# Stress and asthma: Novel insights on genetic, epigenetic, and immunologic mechanisms

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**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. (J Allergy Clin Immunol 2014;134:1009-15.)**

***Key words:*** *Asthma, psychosocial stress, immune system, neuroendocrine system, genetics*

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*Abbreviations used*

ANS: Autonomic nervous system
aOR: Adjusted odds ratio
CRH: Corticotropin-releasing hormone
HA: Handling stimulation
HPA: Hypothalamic-pituitary-adrenocortical
MS: Maternal separation
PACAP: Pituitary adenylate cyclase–activating polypeptide
PTSD: Post-traumatic stress disorder
SES: Socioeconomic status
SNP: Single nucleotide polymorphism

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

In the United States ethnic minorities and the economically disadvantaged are disproportionately exposed to chronic psychosocial stressors (eg, 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 a maternal history of asthma found that parental difficulties in early postnatal life (at age 3 months) were associated with asthma at 6 to 8 years of age.[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 (eg, outdoor air pollution[8] and cigarette smoking[9]), adherence to treatment, and coping mechanisms (eg, shift-and-persist strategies[10] and 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 (ANS) 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 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 adrenocorticotropic hormone. The adrenocorticotropic hormone 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, the effector molecules of which include epinephrine,

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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 and α- and β-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] Through these modulatory influences, chronic stressors potentiate reactivity to asthma triggers, such as allergens and infections, and in doing so might 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 I),[18-32] which might be modified by environmental and lifestyle factors, social support, or comorbidities, as shown in Fig 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).[33] This "missing heritability" of asthma might be explained by unaccounted phenotypic heterogeneity,[34] structural variation (eg, copy number variants),[35] rare genetic variants with strong effects,[36] gene-gene interactions (epistasis),[36] gene-environment interactions,[37,38] or epigenetic mechanisms, such as DNA methylation[39] or microRNAs.[40] Few studies have examined the role of genetic or epigenetic mechanisms on stress-related asthma.

In a study of more than 1200 (predominantly African American) adults exposed to traumatic events, Ressler et al[41] implicated the pituitary adenylate cyclase–activating peptide (PACAP)–PAC1 receptor pathway on the pathogenesis of posttraumatic stress disorder (PTSD).[41] 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 female but not male subjects. For example, the correlation coefficient *(r)* for PACAP38 blood level and PTSD symptoms was 0.497 ($P < .005$) in female subjects but nonsignificant in male subjects ($P > .5$). 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, $P < .0005$). *ADCYAP1R1* mRNA was shown to be inducible after fear conditioning in rodents, which further supports the plausibility of the human findings.[41] A female-specific association between the C allele of rs2267735 and PTSD or PTSD symptoms has been replicated in studies of highly traumatized Chinese[42] and African American[43] adults but not in a study of adults of European or African American descent who were not selected on the basis of traumatic exposures.[44] By using magnetic resonance imaging, the C allele of rs2267735 was recently shown to affect fear responses in the amygdala and hippocampus of women with lifetime history of exposure to traumatic events.[45] 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.[46] 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,[47,48] 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 United States[49-52] and often exposed to violence, both in the household and in the community.[53-55] Our group has shown that physical/sexual abuse and parental stress are associated with asthma in Puerto Rican children.[5,56] Given these findings, known increased susceptibility of Puerto Rican adults to having PTSD after exposure to traumatic events, and experimental evidence suggesting a potential role of *ADCYAP1R1* on regulating expression of the glucocorticoid receptor gene,[57] we examined exposure to violence (assessed by using a validated scale), *ADCYAP1R1*, and asthma in 516 Puerto Rican children aged 6 to 14 years.[18] In this study we demonstrated that exposure to violence is associated with methylation of a CpG site in the promoter of *ADCYAP1R1* (adjusted β value per each 10-point increment in the ETV scale obtained from a linear regression model, 0.5%; 95% CI, 0.1% to 0.9%; $P = .02$) 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; $P = .03$). 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; $P = .03$) in these children.

