

Socioeconomic status and inflammatory processes in childhood asthma: The role of psychological stress

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Background: Although social environment variables such as socioeconomic status (SES) have been linked to childhood asthma, little is known about the psychobiological mechanisms underlying this relationship.

Objectives: The goal of this study was to investigate relationships among SES, psychological stress, and immune processes implicated in asthma.

Methods: Thirty-seven children ages 9 to 18 years, physician-diagnosed with asthma, and 39 healthy children participated. Families were interviewed about chronic life stress, perceptions of threat, and SES. Blood samples were drawn from children to assess stimulated production of cytokines implicated in asthma (IL-4, IL-5, IL-13) and eosinophil counts.

Results: In children with asthma, lower SES was associated with heightened production of IL-5 and IL-13 and higher eosinophil counts (P values < .05). Lower SES also was associated with higher chronic stress and perceived threat (both groups: P values < .05). Higher levels of stress and threat perception were associated with heightened production of IL-5 and IL-13, and higher eosinophil counts in children with asthma (P values < .05). Statistical mediation tests revealed that chronic stress and threat perception represented statistically significant pathways between SES and immune processes in children with asthma (P values < .05). In healthy children, associations were in the opposite direction from the asthma group, though generally not significant.

Conclusion: This is one of the first studies to document empirically a psychobiological explanation for the epidemiologic relationship between low SES and poor asthma outcomes. **Clinical implications:** Associations among SES, psychological stress, and immune pathways suggest that the experience of stress, particularly among lower SES children, has implications for childhood asthma morbidity. (*J Allergy Clin Immunol* 2006;117:1014-20.)

Key words: Socioeconomic status, stress, immune, asthma

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Abbreviations used

FVC: Forced vital capacity
SES: Socioeconomic status

Children from lower socioeconomic status (SES) backgrounds are at greater risk for a variety of poor health outcomes.¹⁻³ For example, they are more likely to have asthma as well as adverse asthma-related events, such as hospitalizations.⁴⁻⁶ Moreover, this relationship is linear, such that increasing SES confers increasing health benefits across the SES spectrum.^{7,8} A variety of explanations has been proposed for the SES gradient in asthma morbidity. These include greater exposure to allergens, reduced access to care, and gene by environment interactions.⁹⁻¹² Recently, explanations have begun to focus on the role of psychosocial factors.¹³⁻¹⁶

Stress, in particular, has been suggested to be an important contributor to asthma.^{17,18} For example, in children with asthma, high levels of ongoing chronic stress plus an acute negative life event increased risk for an asthma attack within 2 weeks of the event.¹⁹ In addition, higher levels of caregiver stress prospectively increased risk of wheezing in infants.²⁰ Furthermore, stress has been linked to inflammatory pathways implicated in asthma, such as T_H2 cytokines. For example, in a sample of patients with asthma, a stressful event (taking a school examination) was associated with enhanced production of IL-5 compared with the response seen in healthy control adolescents.²¹ In patients with asthma, school examinations also were associated with higher eosinophil counts and heightened IL-5 production after antigen challenge relative to a low stress period (no examination).²² In a mouse model of allergic bronchial asthma, stress was associated with increased airway reactivity, increased allergy-induced airway inflammation, and higher eosinophil levels.²³ Cumulatively, these findings highlight immunologic pathways through which psychosocial variables such as stress may plausibly affect asthma outcomes.

However, few studies have directly tested whether these psychological and biological pathways could explain SES effects on asthma morbidity. In this study, we tested whether SES was associated with psychological stress and T_H2 cytokine production in children with asthma. Second,

we tested whether psychological stress constituted 1 pathway linking SES and asthma inflammatory processes. Finally, we compared children with asthma with a group of healthy children to determine whether relationships among SES, stress, and cytokine production differed depending on chronic illness status.

METHODS

Patients

Seventy-six children were recruited from Vancouver through advertisements in physicians' offices, local media, and community settings. Thirty-seven were physician-diagnosed with asthma (82% with allergic asthma), and 39 were free of chronic medical illness. All children were 9 to 18 years old, fluent in English, free of acute respiratory illness at the time of their visit (by parent and child report), and had no chronic illnesses other than asthma. Children gave written assent, and parents provided written consent. The protocol was approved by the University of British Columbia Research Ethics Board.

