They were also able to replicate these findings in a separate group of marines ($n = 96$). Additionally, their findings suggested decreased ability for wound healing during and after combat zone exposure [40]. Although this study was conducted in context of extreme stress exposure experienced in combat, children and adults living in inner-city environments have been reported to experience similar levels of stress and PTSD due to neighborhood violence and other negative exposures in the community [41]. Therefore, these results obtained in a cohort of Marines may be applicable to communities that experience toxic stress.

In another study among adult caregivers of a spouse with dementia, immune response to influenza vaccination was decreased in comparison to a control non-caregiver group [42]. These studies indicate that chronic and toxic stressors may alter cytokine responses and mechanisms of tissue repair and may result in differential responses to viral or bacterial infection and/or tissue recovery from such infections and may even increase susceptibility to infections. These factors are certainly relevant to asthma pathogenesis and treatment outcomes.

The effects of stress on the hypothalamic-pituitary-adrenocortical axis (HPA) and resulting downstream actions have been most widely investigated and discussed as a biological consequence of stress exposure. It has been described that psychosocial stress activates the HPA which results in production of cortisol leading to biological changes which may affect pathophysiology of disease and treatment response (Fig. 2).

Some patients may be more highly impacted by these physiologic changes than others. Children from low socioeconomic backgrounds have been reported to have chronically higher levels of cortisol in comparison to children from high socioeconomic background [43]. Chronic activation of the HPA has been shown to shift immune response from a predominantly T-helper 1 cellular response type to a T-helper 2 response phenotype. This shift increases inflammatory cell production and atopic inflammation. These alterations in immune response as a result of stress exposure has been postulated to play a role in the atopic march and inflammation which may lead to the development of asthma. Chronic activation may also lead to target insensitivity through the downregulation of target tissue receptors.

However, in a study among 500 young, predominantly African-American mothers with asthma and allergic disease from a low socioeconomic background, investigators measured the peripheral blood mononuclear cell cytokine responses to innate and adaptive stimuli and evaluated the association between measures of individual, household neighborhood stress, and depression with cytokine response. The investigators did not find an association between cytokine response patterns and pro-inflammatory responses and composite stressor scores. However, specific domains of stress such as housing-related stress, interpersonal relationship stress, and neighborhood-related stress was associated with cytokine response patterns. Housing stress was positively associated with IL-10 and TNF-α response. Interpersonal problems was associated with increased IFN-γ response while neighborhood factors were negatively associated with CpG-stimulated IFN-γ. The investigators finally observed an inverse relationship between stress exposure and cytokine response for TNF-α, IL-8, IFN-γ, IL-4, IL-5, IL-10, and IL-13 [44–46]. This study highlights the complexity involved with variability and heterogeneity of how stress exposure may impact biological functions. More research in this area is necessary to understand the nuances associated with chronic and acute stressors in relation to biological changes and potential pathophysiology.

Chronic stress exposure has also been associated with molecular changes that may alter response to therapeutic treatments for asthma. In one study conducted in children with and without asthma, mRNA expression of the gene encoding the