Our findings for *ADCYAP1R1* have yet to be replicated, and we cannot exclude reverse causation for the methylation findings (eg, 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 an endogenous bronchodilator, relaxing airway smooth muscle.[58,59] Moreover, PACAP protects against endotoxin-induced allergic airway inflammation in rodents,[60] in which the PAC1 receptor mediates anti-inflammatory effects in allergic airway inflammation.[61] 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[41] 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 in patients with asthma or chronic obstructive pulmonary disease in some studies[19-22] but not in others.[23]

Few studies have examined the effects of psychosocial stress on genome-wide expression in tissues relevant to asthma. In a

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

| Study | Study population | Major findings |
|---|---|---|
| Chen et al, 2013[18] | 516 Puerto Rican children with and without asthma | DNA methylation and an SNP in *ADCYAP1R1* were associated with asthma risk. |
| Tsartsali et al, 2012[19] | 62 Greek children with asthma receiving ICSs | SNPs in *CRHR1* were associated with baseline cortisol levels and cortisol response. |
| Tantisira et al, 2004[20] | 1,117 North American children and adults with asthma | SNPs in *CRHR1* were associated with ICS response in multiple populations. |
| Rogers et al, 2009[21] | 311 North American children with asthma | SNPs in *CRHR1* were associated with poor long-term response to ICSs. |
| Kim et al, 2009[22] | 87 Korean adults with COPD | An SNP in *CRHR1* was associated with reduced ICS response. |
| Dijkstra et al, 2008[23] | 281 Dutch adults with asthma | There was no association between *CRHR1* variants and ICS response. |
| Chen et al, 2009[24] | 31 Canadian children with asthma | Children from low-SES households had increased expression of proinflammatory cytokines. |
| Miller et al, 2009[25] | 103 Healthy Canadian adults | Low SES in early life was associated with upregulation of adrenergic signaling and downregulation of genes with glucocorticoid response elements. |
| Wright et al, 2010[26] | Birth cohort of 557 American inner-city children | Cumulative prenatal maternal stress was associated with increased inflammatory cytokine responses in cord blood. |
| Wright et al, 2004[27] | 499 Infants from Boston, Massachusetts, with a family history of atopy or asthma | Higher postnatal stress in caregivers was associated with increased total IgE levels at age 2 years. |
| Sternthal et al, 2011[28] | Birth cohort study of 510 urban children from Boston, Massachusetts | Children from low-SES households had higher cord blood IgE levels and increased risk of wheeze. |
| Azad et al, 2012[29] | Cross-sectional study of 267 Canadian children | There was no difference in IL-6 production by *ex vivo* PBMCs between children with high SES and children who experienced upward social mobility, but PBMCs from children with persistently low SES had decreased IL-6 production. |
| Miller and Chen, 2006[31] | 77 Children with and without asthma from Vancouver, British Columbia, Canada | Acute and chronic stress were associated with reduced expression of glucocorticoid receptor and β-adrenergic genes in children with asthma but increased expression of these genes in children without asthma. |
| Miller et al, 2009[32] | 143 Children with and without asthma from Vancouver, British Columbia, Canada | Low perceived parental support was associated with higher levels of eosinophil cationic protein and increased resistance to corticosteroids in *ex vivo* PBMCs. |
| Marin et al, 2009[30] | Prospective study of 147 children with and without asthma from Vancouver, British Columbia, Canada | Only asthmatic children with higher levels of chronic stress had increased proinflammatory cytokine production when exposed to acute stressors. |

*COPD*, Chronic obstructive pulmonary disease; *ICS*, inhaled corticosteroid.

genome-wide study of transcriptional profiles from $CD2^+$ T lymphocytes of 31 school-aged children, low socioeconomic status (SES; 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.[24] 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.[24]

Social adversity in early life might program biological systems in a manner predisposing to chronic diseases, such as asthma. In a study of genome-wide transcriptional profiles in PBMCs from 103 healthy adults aged 25 to 40 years, low SES in early life was associated with upregulation of genes bearing responses for the CREB/ATF family of transcription factors conveying adrenergic signals to white blood cells, as well as with downregulation of genes with response elements for the glucocorticoid receptor (which, as noted above, transduces cortisol's anti-inflammatory effects in macrophages and lymphocytes).[25] In this study low SES was also associated with overexpression of transcripts with response elements for nuclear factor κB and increased stimulated production of IL-6 (eg, PBMCs from subjects with low early-life SES produced 51% more IL-6 in response to Toll-like receptor 3 stimulation with the ligand polyinosinic-polycytidylic acid than did those with high early-life SES; $P = .03$). Taken together with those from other studies, these results suggest that low SES 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 have asthma, this programmed resistance might 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 might predispose to asthma or asthma morbidity through effects on the immune system.[62,63] 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

