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Stress and Asthma: Novel Insights on Genetic, Epigenetic and Immunologic Mechanisms

Stacy L. Rosenberg, M.D.[1], **Gregory E. Miller, Ph.D.**[2], **John M. Brehm, M.D., M.P.H.**[1], and **Juan C. Celedón, M.D., Dr.P.H.**[1]

[1]Division of Pediatric Pulmonary Medicine, Allergy and Immunology, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh

[2]Department of Psychology, Northwestern University

Abstract

In the United States, the economically disadvantaged and some ethnic minorities are often exposed to chronic psychosocial stressors and disproportionately affected by asthma. Current evidence suggests a causal association between chronic psychosocial stress and asthma or asthma morbidity. Recent findings suggest potential mechanisms underlying this association, including changes in the methylation and expression of genes that regulate behavioral, autonomic, neuroendocrine, and immunologic responses to stress. There is also evidence suggesting the existence of susceptibility genes that predispose chronically stressed youth to both post-traumatic stress disorder and asthma. In this review, we critically examine published evidence and suggest future directions for research in this field.

Keywords

Asthma; psychosocial stress; immune system; neuroendocrine system; genetics

Introduction

Asthma is a major public health problem in the United States (U.S.), where ~25.7 million children and adults are currently living with asthma[1]. In this country, members of certain ethnic minority groups (e.g. Puerto Ricans and African Americans) and the economically disadvantaged share a disproportionate burden of the "asthma epidemic"[2].

Corresponding Author: Juan C. Celedón, MD, DrPH, FAAAAI Children's Hospital of Pittsburgh of UPMC 4401 Penn Avenue Suite 9130, Rangos Building Pittsburgh PA, 15224 Phone: 412 692 8429 Fax: 412 692 7636 juan.celedon@chp.edu.

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In the U.S., ethnic minorities and the economically disadvantaged are disproportionately exposed to chronic psychosocial stressors (e.g. poverty, discrimination and violence)[3]. A growing body of literature supports a causal link between exposure to these stressors at the individual or community level and asthma or morbidity from asthma in children and adults (recently reviewed by Yonas et al)[4]. For example, physical or sexual abuse during childhood, a major stressor, has been associated with asthma or asthma morbidity in Puerto Rican school-aged children[5], as well as with adult-onset asthma in African American women[6]. Moreover, a birth cohort study of 145 children with maternal history of asthma found that parental difficulties in early post-natal life (at age 3 months) were associated with asthma at ages 6 to 8 years[7]. In another birth cohort study including 708 children in Boston, prenatal exposure to community violence was associated with recurrent wheeze at age 2 years (a risk marker for asthma)[8]. Current evidence also suggests that the relation between stress and asthma is complex and partially mediated and modified by environmental exposures (e.g. outdoor air pollution[8], cigarette smoking[9]), adherence with treatment, and coping mechanisms (e.g. shift-and-persist strategies[10], family support).

Yet on top of these factors, stress is likely to affect the onset and course of asthma by directly acting on pathogenic mechanisms in the airways[11,12]. Although these pathways have yet to be fully elucidated, preliminary evidence suggests a role for stress in modulating lung development, neuroendocrine and autonomic nervous system responses, and the immune system[4,13]. Decades of research show that stressors, when perceived as threatening and unmanageable, modify the activity of the hypothalamic-pituitary-adrenocortical (HPA) axis and the autonomic nervous system (ANS). HPA activation occurs when neurons in the paraventricular nucleus of the hypothalamus secrete corticotropin releasing hormone (CRH). This molecule travels through the hypophyseal portal circulation to the anterior pituitary gland, which responds to its presence by secreting a pulse of adrenocorticotropin hormone (ACTH). The ACTH signal is carried through the peripheral circulation to the adrenal glands, which synthesize and release cortisol in the zona fasciculata. The ANS consists of sympathetic and parasympathetic branches whose effector molecules include epinephrine, and norepinephrine, and acetylcholine. By changing the outflow of these systems, stress alters the systemic balance of glucocorticoids and catecholamines, as well as concentrations of these (and other) hormones in primary and secondary lymphoid organs [14]. Macrophages and lymphocytes have functional receptors for these hormones (glucocorticoid receptors for cortisol, alpha and beta adrenergic receptors for catecholamines), and ligation of those receptors alters these cells' repertoires of gene expression, with downstream implications for trafficking, signaling, proliferation and differentiation, and effector functions[15]. Via these modulatory influences, chronic stressors potentiate reactivity to asthma triggers, e.g., allergens, infections, and in doing so may exacerbate airway inflammation and airflow obstruction[16,17].