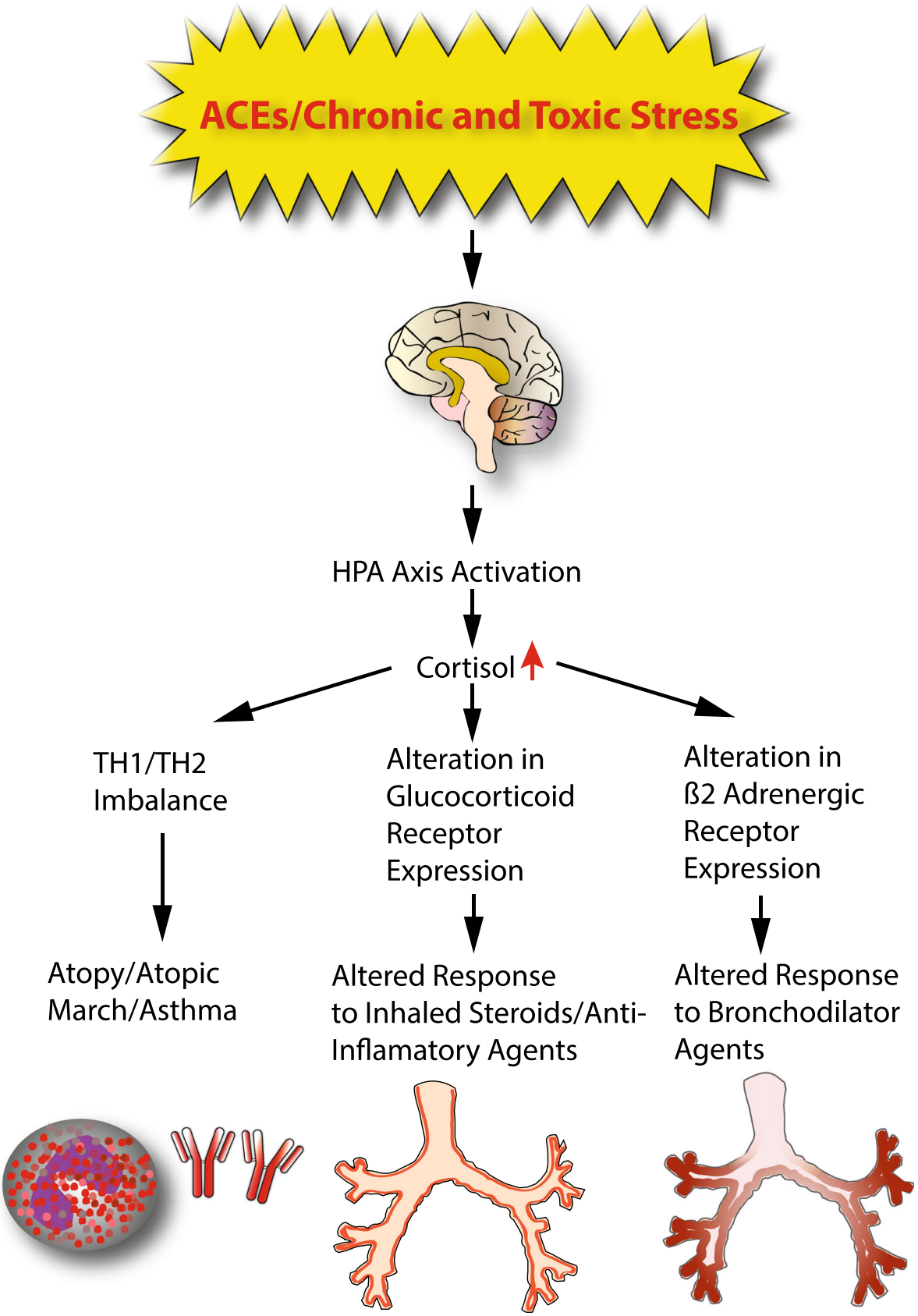


**Fig. 2** The effects of ACEs and chronic and toxic stress on the HPA axis, cortisol and described biological changes and postulated asthma pathophysiology/therapeutic response

beta-adrenergic (*B2AR*) and the glucocorticoid receptor (*GR-α*) was altered among children who experienced chronic stress. However, this effect was not observed in children without asthma which suggest a unique gene-environment interaction among children with asthma. The investigators also observed that changes in molecular expression were most profound among participants who experienced acute stress in the setting of ongoing chronic stress (e.g., family relationship stress in conjunction with an acute illness in a family member). Children with asthma who experienced acute on chronic stress exhibited 9.5- and 5.5-fold changes in mRNA expression of *B2AR* and *GR-α*, respectively [47]. Similarly this same "double acute on chronic exposure" model has also demonstrated differences in cytokine levels among children with asthma. In one study, children who experienced high levels of chronic stress in conjunction with an acute stress event demonstrated higher levels of IL-4, IL-5, and IFN-gamma temporally related to the acute stress event. The authors postulate that their observations may be the result of chronic activation of the HPA which leads to a down-regulation of glucocorticoid receptors and overall receptor insensitivity to the anti-inflammatory effects of cortisol [48]. These studies have importantly provided a potential mechanistic background for the impact of ACEs and chronic and toxic stress on asthma and observed poorer outcomes among those that experience these types of stress.