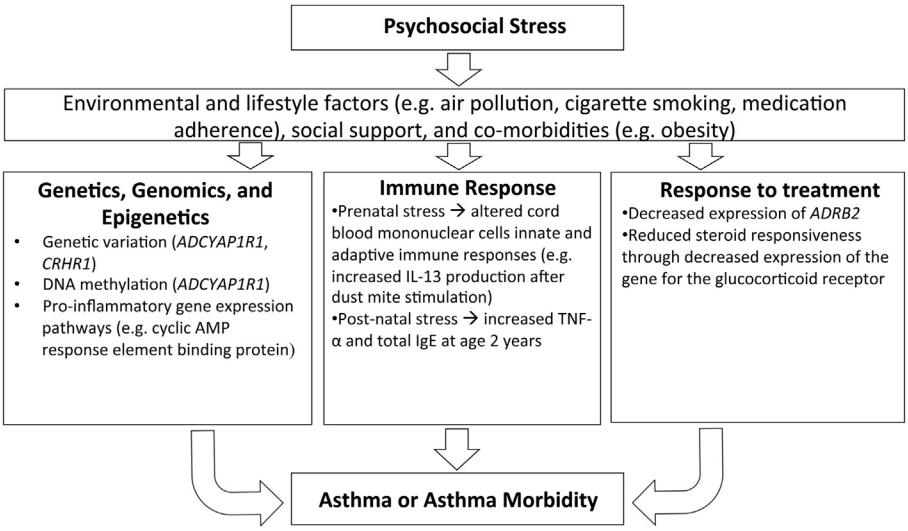


**FIG 1.** Potential causal mechanisms for stress-related asthma or asthma morbidity.

induction of experimental asthma, MS rats had greater number of eosinophils in bronchoalveolar lavage fluid than control or HA rats ($P = .002$). In HA rats induction of experimental asthma was associated with markedly increased levels of adrenocorticotropin compared with that seen in the MS or control groups ($P$ for 1-way ANOVA = .02).[61] Taken together, these results suggest that early postnatal stressors have effects on the neuroendocrine immune system lasting into adult life.

Consistent with results from human studies,[8,64,65] findings in rodents suggest that stress enhances the detrimental effects of environmental exposures on asthma.[66] In particular, rats exposed to both concentrated ambient particles and stress had higher blood levels of C-reactive protein and TNF-α but lower lung function than those exposed only to either concentrated ambient articles or stress.[66] For example, exposure to particulate matter of less than 2.5 μm in diameter was significantly associated with a lower peak expiratory flow in stressed animals (adjusted β value per each microgram per cubic meter increment = $-3.9 \times 10^{-3}$, $P = .003$) but not in nonstressed animals ($P = .92$).

Because prenatal or early postnatal exposures are likely to have major effects on immune system development,[67] there is considerable interest in studying whether stressors can 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,[68] and thus children participating in birth cohort studies must be followed up to age 6 years or greater, when asthma can be confidently diagnosed.

To date, published studies of prenatal and early postnatal 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.[26] 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 PHA-induced IFN-γ levels ($P < .05$ in all instances). Postnatal family stress also seems to influence patterns of early-life immune response relevant to asthma. One birth cohort tracked parental stress levels every 2 months for the initial 24 months of the child's life. In this study greater parental stress between ages 6 and 18 months was associated with a total IgE level of 100 IU/mL or greater (aOR, 2.0; 95% CI, 1.1-3.6; $P < .05$) and larger TNF-α production in offspring at age 2 years.[27]

Early-life stress might lead to programming of neuroendocrine and immune responses in girls that is carried over to adulthood and to pregnancy and ultimately to the child's development.[25] A recent birth cohort study of 510 urban children showed that maternal low SES during childhood was directly associated with cord blood IgE level (adjusted β value from a structural equation model = 0.21, $P = .003$) and indirectly (through prenatal cumulative stress, low SES in adulthood, and air pollution) to recurrent wheeze in their children.[28] In contrast to these findings, a cross-sectional study of 267 Canadian children found no difference in IL-6 production by PBMCs stimulated with LPS between children with persistently high SES since birth and those who experienced upward mobility (going from lower-middle-class to higher-middle-class status), suggesting that some programming effects of early-life stressors can be reversed.[29] In contrast to children with an "upward SES trajectory," those with persistently low SES 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 ($P = .03$) but was not significantly associated with IL-6 in rural children.