More recently, mechanistic research in this area has begun to focus on the role of allelic variation in genes that regulate stress responses, as well as stress-induced changes in DNA methylation patterns and gene expression. In this report, we first review recent findings on potential biologic mechanisms for stress-related asthma (summarized in **Table 1)**, which

may be modified by environmental and lifestyle factors, social support or co-morbidities, as shown in **Figure 1.** We then discuss future directions for research in this field.

Genetics, Genomics and Epigenetics of Stress and Asthma

As for other complex diseases, genome-wide association studies have identified common genetic variants that confer susceptibility to asthma but do not account for a large proportion of its heritability (phenotypic variation explained by genetic factors)[18]. This "missing heritability" of asthma may be explained by unaccounted phenotypic heterogeneity[19], structural variation (e.g. copy number variants)[20], rare genetic variants with strong effects[21], gene-by-gene interactions (epistasis) [21] gene-by-environment interactions[22,23] or epigenetic mechanisms such as DNA methylation[24] or microRNAs[25]. Few studies have examined the role of genetic or epigenetic mechanisms on stress-related asthma.

In a study of over 1,200 (predominantly African American) adults exposed to traumatic events, Ressler and colleagues implicated the pituitary adenylate cyclase activating peptide (PACAP)-PAC1 receptor pathway on the pathogenesis of PTSD[26]. In this study, both PACAP38 (PACAP peptide containing 38 residues) blood levels and the C allele of a functional single nucleotide polymorphism (SNP, rs2267735) in an estrogen-receptor element of the gene for the PAC1 receptor (*ADCYAP1R1*) were significantly associated with PTSD or more PTSD symptoms in females but not in males. For example, the correlation coefficient (r) for PACAP38 blood level and PTSD symptoms was 0.497 ($P < 0.005$) in females but non-significant in males ($P > 0.5$). In contrast to these sex-specific associations, methylation of a CpG site in the promoter of *ADCYAP1R1* (assessed in DNA from white blood cells) was shown to be associated with PTSD or more PTSD symptoms (r for symptoms= 0.35, $P < 0.0005$). To further support the plausibility of the human findings, *ADCYAP1R1* mRNA was shown to be inducible after fear conditioning in rodents[26]. A female-specific association between the C allele of rs2267735 and PTSD or PTSD symptoms has been replicated in studies of highly traumatized Chinese[27] and African American[28] adults, but not in a study of adults of European or African American descent who were not selected on the basis of traumatic exposures[29]. Using magnetic resonance imaging, the C allele of rs2267735 was recently shown to impact fear responses in the amygdala and hippocampus of women with lifetime history of exposure to traumatic events[30]. Of interest, the C allele of rs2267735 was associated with anxiety in school-aged boys and girls, suggesting that any sex-specific effects of this SNP are not present before puberty[31]. In contrast to the published work replicating an association between SNP rs2267735 and PTSD, findings for *ADCYAP1R1* methylation have yet to be replicated for PTSD. Given that PTSD has been associated with asthma or asthma symptoms[32,33], there has been recent interest in studying both methylation and genetic variants in *ADCYAP1R1* and asthma.

Puerto Ricans are disproportionately affected by asthma in the U.S [34-37] and often exposed to violence, both in the household and in the community [38-40]. Our group has shown that physical/sexual abuse and parental stress are associated with asthma in Puerto Rican children[5,41]. Given these findings, known increased susceptibility of Puerto Rican adults to developing PTSD after exposure to traumatic events, and experimental evidence suggesting

a potential role of *ADCYAP1R1* on regulating expression of the glucocorticoid receptor gene[42], we examined exposure to violence (assessed using a validated scale), *ADCYAP1R1* and asthma in 516 Puerto Rican children ages 6 to 14 years[43]. In this study, we demonstrated that exposure to violence is associated with methylation of a CpG site in the promoter of *ADCYAP1R1* (adjusted β per each 10-point increment in the ETV scale, obtained from a linear regression model= 0.5%, 95% confidence interval [CI]=0.1% to 0.9%, P=0.02) and that such methylation is associated with asthma in Puerto Rican children (adjusted odds ratio [aOR] per each 1% increment in methylation, obtained from a logistic regression model=1.3, 95% CI=1.0-1.6, P=0.03). Moreover, we showed that the C allele of SNP rs2267735 (previously implicated in PTSD and anxiety) is associated with 30% increased odds of asthma (95% CI for aOR=1.0-1.7, P=0.03) in these children.

