

Epidemiology of Stress and Asthma: From Constricting Communities and Fragile Families to Epigenetics

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KEYWORDS

• Epidemiology • Stress • Asthma • Epigenetics • Life course
• Transgenerational • Violence

Evidence increasingly links psychosocial stress, including early-life stress-related programming of key response systems, to asthma, atopic disorders more broadly, and lung function.^{1,2} To more fully understand the potential role of psychological stress in the etiology of asthma and other allergic or inflammatory disorders, it is necessary to consider several key theoretic and methodological frameworks from social sciences, psychology, immunology, and child development and extend these to epidemiologic research. Application of recent advances in developmental biology, neurogenomics, and genomic plasticity may inform underlying mechanisms at the most fundamental level. An area of particular interest in childhood asthma research is the search for mechanisms responsible for health disparities across economic and racial/ethnic groups. The psychosocial stress model has been increasingly adopted in this regard³ given the increasing recognition that children are being raised in social contexts that may be as detrimental to their development as established physical environmental factors associated with disease risk.⁴ This review highlights the growing number of epidemiologic studies exploiting these transdisciplinary concepts

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to uniquely inform our understanding of the role of stress and the expression of asthma and allergy during the life course.

NEED FOR A PROSPECTIVE DEVELOPMENTAL FRAMEWORK

This overview considers the developmental origins of both asthma risk¹ and lung structure and function² given that both involve coordinated maturation of interrelated systems: immune, neural, and endocrine. Moreover, although the origins of chronic lung diseases are multifactorial, the underlying mechanisms leading to reduced lung function and exaggerated airway responsiveness involve chronic airway inflammation associated with a cycle of injury, repair, and remodeling.^{5,6} Airway inflammation and remodeling begin and progress even in the presymptomatic state in early childhood.^{7–10} Moreover, the fundamental cause of the airway inflammation is aberrant and/or excessive immune responses to various environmental factors,⁵ and the most common cause of chronic airway inflammation in early childhood is arguably asthma.¹¹

An important step toward identifying children at risk for costly respiratory (ie, asthma, reduced lung function) and other allergic disorders is characterizing mechanisms that lead to and maintain early predisposition. Immune and lung development occur largely in utero and during early childhood. Research continues to delineate early immunophenotypes and early airway response outcomes among children predisposed to asthma (atopic and nonatopic) and other chronic atopic disorders.^{12–15} Regulatory pathways that involve the collaboration of innate and adaptive immune responses are involved. Influences of factors outside the immune system (ie, neurohormonal and autonomic nervous system (ANS) functioning) may also be involved.

Critical Periods of Development and Perinatal Programming

Plasticity is a consequence of environmental exposures in critical periods affecting key physiologic systems involved in developmental processes.¹⁶ Although both asthma and lung function are polygenic traits,^{17,18} maternal factors in particular contribute to the intergenerational correlation.^{17,19,20} The risk of developing atopic disorders is particularly increased if a positive parental history of atopy is present with effects being strongest for maternal history.^{19,20} Studies have also shown a greater correlation in forced expiratory volume in 1 second (FEV₁) and other lung function parameters between mothers (compared with fathers) and offspring.¹⁷ In addition to heritable traits, this may be the result of perinatal programming: the influence of nongenetic or environmental factors in the perinatal period that organize or imprint physiologic systems (Fig. 1).¹

Stress as a Programming Agent

The list of potential bioprogramming agents includes psychological stress. In general, stress may result in biobehavioral states (eg, posttraumatic stress disorder [PTSD], anxiety, depression) with lasting physiologic affects that influence disease risk.^{21–23} Under stress, physiologic systems may operate at higher or lower levels than in normal homeostasis.²⁴ Disturbed regulation of maternal stress systems (eg, hypothalamus-pituitary-adrenal [HPA] axis, ANS) in pregnancy may modulate offspring immune function starting in utero.^{25,26} Nonoptimal early childhood caregiving experiences may also affect these processes in children (eg, maternal psychopathology or insensitivity).^{27–29}