A 2-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.[30] 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 ($P < .05$ 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 6 months before the study visits (because they were

scheduled twice per year), and lack of assessment of corticosteroid responses.

## STRESS AND RESPONSE TO TREATMENT

Stress can increase asthma morbidity by reducing response to inhaled corticosteroids and inhaled $\beta_2$-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 $P < .05$ in both instances).[31] 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 asthmatic children.[32] In this study response to corticosteroids was assessed by measuring production of IL-5, IL-13, and IFN-γ by PBMCs (incubated with a mitogen cocktail) after adding physiologic doses of hydrocortisone.[32] Although limited by a cross-sectional design, findings from the 2 studies referenced above[31,32] support the hypothesis that chronic stress leads to downregulation 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 (eg, questionnaires) or are difficult to implement in large studies (eg, detailed interviews with parents and multiple measures of salivary cortisol to assess circadian rhythm). Measuring cortisol in hair is one potential strategy that 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 (eg, 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 to controller medications? To what extent does having coping mechanisms or social support attenuate the effects of stress on asthma? Does exposure to other environmental exposures (eg, cigarette smoking and air pollution) or comorbidities (eg, obesity) modify the effect of stress on asthma and, if so, to what 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 affect 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 (eg, pulmonary function tests and airway responsiveness), examination of subphenotypes of the "asthma syndrome" (eg, atopic vs nonatopic asthma and eosinophilic vs noneosinophilic asthma), and measurement of cytokine profiles other than $T_H1/T_H2$ (eg, $T_H17$) 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 downregulation 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 might 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 (eg, ethnic minorities and the economically disadvantaged) who experience disproportionate rates of the asthma burden in this country. Such progress could have a major effect in reducing unacceptable health disparities in asthmatic patients in the United States and worldwide.

### REFERENCES

1. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief 2012;(94):1-8.
2. Forno E, Celedon JC. Health disparities in asthma. Am J Respir Crit Care Med 2012;185:1033-5.
3. Matthews KA, Gallo LC. Psychological perspectives on pathways linking socioeconomic status and physical health. Annu Rev Psychol 2011;62:501-30.
4. Yonas MA, Lange NE, Celedon JC. Psychosocial stress and asthma morbidity. Curr Opin Allergy Clin Immunol 2012;12:202-10.
5. Cohen RT, Canino GJ, Bird HR, Celedon JC. Violence, abuse, and asthma in Puerto Rican children. Am J Respir Crit Care Med 2008;178:453-9.
6. Coogan PF, Wise LA, O'Connor GT, Brown TA, Palmer JR, Rosenberg L. Abuse during childhood and adolescence and risk of adult-onset asthma in African American women. J Allergy Clin Immunol 2013;131:1058-63.
7. Klinnert MD, Nelson HS, Price MR, Adinoff AD, Leung DY, Mrazek DA. Onset and persistence of childhood asthma: predictors from infancy. Pediatrics 2001; 108:E69.
8. Chiu YH, Coull BA, Sternthal MJ, Kloog I, Schwartz J, Cohen S, et al. Effects of prenatal community violence and ambient air pollution on childhood wheeze in an urban population. J Allergy Clin Immunol 2014;133:713-22.e4.
9. Chen E, Chim LS, Strunk RC, Miller GE. The role of the social environment in children and adolescents with asthma. Am J Respir Crit Care Med 2007;176: 644-9.
10. Chen E, Strunk RC, Trethewey A, Schreier HM, Maharaj N, Miller GE. Resilience in low-socioeconomic-status children with asthma: adaptations to stress. J Allergy Clin Immunol 2011;128:970-6.
11. Wright RJ. Exploring biopsychosocial influences on asthma expression in both the family and community context. Am J Respir Crit Care Med 2008;177:129-30.
12. Wright RJ. Perinatal stress and early life programming of lung structure and function. Biol Psychol 2010;84:46-56.
13. Bahreinian S, Ball GD, Vander Leek TK, Colman I, McNeil BJ, Becker AB, et al. Allostatic load biomarkers and asthma in adolescents. Am J Respir Crit Care Med 2013;187:144-52.
14. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol 2005;5:243-51.
15. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. Nat Rev Immunol 2011;11:625-32.
16. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. Brain Behav Immun 2007;21:993-9.
17. Wright RJ, Cohen RT, Cohen S. The impact of stress on the development and expression of atopy. Curr Opin Allergy Clin Immunol 2005;5:23-9.
18. Chen W, Boutaoui N, Brehm JM, Han YY, Schmitz C, Cressley A, et al. ADCYAP1R1 and asthma in Puerto Rican children. Am J Respir Crit Care Med 2013;187:584-8.