Our findings for *ADCYAP1R1* have yet to be replicated, and we cannot exclude "reverse causation" for the methylation findings (e.g. asthma leading to increased DNA methylation) in a cross-sectional study. However, the biological plausibility of our results is supported by experimental models showing that PACAP acts as endogenous bronchodilator, relaxing airway smooth muscle[44,45]. Moreover, PACAP protects against endotoxin-induced allergic airway inflammation (AAI) in rodents[46], in which the PAC1 receptor mediates anti-inflammatory effects in AAI[47]. Together with these experimental findings, our results suggest that genetic and epigenetic variation in a susceptibility gene for PTSD and childhood anxiety (*ADCYAP1R1*) is implicated in the pathogenesis of asthma in children disproportionately exposed to violence or traumatic events, such as Puerto Ricans.

CRH, along with signaling of PACAP, regulates anxiety-related behavior[26] and is thus in a candidate pathway for stress-related asthma. SNPs in the gene encoding the main receptor for CRH (*CRHR1*) have been associated with change in lung function in response to inhaled corticosteroids (ICS) in subjects with asthma or chronic obstructive pulmonary disease (COPD) in some studies[48-51] but not in others[52].

Few studies have examined the effects of psychosocial stress on genome-wide expression in tissues relevant to asthma. In a genome-wide study of transcriptional profiles from CD2+ T lymphocytes of 31 school-aged children, low socioeconomic status (a stressor correlated with other stressors such as exposure to violence) was associated with overexpression of genes regulating inflammation, including chemokine activity and cytokine production [53]. In this small study, results from a bioinformatics analysis offered preliminary support for a mediating role of cyclic AMP response element binding protein, nuclear factor Y, and nuclear factor κβ on the observed effects [53].

Social adversity in early life may program biological systems in a manner predisposing to chronic diseases such as asthma. In a study of genome-wide transcriptional profiles in peripheral blood mononuclear cells (PBMCs) from 103 healthy adults aged 25 to 40 years, low socioeconomic status in early life was associated with up-regulation of genes bearing responses for the CREB/ATF family of transcription factors conveying adrenergic signals to white blood cells, as well as with down-regulation of genes with response elements for the glucocorticoid receptor (which, as noted above, transduces cortisol's anti-inflammatory effects in macrophages and lymphocytes)[54]. In this study, low socioeconomic status was

also associated with over-expression of transcripts with response elements for NF-kB, and increased stimulated production of interleukin 6 (e.g. PBMCs from subjects with low early-life SES produced 51% more IL6 in response to TLR3 stimulation with the ligand poly(I:C) than did those with high early-life SES, $P = 0.03$). Taken together with those from other studies, these results suggest that low socioeconomic status in early life programs sustained resistance to glucocorticoid signaling, ultimately leading to increased adrenocortical and inflammatory responses in adulthood. Among those who go on to develop asthma, this programmed resistance may also undermine the efficacy of steroid therapy. Large longitudinal studies are needed to validate and expand on these findings.

Stress, immune responses and asthma

Findings from recent experimental studies suggest that stress may predispose to asthma or asthma morbidity through effects on the immune system[55,56]. In an experimental model, Fischer 344 rats were subjected to repeated handling stimulation (HA), maternal separation (MS), or no intervention at age 4 weeks. At age 5 months, HA rats had increased ex vivo natural killer cell cytotoxicity but no other alterations in immune responses. After induction of experimental asthma, MS rats had greater number of eosinophils in broncho-alveolar lavage than controls or HA rats (P =0.002). In HA rats, induction of experimental asthma was associated with markedly increased levels of adreno-corticotropin compared with the MS or control groups (P for one-way analysis of variance=0.02)[47]. Taken together, these results suggest that early post-natal stressors have effects on the “neuroendocrine immune system” lasting into adult life.