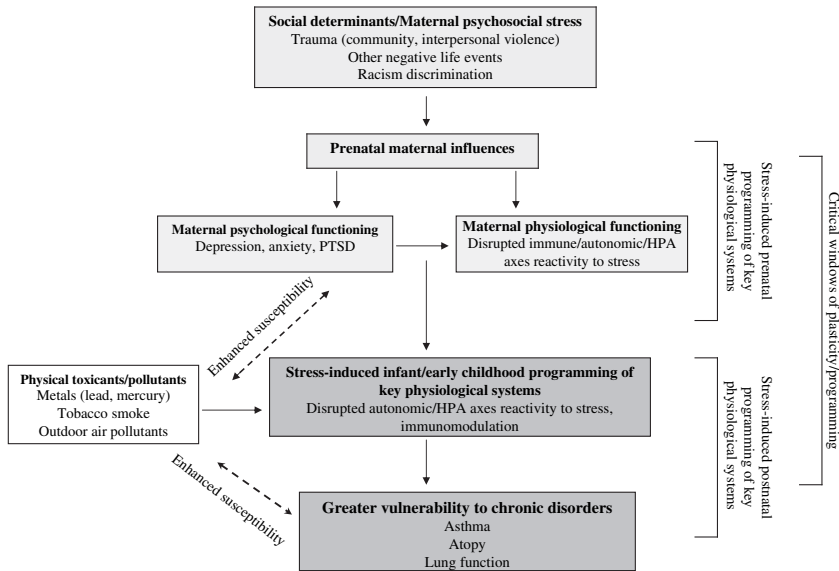


Fig. 1. Conceptual model for stress-induced perinatal programming of asthma, atopy, and lung function.

Immune Programming

Mechanisms of inflammation central to the pathophysiology of asthma phenotypes overlap and may include immune-mediated inflammation associated with a Th2-biased response^{30–32} and a tendency to produce immunoglobulin E (IgE) in response to environmental stimuli (eg, allergens). The Th1–Th2 paradigm involves a complex interaction of T and B lymphocytes, resulting in the production of higher levels of particular cytokines, such as interleukin-4 (IL-4) or IL-13 and the more recently described IL-9, IL-25, and IL-31 as well as lower levels of interferon- γ [IFN- γ].³³ Evidence suggests that those with early (ie, starting in the first 2 to 3 years) sensitization to allergens are at greatest risk of developing chronic atopic disorders, airway inflammation, and obstruction (as reviewed in Ref.²).

However, not all asthma cases are associated with allergy and/or eosinophilic airway inflammation; neutrophilic inflammation may account for a substantial subgroup.^{34,35} Thus, although this paradigm has been useful in understanding the large fraction of individuals with allergic asthma and airway inflammation, it is now accepted that the Th2-biased polarization of adaptive immunity may be only one of several axes that result in enhanced susceptibility to airway inflammation and altered reactivity.³⁶ Antigen-independent responses including innate immune cells (eg, bronchial epithelial cells [ECs], alveolar macrophages, and dendritic cells [DCs]) may also be important^{37,38} and involve novel cytokines (eg, IL-17).³⁹ Factors, including stress,^{1,38} that disrupt maturation of local immune networks (eg, DCs, ECs, regulatory T cells) may predispose to ongoing eosinophilic and neutrophilic inflammation. This may be manifested through the increased expression of both atopic and nonatopic persistent wheeze phenotypes in early childhood although prospective data in humans are sparse.

Immune mechanisms have their roots in utero with an immunologic bias toward a Th2 phenotype.^{40–46} Immune programming can also be influenced by early postnatal environmental influences.^{47,48} Consequently, researchers have begun to examine in vitro responses of peripheral blood mononuclear cells (pBMCs) to allergens or mitogens

to gain a better understanding of the immunodeviations that facilitate the manifestation of asthma and atopy in response to environmental factors,¹² including stress.^{49,50} Epidemiologic studies also incorporate other markers of the developing immune response (eg, IgE). Increased total IgE in cord blood, for example, has been associated with aeroallergen sensitization and the development of allergic diseases in children, particularly in those with a maternal history of atopy.^{51–53} Levels of allergen-specific IgE begin to increase at age 18 to 24 months.⁵⁴ Reactivity to 2 or more allergens is detected in infants as early as 3 months with polysensitization documented after 18 to 24 months,⁵⁵ and may develop even in individuals labeled nonatopic based on a negative skin prick test (SPT).⁵⁶ The influence of stress on the timing and trajectory of these immunophenotypes and their relationship to the later development of clinical disorders has only begun to be studied.

In primates, prenatal stress affects the newborn's antigen response.⁵⁷ Evidence in prenatally stressed adult mice shows dysregulated cellular and humoral immune response on antigen challenge reflected by a Th2 adaptive response and increased IgE.⁵⁸ My group was first to prospectively link early-life caregiver stress to dysregulation of immune function in a birth cohort predisposed to allergy (ie, greater antigen-specific tumor necrosis factor [TNF]-alpha production).⁴⁹ Stress has also been associated with increased natural killer (NK) and NKT cells as well as altering their functional mechanisms,^{59,60} effects correlated with changes in cortisol and ANS input.⁶¹ Our group has also demonstrated an association between increased prenatal maternal stress and increased IL-8 and TNF- α production after microbial stimulation suggesting that stress may operate through Toll-like receptor-dependent pathways.⁶²

As detailed in earlier reviews, both glucocorticoid (GC) action and sympathovagal balance play a role in immunomodulation as well as fetal and postnatal lung development.^{1,2,63} Although research has advanced around the assessment of immune function in stress and asthma,^{33,49,50,64} studies assessing the HPA axis⁶⁵ are scarce and none consider the autonomic response in early development (ie, pregnancy, early childhood). The HPA axis and ANS seem particularly susceptible to stress-induced programming as summarized in the next section.