Psychosocial measures

Socioeconomic status was measured by parent report in 2 ways reflecting family resources: the amount of assets (savings, investments, and so forth) that a family could easily convert to liquid cash in an emergency (family savings), and whether the family owned their own home. These measures are used by the MacArthur Research Network on Socioeconomic Status and Health (<http://www.macses.ucsf.edu>), are standard measures in SES research,^{24,25} and are significantly correlated with each other as well as with prestige-based SES measures, such as parent education and occupation.

Stress was measured in 2 ways: chronic life stress, and perceptions of threat. Chronic stress was assessed with the University of California Los Angeles Life Stress Interview.²⁶ This interview assesses chronic stress over the period of the past 6 months, focusing on family relationships, friendships, school, and home life (parental work stress, family member health, and neighborhood quality). In each domain, an interviewer rated the extent of chronic stress on a 1 to 5 scale with higher numbers reflecting more severe, persistent difficulties. Perceptions of threat were measured by using the Cognitive Appraisal and Understanding of Social Events videos,²⁷ which depicted age-appropriate ambiguous life situations. Children were probed about their interpretation of each situation, and threat interpretations were coded by raters on a 5-point scale, with higher numbers reflecting greater perceived threat. This measure assesses differences in perceptions of threat across individuals when presented with identical situations. The stress experience is theorized to be composed of both the occurrence of a stressful event and the individual's psychological response to the event (perception of stress).²⁸ In the current study, we assess perception with a measure that has been validated in adolescents and shown to explain SES differences in cardiovascular outcomes.²⁹

Immune measures

After assessing psychosocial stress, peripheral blood was drawn into BD Vacutainer Cell Preparation Tubes (Becton Dickinson, Franklin Lakes, NJ) containing sodium heparin, and 3×10^6 PBMCs were isolated through density-gradient centrifugation. PBMCs were resuspended in culture medium consisting of RPMI plus 10% FCS and incubated with phorbol 12-myristate 13-acetate (25 ng/mL) and ionomycin (1 μ g/mL) for a period of 48 hours at 37°C in 5% CO₂. Supernatants were frozen until the end of the study, and then assayed to determine levels of IL-4, IL-5, IL-13, and IFN- γ

using ELISAs. Intra-assay coefficients of variance ranged from 3.68% to 4.76%. A complete blood count with differential was performed to enumerate eosinophil count.

Potential confounders

Pulmonary function was evaluated through spirometry according to American Thoracic Society guidelines.³⁰ FEV₁ and forced vital capacity (FVC) were derived and calculated as a percent of predicted values on the basis of age, sex, ethnicity, and height. Families brought children's asthma medications to the research center, and inhaled corticosteroid use was coded (yes/no), as was β -agonist use (yes/no). Note that using number of doses of medications produced the same pattern of results described below.

Statistical analyses

Our analyses consisted of 4 sets of tests: (1) associations of SES with stress, (2) association of SES with immune processes, (3) associations of stress with immune processes, and (4) statistical mediation tests of the pathway SES \rightarrow stress \rightarrow immune. Hypotheses were tested by using analysis of covariance for categorical variables (home ownership) and multiple regression for continuous variables (SES, stress). In analyses predicting immune measures, potential confounds described above were modeled as covariates, and then medical group, SES/stress, and the interaction of group by SES/stress were entered.

RESULTS

Preliminary analyses

Table I describes the sample characteristics. Children with asthma and healthy children were similar in age, sex, ethnic background, and SES. Controlling for demographic factors, including age, sex, ethnicity, and pubertal status, did not change the pattern of results reported. Children with asthma were similar in chronic life stress and perceived threat compared with healthy children, but they had higher eosinophil counts ($t = 4.10$; $P < .001$) and lower FEV₁ ($t = 2.02$; $P < .05$). The groups did not differ on production of cytokines or FVC. Children with allergic asthma did not differ from children with nonallergic asthma on any immune outcomes (t values ranging from 0.12 to 1.33; P values $> .15$); thus, all children with asthma were considered as a single group to compare with healthy children. Across all children, FEV₁ and FVC were negatively correlated with immune variables, including IL-5, IL-13, and eosinophil count (P values $< .05$).

SES and stress

ANOVAs revealed that owning a home was associated with lower stress in both healthy children and children with asthma. Children living in homes owned by their parents had lower chronic family stress ($F = 20.70$; $P < .001$), chronic home stress ($F = 47.76$; $P < .001$), and perceived threat ($F = 10.52$; $P < .01$). There was no significant interaction between home ownership and medical status, indicating that home ownership had the same effect on stress across the 2 groups of children.