Consistent with results from human studies[8,57,58], findings in rodents suggest that stress enhances the detrimental effects of environmental exposures on asthma[59]. In particular, rats exposed to both concentrated ambient particles and stress had higher blood levels of C-reactive protein and tumor necrosis factor alpha, but lower lung function, than those exposed only to either concentrated ambient articles or stress[59]. For example, exposure to particulate matter 2.5 ($PM_{2.5}$) was significantly associated with a lower peak expiratory flow in stressed animals (adjusted β per each $\mu g/m^3$ increment= -3.9×10^{-3}, P=0.003) but not in non-stressed animals (P=0.92).

Because pre- or early-post natal exposures are likely to have major effects on immune system development[60], there is considerable interest in studying whether stressors may lead to asthma development through alteration of immune responses in early life. However, the relationship between cytokine profiles in early life and asthma is insufficiently understood[61], and thus children participating in birth cohort studies must be followed up to age six years or greater, when asthma can be confidently diagnosed. To date, published studies of pre- and early post-natal stress and childhood asthma are lacking sufficient data on stress or follow up of participants into school age. Nonetheless, emerging evidence suggests that maternal stress influences immune responses and asthma symptoms in infancy. For example, a birth cohort study of 557 inner-city children found that cumulative prenatal maternal stress was associated with cord blood mononuclear cell innate and adaptive cytokine responses[62]. In this study, prenatal maternal stress was associated with increased production of IL-8 and TNF-α after microbial stimuli, as well as with increased IL-13 production after dust mite

stimulation and reduced phytohemagglutinin-induced IFN-γ (P <0.05 in all instances). Post-natal family stress also seems to influence patterns of early-life immune responding relevant to asthma. One birth cohort tracked parents' stress levels every two months for the initial 24 months years of their child's life. In this study, greater parental stress between ages 6 and 18 months was associated with a total IgE ≥100 IU/ml (aOR=2.0, 95% CI=1.1-3.6, P<0.05) and larger TNF-α production in offspring at age 2 years[63].

Early-life stress may lead to programming of neuroendocrine and immune responses in girls that is carried over to adulthood and to pregnancy, and ultimately to child's development[54]. A recent birth cohort study of 510 urban children showed that maternal low socioeconomic status during childhood was directly associated with cord blood IgE level (adjusted β from a structural equation model=0.21, P=0.003) and indirectly (through prenatal cumulative stress, low socioeconomic status in adulthood and air pollution) to recurrent wheeze in their children[64]. In contrast to these findings, a cross-sectional study of 267 Canadian children found no difference in IL-6 production by PBMCs stimulated with lipopolysaccharide between children with persistently high socioeconomic status since birth and those who experienced upward mobility (going from lower-middle to higher-middle status), suggesting that some programming effects of early-life stressors can be reversed [65]. In contrast to children with an "upward SES trajectory", those with persistently low socioeconomic status had increased IL-6 production by stimulated PBMCs, particularly if they were overweight. In addition, atopic asthma was associated with a 54% increment in IL-6 level in urban children (P=0.03) but was not significantly associated with IL-6 in rural children.

A two-year prospective study of 147 children aged 9 to 18 years examined whether acute or chronic stress is associated with cytokine responses or asthma symptoms at school age[66]. In this study, acute stress was associated with increased cytokine (IL-4, IL-5 and IFN-γ) production by PBMCs after mitogenic stimulation, but only in children with asthma and high levels of chronic stress. In this study, chronic stress (particularly in the presence of acute stress) and IL-5 levels were associated with increased symptoms in a subset of 32 children with moderate to severe asthma (P <0.05 in both instances). The main limitations of this study are limited statistical power to assess stress effects on multiple cytokines, the fact that acute stress could have occurred as early as six months before the study visits (since they were scheduled twice per year), and lack of assessment of corticosteroid responses.