HPA Axis

Maternal-fetal stress stimulates placental corticotrophin-releasing hormone (CRH), which in turn is increased in the neonatal circulation.^{1,66–69} This may stimulate the fetal HPA axis, amplify GC excess and activate additional elements of the fetal stress response (ie, catecholamines) influencing developing immune function and the ANS.²⁶ Alterations in stress-induced maternal cortisol may influence fetal immune system development and Th2 cell predominance, perhaps through direct influence of stress hormones on cytokine production.^{70,71} This may induce selective suppression of the Th1-mediated cellular immunity and trigger a shift toward Th2-mediated humoral immunity.⁷² The HPA system is also influenced postnatally through child-caregiver transactions.⁷³ Caregiving during early development predicts the emergence of self-regulation abilities, with sensitive caregiving associated with optimal stress regulation and functioning of the child's HPA system.¹

Studies assessing cortisol and HPA axis responses in early childhood as related to allergy and asthma risk remain sparse and none to date examine the relationship between maternal prenatal cortisol HPA axis responses (hypo- vs hyperreactivity) and childhood risk for asthma and/or allergy.⁶⁵ Bruske-Kirschbaum and colleagues⁷⁴ found an enhanced cortisol responses to stress in infants at high risk for atopic disorders based on parental history and increased level of IgE in cord blood. Ball⁷⁵ also reported a hyper-reactive HPA axis in response to stress among 6-month-old infants with an allergic

mother. This is in contrast to other data showing a hyporesponsive HPA axis in children who already have allergic disease.^{65,76} As proposed by Bruske-Kirschbaum and colleagues,⁶⁵ it may be that the natural history in children predisposed to developing allergy and/or asthma in relation to perinatal stress have a hyperresponsive HPA axis that evolves to become hyporesponsive as time goes on and a specific disorder is expressed and becomes more chronic. Although there are inconsistencies in the literature with regard to the physiologic changes (eg, hormonal disruption) that are associated with various disease outcomes, a blunted HPA axis (more typically characterized by lower morning cortisol level, flattening of the diurnal slope) has been specifically associated with increased susceptibility to autoimmune/inflammatory diseases in overlapping research.^{77,78} How disruption of the maternal prenatal HPA axis is related to childhood asthma and allergy risk and whether children of mothers with a blunted prenatal cortisol response are more likely to develop these disorders is not known. This will only be worked out through prospective epidemiologic studies incorporating biomarkers of the HPA response during these critical perinatal periods of development (for both mothers and children) and their relationship to evolving immunophenotypes and the later development of asthma and atopy.

An alternative hypothesis linking stress, neuroendocrine disruption (ie, HPA axis) and immune function considers a GC resistance model.^{79,80} Insight into the cellular and molecular mechanisms underlying stress-induced steroid resistance is provided in several recent studies. Oxidative stress pathways have been implicated in the link between psychosocial stress and asthma⁷¹ as well as steroid-resistant asthma.^{81,82} This may be particularly relevant in airway inflammation where neutrophilic rather than eosinophilic inflammation predominates.^{83,84} It was recently shown that oxidative stress contributes to steroid resistance in the context of neutrophilic inflammation in a mouse model of acute asthma exacerbations.⁸⁵ Psychological stress is also an oxidant and may thus operate through these same pathways.⁷¹ Although human data in the context of lung disease are sparse in this regard, one recent cross-sectional analysis in adolescents showed that pBMCs harvested from asthmatics who perceived low parental support (ie, greater stress) were more resistant to hydrocortisone's effects on cytokine expression (IL-5, IFN- γ) and activation of eosinophils relative to asthmatics reporting higher parental support.⁸⁶ Examination of mechanisms contributing to steroid resistance in relation to perinatal stress may provide insight into the link between stress, asthma, and airway hyperresponsiveness over subsequent development.