A similar pattern was evident for family savings: children from families with lower savings had more chronic

TABLE I. Descriptive information of sample

	Asthma	Healthy
Age (y)	13.2 ± 2.8	13.4 ± 2.1
Sex (males)	64%	52%
Ethnicity (white)	62%	73%
FEV ₁ (% predicted)*	98.1 ± 15.4	103.1 ± 9.3
FVC (% predicted)	105.8 ± 15.3	107.2 ± 11.0
β-Agonist use†	77%	
Inhaled corticosteroid use†	58%	
Family savings	\$10,000 to \$19,000	\$10,000 to \$19,000
Own home	62%	61%
Chronic stress—family (1-5)	2.4 ± 0.8	2.2 ± 0.9
Chronic stress—home (1-5)	2.6 ± 0.8	2.6 ± 0.9
Chronic stress—school (1-5)	2.3 ± 1.0	2.2 ± 0.9
Chronic stress—friends (1-5)	2.1 ± 0.7	2.3 ± 0.8
Perceived threat (−2 to +2)	−0.3 ± 1.3	−0.4 ± 1.3
IL-4 (pg/mL)	24.9 ± 31.9	32.6 ± 32.2
IL-5 (pg/mL)	134.9 ± 87.1	121.2 ± 99.1
IL-13 (pg/mL)	629.1 ± 372.3	480.6 ± 335.5
IFN-γ (pg/mL)	31,622 ± 23,292	43,555 ± 50,567
Eosinophil count (×10 ⁹ cells/L)*	0.38 ± 0.31	0.16 ± 0.14

Values represent means ± SDs.

*Asthma and healthy groups differ at $P < .05$.

†Coded as whether or not child had used medication in previous 2 weeks.

family stress ($\beta = -.47$; $t = 3.25$; $P < .01$), chronic home stress ($\beta = -.68$; $t = 5.66$; $P < .001$), chronic school stress ($\beta = -.36$; $t = 2.33$; $P < .05$), and perceived threat ($\beta = -.40$; $t = 2.80$; $P < .01$). There were no significant interactions between savings and medical group status in predicting stress.

SES and immune measures

Analyses of covariance indicated that the relationships between SES and immune processes differed for children with asthma versus healthy children. Medical group status interacted with home ownership to predict production of IL-4 ($F = 7.56$; $P < .01$), IL-5 ($F = 5.11$; $P < .05$), IL-13 ($F = 3.88$; $P < .05$), and eosinophil count ($F = 4.69$; $P < .05$). Among children with asthma, production of cytokines and eosinophil count were higher when families rented their home than when families owned their own home. In contrast, among healthy children, production of cytokines did not differ when families rented versus owned their own home (see Fig 1 for illustrative examples).

A similar pattern was evident in analyses with the family savings. Significant interaction effects emerged for group status by family savings for production of IL-5 ($\beta = -.34$; $t = 2.13$; $P < .05$) and IL-13 ($\beta = -.39$; $t = 2.50$; $P < .05$) and for eosinophil counts ($\beta = -.42$; $t = 3.38$; $P < .01$). Among children with asthma, this association was negative: lower SES was related to greater production of IL-5 and IL-13 and higher eosinophil counts (see Fig 2 for an illustrative example). These findings indicate that in children with asthma, the association between SES and adverse immune outcomes is evident

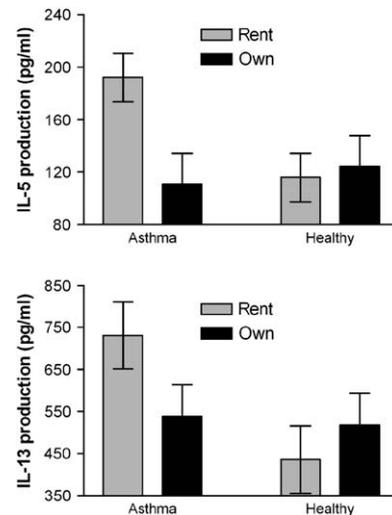


FIG 1. Differences in production of IL-5 and IL-13 for families who rent their homes versus families who own their own home by medical group status.