19. Tsartsali L, Papadopoulos M, Lagona E, Papadimitriou A, Kanaka-Gantenbein C, Louizou E, et al. Association of hypothalamic-pituitary-adrenal axis-related polymorphisms with stress in asthmatic children on inhaled corticosteroids. Neuroimmunomodulation 2012;19:88-95.
20. Tantisira KG, Lake S, Silverman ES, Palmer LF, Lazarus R, Silverman EK, et al. Corticosteroid pharmacogenetics: association of sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids. Hum Mol Genet 2004;13:1353-9.
21. Rogers AJ, Tantisira KG, Fuhlbrigge AL, Litonjua AA, Lasky-Su JA, Szefler SJ, et al. Predictors of poor response during asthma therapy differ with definition of outcome. Pharmacogenomics 2009;10:1231-42.
22. Kim WJ, Sheen SS, Kim TH, Huh JW, Lee JH, Kim EK, et al. Association between CRHR1 polymorphism and improved lung function in response to inhaled corticosteroid in patients with COPD. Respirology 2009;14:260-3.
23. Dijkstra A, Koppelman GH, Vonk JM, Bruinenberg M, Schouten JP, Postma DS. Pharmacogenomics and outcome of asthma: no clinical application for long-term steroid effects by CRHR1 polymorphisms. J Allergy Clin Immunol 2008;121:1510-3.
24. Chen E, Miller GE, Walker HA, Arevalo JM, Sung CY, Cole SW. Genome-wide transcriptional profiling linked to social class in asthma. Thorax 2009;64:38-43.
25. Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, et al. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc Natl Acad Sci U S A 2009;106:14716-21.
26. Wright RJ, Visness CM, Calatroni A, Grayson MH, Gold DR, Sandel MT, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. Am J Respir Crit Care Med 2010;182:25-33.
27. Wright RJ, Finn P, Contreras JP, Cohen S, Wright RO, Staudenmayer J, et al. Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy. J Allergy Clin Immunol 2004;113:1051-7.
28. Sternthal MJ, Coull BA, Chiu YH, Cohen S, Wright RJ. Associations among maternal childhood socioeconomic status, cord blood IgE levels, and repeated wheeze in urban children. J Allergy Clin Immunol 2011;128:337-45.e1.
29. Azad MB, Lissitsyn Y, Miller GE, Becker AB, HayGlass KT, Kozyrskyj AL. Influence of socioeconomic status trajectories on innate immune responsiveness in children. PLoS One 2012;7:e38669.
30. Marin TJ, Chen E, Munch JA, Miller GE. Double-exposure to acute stress and chronic family stress is associated with immune changes in children with asthma. Psychosom Med 2009;71:378-84.
31. Miller GE, Chen E. Life stress and diminished expression of genes encoding glucocorticoid receptor and beta2-adrenergic receptor in children with asthma. Proc Natl Acad Sci U S A 2006;103:5496-501.
32. Miller GE, Gaudin A, Zysk E, Chen E. Parental support and cytokine activity in childhood asthma: the role of glucocorticoid sensitivity. J Allergy Clin Immunol 2009;123:824-30.
33. Torgerson DG, Ampleford EJ, Chiu GY, Gauderman WJ, Gignoux CR, Graves PE, et al. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. Nat Genet 2011;43:887-92.
34. Bonnelykke K, Sleiman P, Nielsen K, Kreiner-Møller E, Mercader JM, Belgrave D, et al. A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations. Nat Genet 2014;46:51-5.
35. Ferreira MA, McRae AF, Medland SE, Nyholt DR, Gordon SD, Wright MJ, et al. Association between ORMDL3, IL1RL1 and a deletion on chromosome 17q21 with asthma risk in Australia. Eur J Hum Genet 2011;19:458-64.
36. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, et al. Finding the missing heritability of complex diseases. Nature 2009;461:747-53.
37. Hunninghake GM, Soto-Quiros ME, Lasky-Su J, Avila L, Ly NP, Liang C, et al. Dust mite exposure modifies the effect of functional IL10 polymorphisms on allergy and asthma exacerbations. J Allergy Clin Immunol 2008;122:93-8, e1-5.
38. Bouzigon E, Corda E, Aschard H, Dizier MH, Boland A, Bousquet J, et al. Effect of 17q21 variants and smoking exposure in early-onset asthma. N Engl J Med 2008;359:1985-94.
39. Perera F, Tang WY, Herbstman J, Tang D, Levin L, Miller R, et al. Relation of DNA methylation of 5′-CpG island of ACSL3 to transplacental exposure to airborne polycyclic aromatic hydrocarbons and childhood asthma. PLoS One 2009;4:e4488.
40. Levanen B, Bhakta NR, Torregrosa Paredes P, Tang D, Levin L, Miller R, et al. Altered microRNA profiles in bronchoalveolar lavage fluid exosomes in asthmatic patients. J Allergy Clin Immunol 2013;131:894-903.
41. Ressler KJ, Mercer KB, Bradley B, Jovanovic T, Mahan A, Kerley K, et al. Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. Nature 2011;470:492-7.
42. Wang L, Cao C, Wang R, Qing Y, Zhang J, Zhang XY. PAC1 receptor (ADCYAP1R1) genotype is associated with PTSD's emotional numbing symptoms in Chinese earthquake survivors. J Affect Disord 2013;150:156-9.
43. Almli LM, Mercer KB, Kerley K, Feng H, Bradley B, Bonneely KN, et al. ADCYAP1R1 genotype associates with post-traumatic stress symptoms in highly traumatized African-American females. Am J Med Genet B Neuropsychiatr Genet 2013;162B:262-72.
44. Chang SC, Xie P, Anton RF, De Vivo I, Farrer LA, Kranzier HR, et al. No association between ADCYAP1R1 and post-traumatic stress disorder in two independent samples. Mol Psychiatry 2012;17:239-41.
45. Stevens JS, Almli LM, Fani N, Gutman DA, Bradley B, Norrholm SD, et al. PACAP receptor gene polymorphism impacts fear responses in the amygdala and hippocampus. Proc Natl Acad Sci U S A 2014;111:3158-63.
46. Jovanovic T, Norrholm SD, Davis J, Mercer KB, Almli L, Nelson A, et al. PAC1 receptor (ADCYAP1R1) genotype is associated with dark-enhanced startle in children. Mol Psychiatry 2013;18:742-3.
47. Spitzer C, Koch B, Grabe HJ, Ewert R, Barnow S, Felix SB, et al. Association of airflow limitation with trauma exposure and post-traumatic stress disorder. Eur Respir J 2011;37:1068-75.
48. Brackbill RM, Hadler JL, DiGrande L, Ekenga C, Farfel F, Friedman S, et al. Asthma and posttraumatic stress symptoms 5 to 6 years following exposure to the World Trade Center terrorist attack. JAMA 2009;302:502-16.
49. Hunninghake GM, Weiss ST, Celedon JC. Asthma in Hispanics. Am J Respir Crit Care Med 2006;173:143-63.
50. Carter-Pokras OD, Gergen PJ. Reported asthma among Puerto Rican, Mexican-American, and Cuban children, 1982 through 1984. Am J Public Health 1993;83:580-2.
51. Cohen RT, Canino GJ, Bird HR, Shen S, Rosner BA, Celedon JC. Area of residence, birthplace, and asthma in Puerto Rican children. Chest 2007;131:1331-8.
52. David MMA, Hanrahan JP, Carey V, Speizer FE, Tager IB. Respiratory symptoms in urban Hispanic and non-Hispanic white women. Am J Respir Crit Care Med 1996;153:1285-91.