Future studies designed to examine mechanisms underlying stress-induced programming of asthma and allergy should consider the theoretic and methodological challenges in the study of the HPA axis in early development highlighted in prior reviews.^{87–91} Given the need for repeated sampling, saliva is often the preferred method given it is noninvasive and salivary cortisol follows a time course nearly identical to plasma cortisol.⁹² In pregnant women, hair sampling has been proposed as a way of providing a retrospective calendar of cortisol production over the course of pregnancy.^{93,94} The HPA system remains highly reactive and labile in early infancy and starts to become organized between 2 and 6 months of age through transactions between the child and caregiver.^{95,96} Studies of children in naturalistic environments suggest interesting individual differences exist.^{96–99} By a few months after birth, cortisol production follows a circadian rhythm and is entrained to the sleep-wake cycle.¹⁰⁰ However, individuals may vary in the age at which they acquire particular components of this variation (eg, diurnal rhythm, cortisol-awakening response).^{95,101} It has been proposed that the age of appearance (ie, early vs late), stability, and curve profile may be characteristic of developmentally distinct groups of infants and may have differential influence on

subsequent health.^{95,102} Children's sleep-wake cycle varies greatly over the day in early development and, as in older samples, analyses must consider time from awakening but also napping characteristics (eg, time of napping, total number, and duration of naps).¹⁰³ There are also gender effects.¹⁰⁴ Moreover, different methods of analysis may contribute to different conclusions related to profiles throughout the day and age of appearance of the circadian rhythm.^{95,105} Understanding this complexity and accounting for these factors in research examining alterations in adaptations of HPA axis activity in relation to perinatal stress and subsequent disease risk (eg, asthma) is important; not doing so may obscure true patterns and associations.

When incorporating salivary collection protocols into larger epidemiologic studies,^{90,91} the burden on participants and staff in light of other activities, and balancing the number of samples needed to accurately assess the HPA response versus the likelihood that the most interesting participants (eg, those most stressed, mothers/children with psychopathology) may be overwhelmed, must be considered. How samples are collected may need to vary with the age and developmental stage of the participant (eg, absorbent cotton rolls, passive drool, and so forth), each with their own tradeoffs. Possible confounders, mediators, and moderators of stress effects relevant to the life stage being examined also need to be addressed. For example, dysregulation of the HPA axis in pregnant women (and older children) may differ based on current psychological functioning (depression, PTSD) as different biologic profiles may be associated with specific psychopathology.^{106,107} Also in pregnant women, stage of gestation (weeks pregnant at time of cortisol sampling) and other prenatal factors (eg, prenatal alcohol and tobacco use, maternal body mass index calculated as weight in kilograms divided by the square of height in meters) may be important (for reviews see Refs.^{108,109}). Child temperament,¹¹⁰ an individual characteristic that dictates the tendency to express particular emotions with a certain intensity, is an important factor to consider in early child development.

Autonomic Reactivity

Animal and human studies support the connection between an adverse intrauterine environment as well as experiences in early postnatal life and alterations of ANS functioning (eg, sympathovagal balance).^{111–114} The ANS, in turn, plays an important role in immunoregulation.^{115–117} Animal research suggests that neural control of airway smooth muscle and irritant receptor systems are sensitive to environmental programming.¹¹¹ Respiratory and vagal systems undergo postnatal maturation to establish an integration of respiratory and cardiovascular function.^{118,119} Much remains to be learned about the vulnerability of these systems to perinatal environmental influences and early programming.¹²⁰ In humans, autonomic responses show developmental changes with relative stability between 6 and 12 months of age.¹²¹ It seems plausible that disruption of neuroendocrine and vagal antiinflammatory pathways may predispose some individuals to immunodeviations and consequent excessive inflammatory responses that may result in altered respiratory responses in early life. The balance between functional parasympathetic and sympathetic activity in relation to emotional stimuli and immune function may be important for airway inflammation and enhanced airway reactivity to a psychological stressor, although this has not been examined in human research. My group has demonstrated differential stress reactivity as indexed by prenatal HPA axis disruption¹²² and cardiorespiratory parameters in infancy¹²³ in an urban pregnancy cohort designed to study the effects of prenatal maternal and early-life stress on urban childhood asthma risk. Future analyses will examine links between stress-elicited changes in these systems and asthma risk and lung function as these children get older.

Prenatal stress increases allergen-induced airway inflammation in mice offspring.^{124,125} Similarly, allergen aerosol challenge is associated with increased airway hyperresponsiveness in prenatally stressed mice.⁵⁸ Others show exacerbations in airway inflammation in ovalbumin-sensitized rats after repeated psychosocial challenge.^{126–130} In humans, reversible airway obstruction has been demonstrated during psychological challenge; cholinergic blockade supports a vagal origin.^{131,132} Negative affect in particular increase airway resistance.¹³³ Vagal excitation to the airways is the supported mechanism.¹³⁴ Airway responses to induction of depressed mood is correlated with increased respiratory sinus arrhythmia in asthmatics.^{135,136} Individuals with a tendency toward greater vagal system response to distress may be prone to exaggerated airway narrowing in such situations, although this has not been studied in young children.