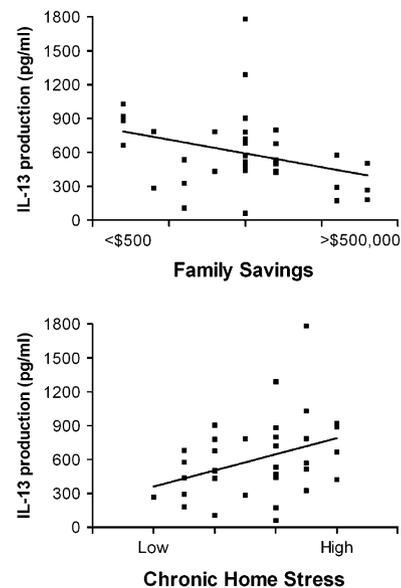


FIG 2. Top panel, Association of family savings with production of IL-13 among children with asthma. Bottom panel, Association of chronic home stress with production of IL-13 among children with asthma.

across categoric (home ownership) and continuous (family savings) indicators of SES. In contrast, among healthy children, associations between SES and immune outcomes were positive, but not significant. No associations with IFN- γ were found in either group (Table II).

Stress and immune measures

Correlations among the different indicators of stress ranged from $r = .12$ to $.48$. Regression analyses revealed that the relationships between stress and immune processes also differed for children with asthma versus

healthy children. Significant interaction effects emerged for group status by chronic family stress for production of IL-5 ($\beta = .54$; $t = 3.31$; $P < .01$) and IL-13 ($\beta = .54$; $t = 3.32$; $P < .01$). Among children with asthma, higher family stress was associated with greater production of IL-5 and IL-13. In contrast, among healthy children, higher stress was associated with lower IL-5 and IL-13 (Table II).

Similar interaction effects emerged for group status by chronic home stress for IL-5 ($\beta = .44$; $t = 2.73$; $P < .01$), IL-13 ($\beta = .39$; $t = 2.42$; $P < .05$), and eosinophil count ($\beta = .34$; $t = 2.42$; $P < .05$). As with chronic family stress, among children with asthma, higher levels of home stress were associated with higher IL-5, IL-13, and eosinophil counts (Fig 2). In contrast, among healthy children, higher home stress was associated with lower levels of these immune processes, although associations were not significant (Table II). No interaction effects were found for chronic stress related to school or friendships.

For perceived threat, significant interactions with group status were found for production of IL-5 ($\beta = .40$; $t = 2.48$; $P < .05$) and eosinophil counts ($\beta = .30$; $t = 2.13$; $P < .05$). Among children with asthma, greater threat interpretations were associated with marginally higher production of IL-5 and significantly higher eosinophil counts, whereas among healthy children, greater threat interpretations were associated with marginally lower IL-5 (Table II). No associations were found for chronic stress or perceived threat with IL-4 or IFN- γ .

Stress as a pathway?

Although this study was observational and cross-sectional, and thus we were not able to determine whether SES influences stress, which in turn influences immune processes, we were able to conduct statistical mediation tests to assess whether our data are consistent with such an explanation. To do this, we applied the Sobel test with the distributional properties recommended by MacKinnon et al.³¹ This statistic tests the significance of the indirect pathway (SES \rightarrow stress \rightarrow immune) using a products of coefficient test, with $z > .97$ indicating a statistically significant pathway. Pathways were tested only within the group of children with asthma, given that the SES-immune and stress-immune associations were significant only in this group.

We first tested pathways between SES (family savings) and production of IL-5 among children with asthma. Chronic family stress formed a significant pathway linking savings and IL-5 ($z = 1.58$; $P < .05$), as did chronic home stress ($z = 1.69$; $P < .05$). In addition, perceived threat emerged as a significant pathway linking savings and IL-5 ($z = 1.07$; $P < .05$).

We next tested pathways between savings and production of IL-13 in children with asthma. Chronic family stress formed a significant pathway linking savings and IL-13 ($z = 1.63$; $P < .05$), as did chronic home stress ($z = 1.17$; $P < .05$). In addition, threat interpretations emerged as a significant pathway between savings and IL-13 ($z = .98$; $P < .05$).

TABLE II. Regression coefficients for SES/stress and immune processes by medical group

	Asthma β	Healthy β
SES and IL-5	-.28†	.22
SES and IL-13	-.38*	.21
SES and eosinophil count	-.59***	.03
Chronic family stress and IL-5	.52**	-.26†
Chronic family stress and IL-13	.55**	-.24
Chronic home stress and IL-5	.40*	-.23
Chronic home stress and IL-13	.40*	-.16
Chronic home stress and eosinophil count	.41**	-.08
Perceived threat and IL-5	.28†	-.29†
Perceived threat and eosinophil count	.37*	-.06

For SES, IL-4 and IFN- γ did not show a significant group by SES interaction, and thus coefficients are not presented separately by group. Similarly, for outcomes in which there were no significant interaction effects of group by stress, coefficients are not presented separately by group.
† $P < .10$; * $P < .05$; ** $P < .01$; *** $P < .001$.