53. Martinez-Taboas A, Canino G, Wang MQ, Garcia P, Bravo M. Prevalence and victimization correlates of pathological dissociation in a community sample of youths. J Trauma Stress 2006;19:439-48.
54. Purugganan OH, Stein RE, Silver EJ, Benenson BS. Exposure to violence among urban school-aged children: is it only on television? Pediatrics 2000;106:949-53.
55. Vermeiren R, Schwab-Stone M, Deboutte D, Leckman PE, Ruchkin V. Violence exposure and substance use in adolescents: findings from three countries. Pediatrics 2003;111:535-40.
56. Lange NE, Bunyavanich S, Silberg JL, Canino G, Rosner BA, Celedon JC. Parental psychosocial stress and asthma morbidity in Puerto Rican twins. J Allergy Clin Immunol 2011;127:734-40, e1-7.
57. Hashimoto H, Hashimoto R, Shintani N, Tanaka K, Yamamoto A, Hatanaka M, et al. Depression-like behavior in the forced swimming test in PACAP-deficient mice: amelioration by the atypical antipsychotic risperidone. J Neurochem 2009;110:595-602.
58. Kinhult J, Andersson JA, Uddman R, Stjarne P, Cardell LO. Pituitary adenylate cyclase-activating peptide 38 a potent endogenously produced dilator of human airways. Eur Respir J 2000;15:243-7.
59. Foda HD, Sharaf HH, Absood A, Said SI. Pituitary adenylate cyclase-activating peptide (PACAP), a VIP-like peptide, has prolonged airway smooth muscle relaxant activity. Peptides 1995;16:1057-61.
60. Elekes K, Sandor K, Moricz A, Kereskai L, Kemeny A, Szoke E, et al. Pituitary adenylate cyclase-activating polypeptide plays an anti-inflammatory role in endotoxin-induced airway inflammation: in vivo study with gene-deleted mice. Peptides 2011;32:1439-46.
61. Lauenstein HD, Quarcoo D, Plappert L, Schleh C, Nassimi M, Pilzner C, et al. Pituitary adenylate cyclase-activating peptide receptor 1 mediates anti-inflammatory effects in allergic airway inflammation in mice. Clin Exp Allergy 2011;41:592-601.
62. Kang DH, Weaver MT. Airway cytokine responses to acute and repeated stress in a murine model of allergic asthma. Biol Psychol 2010;84:66-73.
63. Kruschinski C, Skripuletz T, Bedoui S, Raber K, Straub RH, Hoffmann T, et al. Postnatal life events affect the severity of asthmatic airway inflammation in the adult rat. J Immunol 2008;180:3919-25.
64. Islam T, Urman R, Gauderman WJ, Milam J, Lurmann F, Shankardass K, et al. Parental stress increases the detrimental effect of traffic exposure on children's lung function. Am J Respir Crit Care Med 2011;184:822-7.
65. Peters JL, Cohen S, Staudenmayer J, Hosen J, Platts-Mills TA, Wright RJ. Prenatal negative life events increases cord blood IgE: interactions with dust mite allergen and maternal atopy. Allergy 2012;67:545-51.

66. Clougherty JE, Rossi CA, Lawrence J, Long MS, Diaz EA, Lim RH, et al. Chronic social stress and susceptibility to concentrated ambient fine particles in rats. Environ Health Perspect 2010;118:769-75.
67. Ly NP, Litonjua A, Gold DR, Celedon JC. Gut microbiota, probiotics, and vitamin D: interrelated exposures influencing allergy, asthma, and obesity? J Allergy Clin Immunol 2011;127:1087-96.
68. Ngoc PL, Gold DR, Tzianabos AO, Weiss ST, Celedon JC. Cytokines, allergy, and asthma. Curr Opin Allergy Clin Immunol 2005;5:161-6.
69. Kirschbaum C, Tietze A, Skoluda N, Dettenborn L. Hair as a retrospective calendar of cortisol production-Increased cortisol incorporation into hair in the third trimester of pregnancy. Psychoneuroendocrinology 2009;34:32-7.