Stress and Response to Treatment

Stress may increase asthma morbidity by reducing response to inhaled corticosteroids and inhaled beta2 agonists. Acute stress and chronic stress have been associated with reduced expression of the genes encoding the glucocorticoid receptor (by 5.5 fold) and the beta-2 adrenergic receptor (by 9.5 fold) in leukocytes of children with asthma (adjusted P <0.05 in both instances)[67]. In another study including 143 school-aged children, perception of low parental support was associated with reduced response to corticosteroids *in vitro* and higher circulating levels of eosinophil cationic protein in children with asthma[68]. In this study, response to corticosteroids was assessed by measuring production of IL-5, IL-13 and IFN-γ by peripheral blood mononuclear cells (incubated with a mitogen cocktail) after adding physiologic doses of hydrocortisone[68]. Although limited by a cross-sectional design,

findings from the two studies referenced above[6768] support the hypothesis that chronic stress leads to down-regulation of glucocorticoid receptor expression and function. Nevertheless, these findings must be substantiated with in vivo measurements of glucocorticoid sensitivity.

Future Directions

Development of novel indicators or biomarkers of chronic stress is imperative, given that currently used indicators of stress cannot be used in young children (e.g. questionnaires) or are difficult to implement in large studies (e.g. detailed interviews with parents, multiple measures of salivary cortisol to assess circadian rhythm). Measuring cortisol in hair is one potential strategy, which has the advantage of capturing more chronic HPA activity, as experienced over a several-month timeframe[69]. Moreover, one could gain novel insights into stress-related asthma by examining the relation between chronic stress and gene expression and epigenetic changes in tissues relevant to asthma (e.g. airway epithelium and lymphocytes).

Accounting for mediators and modifiers of the effect of stress on asthma is key in future longitudinal studies of stress and asthma or asthma morbidity. For example, which proportion of the effect of stress on asthma morbidity or treatment response is explained by reduced adherence with controller medications? To which extent does having coping mechanisms or social support attenuate the effects of stress on asthma? Does exposure to other environmental exposures (e.g. cigarette smoking, air pollution) or co-morbidities (e.g. obesity) modify the effect of stress on asthma, and –if so- to which extent? Does stress lead to epigenetic changes in tissues relevant to the pathogenesis of asthma? Do variants that confer susceptibility to stress-related mental illness or anxiety impact asthma (by themselves or interacting with stress) on populations at risk?

Phenotypic assessment of asthma and immune responses has been often overlooked in studies of stress and asthma. Sufficiently long follow up of ongoing birth cohort studies, assessment of objective markers of disease severity or control (e.g. pulmonary function tests and airway responsiveness), examining sub-phenotypes of the “asthma syndrome” (e.g. atopic vs. non-atopic asthma, eosinophilic vs. non-eosinophilic asthma), and measuring cytokine profiles other than Th1/Th2 (e.g. Th17) will be important in future studies of stress and asthma.

Studying the role of stress on treatment responses in vivo is a high priority. Does stress reduce the efficacy of treatment responses, independently of adherence with medications? If so, is this mediated by down-regulation of the glucocorticoid receptor? Are the effects of stress on treatment response (if any) more marked in populations exposed to heavily traumatic events?

In summary, there is compelling evidence for a link between chronic psychosocial stress and the onset and course of asthma. Over the past decade, there has been substantial progress identifying alterations in the HPA axis and the ANS, as well as immunologic mechanisms likely to underlie these phenomena. More recently, studies have begun to highlight specific signal transduction pathways through which stress modulates epigenetic and transcriptional

activity in asthma-relevant cells, and to identify susceptibility genes that may confer risk for stress-related exacerbations of asthma. Further understanding of these mechanisms will improve our capacity to prevent and treat asthma, particularly in vulnerable populations (e.g. ethnic minorities and the economically disadvantaged) who experience disproportionate rates of the asthma burden in this country. Such progress could have a major impact in reducing unacceptable health disparities in asthma in the United States and worldwide.

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Abbreviations

PACAP	Pituitary adenylate cyclase-activating polypeptide
CRH	Corticotropin releasing hormone
SNP	Single nucleotide polymorphisms
ICS	Inhaled corticosteroids
COPD	Chronic obstructive pulmonary disease
PTSD	Post-traumatic stress disorder
CBMC	Cord blood mononuclear cell