Last, we tested pathways between SES and eosinophil counts in children with asthma. In this case, chronic family stress and chronic home stress did not form statistically significant pathways ($z = .92$ and $.13$, respectively). However, threat interpretations did emerge as a significant pathway linking savings and eosinophil counts ($z = 1.17$; $P < .05$).

When we directly compared the effects of chronic family stress, chronic home stress, and threat interpretations, we found evidence that family stress and threat interpretations formed the strongest pathways in children with asthma. When the 3 stress variables were included simultaneously in regression equations of statistical mediation (identical to above, but with 3 possible mediators instead of 1), family stress ($z = 1.60$; $P < .05$) and threat interpretations ($z = 1.42$; $P < .05$) each independently formed significant pathways between SES and IL-13, but home stress did not. For SES and IL-5, only family stress independently emerged as a significant pathway ($z = 1.32$; $P < .05$). Finally, as reported, threat interpretations, but not family or home stress, were a significant pathway between SES and eosinophil count. Overall, these findings are consistent with the explanation that psychological stress serves as 1 pathway linking lower SES and heightened inflammatory processes in children with asthma.

Alternative explanations for the role of stress?

It is possible that stress is confounded with other commonly implicated factors in asthma, and that in the analyses described, stress merely serves as a proxy for them. Thus, we tested whether factors such as exposure to pets, exposure to smoke, and child smoking might explain our findings. To do this, we ran a new set of analyses statistically controlling for each of these variables. After adjusting for pet exposure, child exposure to smoke, and child's smoking status, all interactions between chronic family stress by medical group, chronic home stress by

medical group, and perceived threat by medical group remained significant. These findings indicate that stress's association with inflammatory processes is independent of these other potential asthma triggers.

DISCUSSION

The current study demonstrated in a sample of children with asthma that (1) lower SES is associated with heightened production of the T_H2 cytokines IL-5 and IL-13 and higher eosinophil counts, (2) lower SES is associated with higher levels of chronic stress and greater perceptions of threat, (3) higher levels of chronic stress and perceived threat are associated with heightened production of IL-5 and IL-13 and eosinophil counts, and (4) chronic stress and perceived threat explain much of the relationship between SES and immune processes.

These findings provide some of the first empirical evidence connecting factors across epidemiologic, psychological, and biological levels of analysis. At the epidemiologic level, researchers have documented that lower SES is associated with poorer asthma outcomes, such as higher hospitalization rates.^{5,32} However, this research has not generally probed the mechanisms behind such relationships. Biopsychosocial models of asthma^{13,33} have proposed that psychological factors such as stress contribute to asthma pathogenesis via activation of autonomic, hypothalamic-pituitary-adrenal, and immune pathways. Our findings are consistent with the predictions of these models, and suggest that these pathways may explain SES gradients in asthma. Specifically, our results are consistent with the view that stress operates as a pathway linking SES with immune dysregulation, which in turn may contribute to asthma morbidity. Previous research on stress-immune relationships supports this notion, finding that caregiver stress early in life is associated with total IgE and allergen-induced proliferation in young children predisposed to atopy.³⁴

Our findings are consistent with the linear SES-health relationship observed at the epidemiologic level.^{7,35} In the current study, we found that SES had linear associations with chronic stress and perceived threat, and in turn, that chronic stress and perceived threat had linear relationships with cytokine production and eosinophil counts in children with asthma. In previous pilot research, we documented group differences in cytokine production among children with asthma from low versus high SES neighborhoods.³⁶ Other researchers have demonstrated effects of low versus high SES on cytokines in healthy individuals,^{37,38} and on IgE levels in a sample with high rates of allergic disease.³⁹ However, this is the first study to document psychobiological explanations for the linear SES effect in children with asthma.

In the current study, we focused on inflammatory processes implicated in asthma. Researchers have proposed that asthma involves activation of T_H2 cells, which promote B-cell proliferation and differentiation and antibody synthesis through secretion of cytokines such as IL-4,

IL-5, and IL-13. These cytokines are believed to be important in the orchestration of airway inflammation and hyperresponsiveness.⁴⁰⁻⁴³ In addition, eosinophil counts are associated with symptoms and severity of asthma.^{44,45} Thus, our findings of associations between lower SES and increased production of IL-5 and IL-13 as well as higher eosinophil counts in children with asthma suggest that these immune profiles may help explain the poorer clinical profiles that many lower SES children with asthma have.