Need for the Integration of Stress Systems in Research

These data suggest that stress-elicited disruption of interrelated systems (autonomic, neuroendocrine, and immune systems) may lead to increased vulnerability to early allergic sensitization, which predisposes to persistent atopic disorders. To date, most studies examining links between stress-elicited disruption of physiologic systems and various health outcomes have examined one system in isolation from the others. However, recent findings specifically related to HPA and ANS functioning highlight the need to consider these systems simultaneously because of interactive influences.^{137–139} Studies that do not assess the interactions among these systems may obscure stress-related influences on asthma and allergy expression.

GENETICS

Most advances in our knowledge of the genetic and molecular events underlying the neurobiology of the stress response have occurred in animal models¹⁴⁰ and psychiatric outcomes in humans.¹⁴¹ These animal data suggest that studies to determine the role of genetics in modifying the risk of the social/physical environment experienced through psychological stress may further inform pathways through which stress may affect asthma expression. Genetic factors of potential importance include those that influence immune development and airway inflammation in early life, corticosteroid regulatory genes, adrenergic system regulatory genes, biotransformation genes, and cytokine pathway genes.

Genes expressed in the lung involved in determining the effects of oxidative stress, specifically the glutathione S-transferase, have been found to be functionally and clinically significant in recent studies in relation to atopic risk. Gilliland and colleagues¹⁴² found that specific GSTP1 variants are associated with increased histamine and IgE responses to air pollution oxidants and allergens in vivo. Maternal genetics related to oxidative stress genes may influence the child's atopic risk beginning in utero.¹⁴³ Variants of the GC receptor gene may contribute to interindividual variability in HPA axis activity and GC sensitivity in response to stress.^{144,145} Studies related to factors regulating the feedback mechanisms involved in the GC response to stress are also of interest.¹⁴⁶ A recent study examined polymorphisms of the TNF-alpha promoter region (TNF-308G/A) and linked specific variants to increased C-reactive protein (CRP), a proinflammatory marker.¹⁴⁷ These are potentially interesting candidate genes to include in future studies of risk for atopic disease. Such studies that consider gene × environment interactions (ie, stress by pathway genes) may inform specific mechanisms related to stress and atopy.

EPIGENETICS: A FUNDAMENTAL PROGRAMMING MECHANISM

Programming effects of stress on respiratory outcomes may operate at a more fundamental molecular level, through epigenetic programming. Epigenetics may be at the roots of developmental plasticity imprinting environmental experiences on the fixed genome,¹⁴⁸ although data are scarce for respiratory health and allergic disorders.^{149,150} Determining the range of environmental exposures that affect the epigenome during development was a research priority identified at the recent National Heart Lung and Blood Institute *Pediatric Pulmonary Disease Strategic Planning Workshop*.¹⁵¹ DNA methylation is an adaptable epigenetic mechanism that modifies genome function by the addition of methyl groups to cytosine to form 5-methyl-cytosine. DNA methylation marks are largely established early in life¹⁶ and may ensure stable regulation that mediates persistent changes in biologic and behavioral phenotypes over the lifespan. DNA methylation of many genes changes with disease status and in response to environmental signals including chemical exposures such as diet, drugs, and toxins. Recent findings also implicate psychological stress as shown in behavioral studies that demonstrated epigenetic changes during fear conditioning^{152,153} and from evidence of epigenetic programming related to maternal care.^{154,155}

The epigenome may be particularly sensitive to dysregulation in early development when DNA synthesis rates are highest. Genes involved in HPA axis functioning seem particularly susceptible to stress-related programming.⁷³ These include GC receptor expression, the activation of which alters HPA activity through negative feedback inhibition. The human GC receptor promoter region is extensively methylated with diverse methylation profiles demonstrated in normal donors.¹⁵⁶ The intracellular access of GCs to their receptors is also modulated by the 11 β -hydroxysteroid dehydrogenase (11 β HSD) enzymes, which interconvert biologically active 11 β -hydroxyglucocorticoids and inactive 11-ketosteroids.¹⁵⁷ Although compromised 11 β HSD2 activity can be caused by loss of function mutations of the gene encoding 11 β HSD2, the frequency of such mutations is extremely low. Thus, other mechanisms accounting for the inter-individual variability in 11 β HSD2 enzyme activity should be considered. The 11 β HSD2 promoter comprises a highly (G + C)-rich (or GC-rich) core, contains more than 80% GC, lacks a TATA-like element, and has 2 typical CpG islands raising the possibility that methylation may play a role in the epigenetically determined interindividual variable expression of 11 β HSD2. Another candidate pathway implicated in both airway inflammation¹⁵⁸ and autonomic response¹⁵⁹ is the nitric oxide (NO) signaling pathways. Alterations of NO expression occur in the context of psychological stress and stress-related behaviors.¹⁶⁰ The inducible nitric oxide synthase (NOS) genes are also susceptible to epigenetic programming.¹⁶¹