Furthermore, studies suggest that efficacy of current therapeutic treatments for asthma (e.g., glucocorticoids) may be altered during acute and chronic stress events. One study among children has demonstrated that decreased bronchodilator response was associated with child stress. Brehm et al. observed that children with higher levels of stress exposure experienced less of a response to conventional bronchodilator therapy. In their study among a cohort of 350 children in Puerto Rico, they found an additive effect of stress exposure with presence of a single nucleotide polymorphism (SNP) in *ADCYAP1R1*. Children who carried the *ADCYAP1R1* SNP overall had reduced bronchodilator response to a short-acting beta agonist, and the reduction in response was compounded by children who exhibited symptoms of high stress exposure. The investigators also noticed a decrease in bronchodilator response in children whose mothers reported higher levels of stress, indicating household stress may also play a role in a child's response to medications. These data suggest that stress may have epigenetic effects especially among those who carry specific genetic polymorphisms leading to alterations in drug effect in these children [49]. ACEs and chronic and toxic stress should be further explored in the context of impact on biological pathways of inflammatory disease and how alterations of these pathways may affect therapeutic response.

## The Chronic Stress of Racial Discrimination

Throughout American history, racial/ethnic minority and marginalized populations have suffered from poor health as a result of lack of and disproportionate distribution of health resources [50]. However, more recently, investigators have begun to explore the impact of racism and discrimination as a chronic stressor on human biology and disease. Racial discrimination is a unique stressor experienced by some racial and ethnic groups. Chronic disease and poor outcomes have been linked to experiences of racial discrimination. One well researched area includes that of maternal and child health. Disproportionately high infant and maternal mortality rates experienced by African-American women have been clearly linked to components of racial discrimination [51–53]. In their first year of life, African-American infants currently experience twice the risk of dying and this gap in survival has persisted over the last 70 years of data. Pre-term infants are especially vulnerable to infant death. While the risk of a pre-term infant decreases with age amongst the white population, it increases with age in the African-American population after correction for education level and prenatal care. These findings have introduced the concept of "weathering," a phenomena whereby African-American women are chronically subjected to conditions and factors that poorly impact their health and therefore that of their children [54].

Similarly, the psychosocial stress of racism and discrimination have been linked with asthma outcomes among racial/ethnic minority populations. African-Americans in the USA experience disproportionate rates of asthma and excessive asthma burden. However, as previously mentioned, this disparity has not been fully explained by traditionally explored variables (e.g., allergen exposure). In a prospective study among 1068 African-American women with asthma conducted between 1997 and 2011, investigators explored the relationship between perceived racial discrimination among participants and asthma-related outcomes. Women who reported persistent levels of racism between 1997 and 2011 had highest rates of asthma in the study [55]. A recent study among African-American and Hispanic children also revealed that experiences of perceived racial discrimination was associated with a 78% increased odds of having asthma in comparison with those who did not report experiencing racism among the African-American children after controlling for socioeconomic and other relevant factors. In addition, the African-American children in this study had 97% greater odds of poor asthma control. They did not observe similar associations among Mexican-American children [56]. This study importantly suggests a link between children experiencing racism

and asthma/asthma morbidity and also demonstrates that racism experienced by African-Americans may be uniquely associated with disease and outcomes. Studies have also suggested that higher levels of racial discriminatory experiences are associated with increased inflammation as measured by cytokine levels (e.g., IL-1, IL-6, IL-8, IL-10, TNFα, IFN-γ) [57].

A study conducted in the UK aimed to explore the impact of air pollution on asthma in minority populations and the influence of racism on this interaction. The investigators quantified discriminatory racial experiences utilizing questions such as "Has anyone made you feel bad or hassled you because of your race, skin colour or where you were born?". They found an increased risk of having asthma among participants who were exposed to both racism and air pollution (quantified by neighborhood air particulate matter) [58]. Experiencing racism has also been associated with known contributors to asthma morbidity. A study conducted among racial minority populations in London enrolled adolescents and followed them to early adulthood. They observed that experiences of racism was associated with initiating smoking during adolescence through early adulthood [59].