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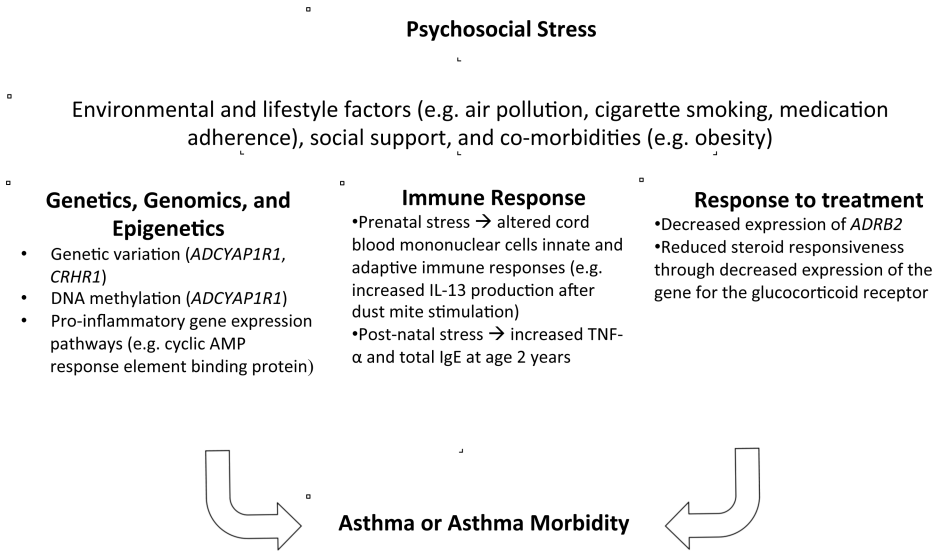

Figure 1.
Potential causal mechanisms for stress-related asthma or asthma morbidity.

Table 1

Selected human studies of potential genetic, epigenetic and immunologic mechanisms for stress-related asthma or asthma morbidity

Study (first author, year, reference number)	Study population	Major findings
Chen, 2013,[43]	516 Puerto Rican children with and without asthma	DNA methylation and a SNP in *ADCYAP1R1* were associated with asthma risk
Tsartsali, 2012,[48]	62 Greek children with asthma, on ICS	SNPs in *CRHR1* were associated with baseline Cortisol levels and Cortisol response
Tantisira, 2004,[49]	1,117 North American children and adults with asthma	SNPs in *CRHR1* were associated with ICS response in multiple populations
Rogers, 2009,[50]	311 North American children with asthma	SNPs in *CRHR1* were associated with poor long-term response to ICS
Kim, 2009,[70]	87 Korean adults with COPD	A SNP in *CRHR1* was associated with reduced ICS response
Dijkstra,2008,[52]	281 Dutch adults with asthma	No association between *CRHR1* variants and ICS response
Chen, 2009, [53]	31 Canadian children with asthma	Children from low SES households had increased expression of pro-inflammatory cytokines
Miller, 2009,[54]	103 healthy Canadian adults	Low SES in early life was associated with up-regulation of adrenergic signaling and down-regulation of genes with glucocorticoid response elements
Wright, 2010, [62]	Birth cohort of 557 American inner-city children	Cumulative prenatal maternal stress was associated with increased inflammatory cytokine responses in cord blood
Wright, 2004, [63]	499 infants from Boston, MA with family history of atopy or asthma	Higher post-natal stress in caregivers was associated with increased total IgE at age 2 years
Sternthal, 2011, [64]	Birth cohortstudy of 510 urban children from Boston, MA	Children from low SES households had higher cord blood IgE and increased risk of wheeze
Azad, 2012, [65]	Cross-sectional study of 267 Canadian children	No difference in IL-6 production by *ex vivo* PBMCs between children with high SES and children who experienced upward social mobility, but PBMC's from children with persistently low SES had decreased IL-6 production

Study (first author, year, reference number)	Study population	Major findings
Miller, 2006, [67]	77 children with and without asthma from Vancouver, BC	Acute and chronic stress were associated with reduced expression of glucocorticoid receptor and beta-adrenergic genes in children with asthma, but with increased expression of these genes in children without asthma
Miller, 2009, [68]	143 children with and without asthma from Vancouver, BC	Low perceived parental support was associated with higher levels of eosinophil cationic protein and increased resistance to corticosteroids in *ex vivo* PBMCs
Marin, 2009, [66]	Prospective study of 147 children with and without asthma from Vancouver, BC	Only asthmatic children with higher levels of chronic stress had increased pro-inflammatory cytokine production when exposed to acute stressors