The notion that variability in methylation between individuals may reflect an important epigenetic mechanism is suggested by recent studies in both animals and humans. Epigenetic modulation of the 11 β HSD2 gene has been demonstrated recently in a rodent model and cultured cell lines,¹⁶² although epigenetic regulation of this gene is not well characterized in humans. Weaver and colleagues¹⁶³ have demonstrated differential methylation patterns of the Ngfi-A-binding site in GC receptor promoter 1₇ in the rat brain in offspring that had received poor maternal care versus those that had received better maternal care. When pups were cross-fostered between dams providing good or poor postnatal care, the pups developed the epigenome of the foster mother. This same group reported increased methylation in a neuron-specific GC receptor (NR3C1) promoter as well as decreased levels of GC receptor mRNA from hippocampus tissue obtained from suicide victims with a history of childhood abuse.¹⁶⁴ Recent human data demonstrate that methylation of exon 1F in

fetal cord blood was sensitive to maternal mood in the perinatal period and the infant's HPA stress reactivity.¹⁶⁵

In summary, genetic and epigenetic studies tell us that exposure to altered GC receptor response through early development, even beginning in utero, programs major changes in the endogenous neuroendocrine and immune mechanisms that may, in turn, lead to increased vulnerability to asthma. Whether alterations in DNA methylation underlie stress-induced phenotypic plasticity related to lung structure and function or asthma risk remains largely unexplored. It will be important to begin to understand factors related to developmental programming of GC sensitivity during critical periods of development that may play a role in disease etiology as well as subsequent morbidity.

Characterizing Stress in Epidemiologic Studies

The cause of health problems is increasingly recognized as a result of the complex interplay of influences operating at several levels, including the individual, the family, and the community (Fig. 2). Ecological views on health recognize that individual-level health risks and behaviors have multilevel determinants, in part influenced by the social context within which people live.¹⁶⁶ That is, chronic stress experiences are significantly influenced by the characteristics of the families, homes, and communities in which we live.^{167,168} Both physical and social factors can be a source of environmental demands that contribute to stress experienced by populations living in a particular area.¹⁶⁹

Taking a multilevel approach to examining stress effects on asthma expression may be particularly relevant to the understanding of disparities based on race/ethnicity and socioeconomic status.¹⁶⁸ This includes an environmental justice perspective underscoring the role of structural and macrosocial forces that shape exposure and vulnerability to diseases may better inform the complex social patterning of asthma.¹⁶⁸ According to this framework, asthma rates are higher and the associated morbidity is greater among the poor because they bear a disproportionate burden of exposure to suboptimal, unhealthy environmental conditions. Upstream social and economic factors determine differential exposures to relevant asthma pathogens and

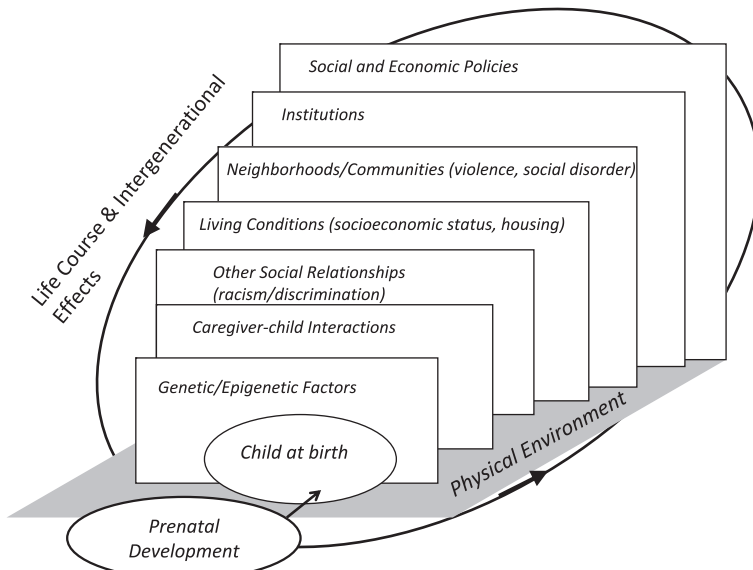


Fig. 2. Characterizing stress across the life course: an ecological approach.

toxicants.¹⁷⁰ Also, understanding the upstream factors (eg, social and economic policies) that contribute to the varying social conditions for populations and individuals being studied will better inform needed interventions.