Racism and discrimination is an important chronic stressor that may be uniquely relevant among specific populations and especially relevant among populations known to suffer disproportionately from asthma.

## Assessing Chronic and Toxic Stress

The "Conventional" ACE questionnaire which was utilized to conduct an evaluation of childhood traumatic events and impact on disease outcomes among adults in the 1980s is still considered the gold standard instrument for assessing chronic stress among children and adults. The instrument focuses on the main domains of abuse (emotional, physical, or sexual), and household dysfunction (parental separation or divorce, having a battered mother or a substance abusing, criminal, or mentally ill household member) [9]. More recently, investigators have developed and expanded the questionnaire. The Expanded ACEs takes into account the fact that many children/adults experience stressors outside of the household that may not be addressed by the conventional ACE tool. As the Conventional ACE questionnaire was developed among a population of primarily Caucasian middle class and insured participants, investigators recognized the need to develop additions to this tool which provides a more complete assessment among various populations. The Expanded ACE tool provides insight into community-driven stress exposures (included experiencing racism, witnessing violence, living in an unsafe neighborhood, experiencing bullying, and a having a history of living in foster care) [12]. In utilizing both the Conventional and Expanded ACE questionnaires, rates of exposure (e.g., ≥ 1 ACEs) are used in data analysis. Both the Conventional and Expanded ACE questionnaires have been used in exploring the association between chronic/toxic stress and asthma and the coupling of these questionnaires in research is now becoming standard practice.

The Crisis in Family Systems (CRISYS) questionnaire is another tool that has been developed to assess various types of stress that one may experience and potentially impact overall health [13]. The self-report tool which measures daily life stressors, major life stressors, and chronic stressors was designed to capture the variability of experiences related to stressors among respondents. For example, a respondent may indicate that money problems are a daily hassle type of stress where others may indicate that such a stressor is a chronic stressor. The questionnaire has been utilized by comparing the total number of stressors experienced and number of stressors rated as negative also in recognition that some life events may be perceived as positive or negative based on an individual's unique experience (e.g., becoming pregnant). The questionnaire was constructed to represent a broad range of events relevant to contemporary urban life such as financial issues, legal issues, career, relationships, medical issues, safety, home issues, authority issues, and prejudice. This 64-item questionnaire has been validated among a largely African-American cohort of parents who live in an inner-city environment and has also been used in asthma research [14].

Although experiences of general racism are included as one question item within the Expanded ACE questionnaire, other tools have been developed to provide more in-depth measures of experiences of racism as a stressor. The Schedule of Racist Events is an 18-item self-report inventory that assesses the frequency of specific racist events that one may have experienced in the past year or in one's lifetime (e.g., being discriminated against on a job) and also how stressful that invent was. The measure was validated among an African-American population that varied in income, educational background, and marital status. Investigators observed that the frequency and associated stress of racism impact physical and mental health [60].

As chronic/toxic stress varies in phenotype, investigators and clinicians should utilize appropriate tools to assess relevant stressors specific to the population being evaluated.

## Interventions to Address Chronic and Toxic Stress

In recognizing the wide impact of ACEs, chronic stress, and toxic stress on health and health outcomes, interventions that prevent or mitigate negative outcomes from stress exposure have been explored. Mind-body interventions such as yoga and meditation have been demonstrated effective in decreasing stress even among those who experience PTSD [61, 62].

The effectiveness of such interventions has also been investigated among those with asthma. In a randomized controlled trial conducted among adults with asthma, investigators demonstrated that participants who underwent a comprehensive yoga-based lifestyle modification in conjunction with standard asthma care vs. those who were assigned to a "placebo" and followed standard care had improvement in pulmonary function, reduction of exercise-induced bronchoconstriction, and quality of life scores [63]. Another randomized study among young adults with asthma also suggested that yoga and meditation practices decreased rescue medication use and overall promoted relaxation and positive attitude [15].