Among healthy children, associations between stress and immune processes were generally nonsignificant, and if any trend emerged, it was in the opposite direction from children with asthma. These findings suggest that in healthy children, stress does not have a potent influence on the immune response, although in some cases it is able to diminish T_H2 cytokine production. The latter pattern is consistent with the general literature on stress and immunity in healthy individuals. A meta-analysis of this work showed that chronic stressors are associated with down-regulation of cellular immunity, as manifest by reduced natural killer cell activity, blunted lymphocyte proliferation, and diminished cytokine production.^{46,47} Collectively, these findings suggest that stress affects the immune system differently in healthy children and children with asthma. Apart from stress effects, group averages for stimulated cytokine production did not differ for children with asthma versus healthy children; however, children with asthma did have higher eosinophil counts. This suggests that in our sample, asthma is associated with indicators of ongoing inflammation (eosinophil counts), but not with the extent of stimulated cytokine production. This may reflect the fact that many of the patients in our sample had mild, well controlled disease. These patterns could also suggest gene by environment interactions, in which different genetic predispositions interact with the social environment (eg, stress) to produce different effects in healthy versus asthmatic children. Future studies that test social environmental factors would add to existing knowledge about physical environment factors, such as air pollutants and respiratory viruses, in gene-environment studies of asthma.^{17,48}

One alternative explanation for the study findings is that inflammatory processes may affect the stress that families experience, rather than stress affecting immune processes, as our model implies. Although we cannot rule out this explanation because of the cross-sectional design of the study, we believe it is a less compelling explanation for 2 reasons. First, this explanation is difficult to apply to SES-immune associations, because immune processes in the child are unlikely to affect the SES of the parents. Second, if asthma-related inflammatory processes shape the stresses that families experience, one might expect these processes to be associated with a greater effect of asthma on the family. However, no significant associations were found between asthma-related effects on the family or caregiver and immune measures in this study (data not presented). This suggests that general life stresses relate to immune processes, rather than immune processes

affecting the specific stresses and burdens of asthma on the family.

Limitations of the current study include the small sample and the cross-sectional observational design. It was not possible to manipulate either SES or life stress experiences experimentally in this study. However, future research could study these relationships prospectively to determine whether changes in SES precede changes in stress and changes in asthma inflammatory processes. In addition, in a study such as this one with no obvious clinical benefit, it was not feasible to withdraw children from current medications, so we had to control statistically for medication usage in analyses. It should be noted that the cytokine production assay used a substance that stimulates cells generally, rather than a stimulus specific to asthma (eg, a specific allergen). We recruited a community sample and did not select for positive response to any specific allergen; thus, a more specific stimulus would not have elicited a response across all children in this sample. In addition, immune processes were measured from peripheral blood cells. Future studies that are able to obtain cells directly from the airways using techniques such as bronchoalveolar lavage would provide important information about more proximal processes. Finally, this study focused on the role of 1 primary psychosocial factor, stress. Future studies are needed that evaluate in detail the relative contributions of stress versus other factors (eg, allergen exposure, health behaviors, health care access) in the SES-asthma relationship.

Overall, our findings suggest that across all children, growing up in a lower SES family is associated with experiencing greater chronic life stress, both at home and at school, consistent with previous research showing that lower SES children are more vulnerable to family conflict and poor quality family relationships^{49,50} and higher incidences of neighborhood violence,⁵¹ and are more likely to struggle academically.⁵² In addition, children from lower SES families are more likely to perceive a given situation as threatening compared with higher SES children faced with the same situation. This suggests that lower SES children not only experience more objective life stressors but also subjectively experience the same situation as more stressful.

In turn, these stress experiences are associated with biological processes in children with asthma. The chronic difficulties children with asthma face in their home and family life, as well as perceptions of threat, were associated with heightened production of cytokines implicated in asthma and higher levels of basal eosinophils. This suggests that stress dysregulates immune processes in children with asthma, possibly shifting responses toward a T_H2 profile, as well as sensitizing the T_H2 system to responding more aggressively to allergen exposure.^{21,22,34} In addition, chronic stress may affect other biological systems—for example, producing a hypoactive hypothalamic-pituitary-adrenal axis,⁵³ which in turn might not be able to regulate inflammatory processes adequately, or activating the parasympathetic nervous system,⁵⁴ which could then operate together with inflammation to constrict

bronchial airways. These processes might then have implications for exacerbations of clinical symptoms in children with asthma and high stress. Overall, these findings help advance our understanding of how the larger social context (eg, SES) may affect the lives of children with asthma in a manner that has implications for biological health outcomes.

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