Thus, a challenge in any epidemiologic study linking stress to health is how to measure and characterize the stressor(s). An important consideration is the prevalence of the stressor(s) of interest in a particular population. The decision can also be theoretically guided by our empirical understanding of how certain stressor characteristics influence behavioral and physiologic correlates that may have a particular pathogenic effect. The latter may vary based on the condition being considered and our understanding of the natural history of the disorder being considered. Although it can be acknowledged that there are inconsistencies in the literature with regard to the physiologic changes (eg, hormonal disruption) that are associated with various disease outcomes, a blunted HPA axis (more typically characterized by lower morning cortisol level and flattening of the diurnal slope) has been specifically associated with increased susceptibility to autoimmune/inflammatory diseases.^{77,78} This is also a pattern frequently described in the setting of extreme chronic stress that includes traumatic stressors (even occurring remote to the timing of study) and cumulative stressors that are chronic or co-occur. Stress exposure can be conceptualized as extreme if the individual experiences (1) multiple stressors in the same period, (2) chronic stressors in repeated developmental periods, or (3) the nature of the stress is extreme (eg, trauma).

Given the earlier discussion on perinatal programming, experiences of women of child-bearing age is particularly relevant. Women with low income, especially ethnic minorities, report greater and more frequent exposure to chronic extreme stress and greater psychological distress as a result. For example, in a study examining stressors immediately before or during pregnancy among a sample of 143,452 women,¹⁷¹ stress exposure increased as income decreased, with 57% of women on low income experiencing at least 1 chronic stressor (eg, economic hardship 37%, job loss 19%, separation or divorce 15%, incarceration of partner 8%, and domestic violence 5%); 29% experienced multiple stressors concurrently. The effects of these stress exposures may be compounded among minorities by racism-related stressors.

Traumatic stressors may warrant particular consideration for many reasons.⁷³ Trauma, like other stress, occurs at increased rates among low-income minority populations.^{172,173} Holman and colleagues¹⁷³ examined the rates of trauma in an ethnically diverse, community-based sample (N = 1456). Nearly 10% experienced a trauma in the past year; 57% reported at least 1 lifetime event including interpersonal violence occurring outside the family (21%), acute losses or accidents (17%), witnessing death or violence (13%), and domestic violence (12%). Hien and Bukszan¹⁷⁴ examined lifetime interpersonal violence among a control group of urban women on low income, predominantly Latina or blacks, who had been screened for the absence of psychopathology. Almost 28% of these urban women reported a history of childhood abuse, compared with general population estimates of 10%. Urban minority women also experience heightened levels of community violence.^{175,176} Other studies have documented increased rates of PTSD and depression in urban samples.⁷³ The perinatal period is a vulnerable time to experience more intense psychological symptoms, particularly for women on low income. Compared with other forms of stress, trauma is more likely to result in psychological morbidity (eg, PTSD, depression) and persistent psychophysiologic changes (HPA axis, sympathetic-adrenal-medullary system). These effects often persist years after the exposure, particularly when the exposure occurs during a critical developmental window (eg, when stress regulatory systems are becoming consolidated in the mother).

Life Course Perspective and Intergenerational Effects

Other studies provide evidence supporting the intergenerational transmission of psychophysiological vulnerability in traumatized populations. Although studies of maternal stress and infant outcomes typically examine events occurring during pregnancy, we recently considered stress (interpersonal trauma [IPT]) during the mother's life course in relation to early immune markers in their children.¹⁷⁷ The life-course perspective posits that some stressors may influence health through 2 mechanisms, early programming and cumulative pathways, in addition to more immediate effects. Early programming may occur if exposures during sensitive developmental periods in the mother have lasting psychobiologic sequelae. Exposure to IPT in earlier life can generate disrupted physiologic stress responses even several years after the trauma. Thus, maternal IPT may be linked to infant health through more latent effects (ie, lasting effects from abuse in childhood/adolescence), proximate effects (ie, trauma experienced in or around the pregnancy) and cumulative life-course effects (ie, allostatic load of accumulated traumas in the mother's life). We investigated the relationship between maternal IPT experienced in her life course and total IgE in cord blood, a biomarker of atopic risk at birth, in an urban population-based study. We demonstrated that infants born to mothers with chronic trauma exposure (ie, both early in life and more proximate to the pregnancy) would be at greatest risk of expressing increased IgE.