Other muscle relaxation techniques have also been explored in their ability to improve lung function, such as prayer, meditation, or biofeedback techniques. Lehrer et al. conducted a study among adults with asthma utilizing heart rate variability biofeedback techniques and also revealed that use of the intervention led to decreased medication needs and improved pulmonary function [16]. However, the general consensus from the currently available body of literature suggests that mind-body interventions may have only modest impact on asthma. A Cochrane review to assess the effects of yoga in those with asthma included review of 15 randomized controlled trials (1048 participants) concluded that there was moderate-quality evidence that yoga may lead to small improvements in asthma quality of life and symptoms [17]. Further studies in larger and more diverse cohorts (most trials have been conducted in India) are necessary to better understand the potential effect of mind-body techniques on asthma especially among those who are highly impacted by asthma and among those who experience ACE and chronic and toxic stress.

Beyond external interventions, resilience, an internal factor that may be innate or learned, has also been explored as protective in the impact of psychosocial stress on health. Resilience has been described to allow one to positively cope with trauma and stressors and is defined in Merriam-Webster as "an ability to recover from or adjust easily to misfortune or change." In the scientific literature, it has been defined as "dynamic process encompassing positive adaptation within the context of significant adversity" [18]. A specific resilience mechanism was explored in one study conducted by Chen et al. among children age 9 to 18 years old with asthma. The investigators aimed to determine the effect of using a "shift-and-persist" strategy among children with asthma on asthma outcomes. "Shift-and-persist" is described as when one works to reinterpret stressors in positive light (shifting) while remaining optimistic regarding the future and what it may hold (persisting). In their study, they found that children from low-income households who utilized "shift-and-persist" had lower markers of inflammation at baseline (e.g., eosinophil counts) and had lower rescue inhaler use and school absences at 6 months after enrollment. Interestingly, this effect was not observed among children of high socioeconomic status [19]. This study is important because it reveals the possibility of disease modification as a result of a psychological intervention and also highlights a possible intervention that may be "taught" to children/adults who are experiencing chronic stressors in conjunction with standard guideline-based asthma care.

It is important to identify interventions that may allow patients to cope with ACEs and chronic and toxic stress and decrease the effect of psychosocial stress on health and health outcomes. Additionally, internal factors or traits may also be amplified and targeted to allowing coping and prevent associated negative outcomes.

## Limitations in Examining the Impact of Stress in Asthma

The ACE questionnaire is currently among the most widely used tools in the clinical and research setting for measuring chronic and toxic stress. However, like the vast majority of psychological conditions (e.g., depression, anxiety), there are currently no objective measures of chronic or toxic stress. As described, stress exposure has been shown to affect the hypothalamic-pituitary axis, gene expression, and cytokine response. However, these biological changes have not been translated into clinically feasible biomarkers for determining and/or quantifying chronic or toxic stress. Telomere length has been investigated as one potential biomarker of stress exposure; however, feasibility and validation of telomere length as a biomarker in measuring stress are of yet to be realized [20].

Furthermore, differences between chronic vs. toxic stress exposure have not been clearly delineated. Although there is clear overlap between the terms of chronic and toxic stress, the psychological and biological impact of a chronic stressor such as being exposed to parents that argue vs. that of being sexually abused is likely very different. Further work is needed to understand the heterogeneity among chronic and toxic stress exposure and their potential impact on health from both a psychological and biological/pathophysiological standpoint. Reliable objective biomarkers are also needed to measure and quantify and differentiate stressors.

## Conclusions

Asthma is a heterogeneous disease with variability in underlying pathophysiology, relevant triggers, and therapeutic response. ACEs and chronic and toxic stress are an additional exposure in one's environment that has shown to increase the risk and morbidity of asthma and result in associated biological changes. However, this environmental exposure is not regularly considered in the evaluation and management of

asthma and inflammatory disease. Targeted interventions to address the exposure of stress may improve outcomes among those with asthma. Psychosocial stress may also be especially relevant among populations with high rates of asthma and asthma morbidity in conjunction with high rates of chronic and toxic stress. Interventions to address relevant stressors among patients combined with standard treatments may lead to improvements in the effectiveness of asthma management. Further research should be conducted to better define the impact of environmental stress on pathophysiology, disease, and outcomes in children and adults with asthma.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Statement of Human and Animal Rights** This article does not contain any studies with human participants or animals performed by any of the authors.

**Ethical Approval and Informed Consent** Not applicable.

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