Constricting Communities

Indicators of neighborhood disadvantage, characterized by the presence of several area-level stressors including poverty, unemployment/underemployment, percentage of unskilled laborers, limited social capital or social cohesion, substandard housing, and high crime/violence exposure rates, have been investigated in relation to urban children's development.¹⁶⁸ Such stress is chronic and can affect all individuals in a given environment regardless of their individual-level risks.

For example, accumulating evidence suggests that community violence may contribute to the burden of asthma in urban populations.⁵ Increased exposure is associated with more symptom days,¹⁰ higher hospitalization rates,¹¹ increased asthma prevalence among children in communities with both increased levels of crime/violence and other environmental hazards (ie, ambient air pollutants),¹² and increased risk of wheezing at ages 2 to 3 years.¹³ In a longitudinal multilevel study including 2071 children aged 0 to 9 years at enrollment from the Project on Human Development in Chicago Neighborhoods (PHDCN), we demonstrated a significant association between exposure to community violence and increased risk for asthma development in urban children.¹⁷⁸ This association was robust in controlling for important individual-level factors (race/ethnicity, socioeconomic status, maternal health behaviors, family violence), and neighborhood-level confounders (concentrated disadvantage, social disorder, and collective efficacy).

Housing Stressors

Recent reviews highlight several subjective housing characteristics that have been linked to adverse psychological outcomes. This subjective emotional dimension of housing may influence asthma outcomes,¹⁷⁹ although this is only starting to be empirically explored.¹⁸⁰

Family Factors

There have been several examples from the asthma epidemiology literature showing associations between early caregiver stress and the development of asthmatic

phenotypes in early childhood.^{181,182} We recently demonstrated that maternal ability to maintain positive caregiving processes in the context of even more extreme stress may buffer the effects on child asthma risk. We examined the prospective relationship between maternal intimate partner violence (IPV) and asthma onset in children in the Fragile Families and Child Wellbeing Study (N = 3117), a birth cohort. Maternal reports of IPV were assessed after the child's birth and at 12 and 36 months. Mothers also indicated how many days a week they participated in activities with the child and the amount and type of educational/recreational toys available for the child. Maternal reports of physician-diagnosed asthma by age 36 months was the outcome. In adjusted analysis, children of mothers experiencing IPV chronically (at all time periods), compared with those not exposed, had a 2-fold increased risk of developing asthma. In stratified analysis, children of mothers experiencing IPV and low levels of mother-child activities (relative risk [RR] 2.7, 95% confidence interval [CI] 1.6, 4.7) had a significant increased risk for asthma. Those exposed to IPV and high levels of mother-child activities had a lower risk for asthma (RR 1.6, 95% CI 0.9, 3.2). Earlier the relationship between parental support and GC resistance in adolescent asthmatics was discussed.⁸⁶

Although beyond the scope of the current discussion given space limitations, the developmental timing of exposures during the life course relative to specific asthma outcomes must be considered whether individual or contextual factors are being considered. Factors leading to the onset, remission, or persistence of asthma during the life course may be influenced by social experiences and physical exposures beginning in utero, a series of social and biologic experiences initiated by early childhood exposure, or cumulative exposure to toxic biologic or social factors at critical periods of development (see [Fig. 2](#)). It is important to consider stress at these multiple levels given that they are interrelated throughout the life course. If we can understand at what level stress is occurring and perhaps has the greatest effect on asthma expression, this may inform the most effective interventions.

Stress-enhancing Effects on Physical Environmental Exposures

Because of the covariance in exposures and evidence that social stress and other environmental toxins (eg, pollutants, tobacco smoke) may influence common physiologic pathways (eg, oxidative stress, proinflammatory immune pathways, autonomic disruption), understanding the potential synergistic effects promises to more completely inform children's asthma risk.⁴ Epidemiologic studies have demonstrated synergistic effects of stress and air pollution on asthma expression among children and adolescents.^{183–185} We need to better understand how the physical and psychological demands of living in a relatively deprived environment may potentiate an individual's susceptibility to cumulative exposures across these domains.

SUMMARY

The evidence points toward the need to consider social environmental factors (ie, stress) as mainstream in asthma epidemiologic research. The likelihood of multiple mechanistic pathways with complex interdependencies must be considered when examining the integrative influence of stress independently, as well as the interaction of social and physical environmental toxins on asthma and atopy. Because these factors tend to cluster in the most socially disadvantaged, this line of research may better inform the etiology of growing health disparities. Design of future epidemiologic studies and effective intervention programs will need to address social stress and physical environmental toxins jointly to affect outcomes on a public health scale more effectively.

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