Background: Stress is known to worsen the course of asthma, but the underlying mechanisms are poorly understood. This problem is especially difficult because stress elicits secretion of cortisol, a hormone that dampens airway inflammation and ameliorates asthma symptoms.

Objective: This article proposes that stress affects asthma by inducing resistance to the anti-inflammatory properties of glucocorticoids. To evaluate this hypothesis, we examine whether a particular kind of stress in children’s lives, not feeling supported or understood by parents, is associated with measures of lymphocyte resistance to glucocorticoids and indices of eosinophil mobilization and activation.

Methods: Children with asthma (n = 67) and medically healthy children (n = 76) completed standardized questionnaires about support from their parents. PBMCs were collected and incubated with a mitogen cocktail in the presence of physiologic concentrations of hydrocortisone. Production of IL-5, IL-13, and IFN-γ was measured by means of ELISA. Circulating eosinophils were enumerated with a hematology analyzer, and the extent of their activation was indexed by means of ELISA for eosinophil cationic protein.

Results: To the extent that children with asthma perceived low support from their parents, children were more resistant to hydrocortisone’s anti-inflammatory effects on IL-5 and IFN-γ production and had higher circulating levels of eosinophil cationic protein. These associations were independent of socioeconomic conditions, cigarette exposure, disease severity, and medication use.

Conclusions: These patterns suggest the hypothesis that strained parent-child relations, and perhaps stress more generally, brings about adverse outcomes in asthma by diminishing cortisol’s ability to regulate cytokine activity and subsequent airway inflammation. (J Allergy Clin Immunol 2009;123:824-30.)

Key words: Social support, cortisol, cytokines, stress, glucocorticoid receptor

At least since the time of the 12th-century physician-philosopher Maimonides, doctors and patients have believed that stress contributes to asthma. However, it has only been in recent decades that evidence has emerged to support this view. Stress that arises from turmoil within the family seems to be particularly detrimental. For example, prospective studies have found that wheezing and asthma are more likely to develop in children whose families report parenting difficulties, high stress, or mood problems. Also, in studies of children with existing asthma, family difficulties have been linked with increased symptom expression, worse pulmonary function, and the onset of attacks.

The mechanisms responsible for these associations are not well understood. Historically, much of the blame for stress-related diseases has been assigned to the hypothalamic-pituitary-adrenocortical axis, which releases cortisol into the circulation after many psychologically demanding experiences. Cortisol has a wide variety of physiologic consequences, including mobilization of glucose, regulation of vascular tone and fluid volume, and modulation of immune function. This chain of events seems unlikely to contribute to stress-related asthma, however, because one of cortisol’s major actions in the immune system is to suppress inflammation. In fact, to the extent that stress provokes a cortisol surge, it might theoretically be expected to dampen airway inflammation and by doing so ameliorate symptoms of asthma, as it does when administered therapeutically as inhaled systemic corticosteroid. Of course, evidence suggests just the opposite pattern: that stress amplifies the immune response to allergens and irritants and increases the frequency and severity of symptoms.

To resolve this paradox and identify underlying mechanisms, we have advanced the hypothesis that chronic stress fosters resistance to glucocorticoids. This view suggests that chronic stress triggers persistent secretion of cortisol, which leads to compensatory downregulation of glucocorticoid receptor (GR) expression and functioning. In patients with asthma, such dynamics could enable airway inflammation to flourish and also diminish the efficacy of therapeutics that work through GRs. In an earlier project with asthmatic patients, we found evidence consistent with this scenario: high levels of chronic turmoil in the family, especially when coupled with other stressors, were linked with a 5.5-fold reduction in leukocyte GR mRNA. Although these findings suggest that family turmoil can downregulate GR expression, it remains unclear whether it also has functional implications for the cellular processes that drive asthma.

The current project enrolled children with asthma and healthy control subjects to answer this question. We assessed an important
component of children's familial relationships: how much support and understanding they felt from their parents. We also collected PBMCs and, after incubating them with mitogens and cortisol, measured production of Tg1 (IFN-γ) and Tg2 (IL-5 and IL-13) cytokines that regulate allergic immune responses. We predicted that among children with asthma, low family support would be associated with decreased sensitivity to cortisol's suppressive influences on cytokine production. We also predicted that as a downstream consequence of this dynamic, children with low support would show higher eosinophil counts and more eosinophil cationic protein (ECP). ECP is a cytotoxic protein released from the granules of activated eosinophils and is considered a surrogate marker of inflammation in the airways.

### METHODS

#### Sample

The sample consisted of 67 children with asthma and 76 medically healthy children. All were recruited from Vancouver, British Columbia, through advertisements in physician’s offices, newspapers and magazines, and community settings. Children were eligible if they were 9 to 18 years of age, fluent in English, and free of upper respiratory illness for the past 4 weeks. Children in the asthma group had to have a physician’s diagnosis and be free of other chronic medical illnesses. Healthy control subjects were required to have a history without chronic illness. The protocol was approved by the University of British Columbia’s Research Ethics Board. All children provided written assent before participating and had a parent or guardian provide written consent.

#### Parental support

Children completed the family subscale of the Social Support Scale for Children, a self-report instrument that has been extensively validated. They were asked to rate the degree to which 6 statements described their parental relationships, such as “Some kids have parents who care about their feelings” and “Some kids have parents who like them as they are.” Responses were given on a 4-point scale. The scale’s items were internally consistent (Cronbach’s α = .73), but the distribution was skewed, with most children having scores on the higher end. We therefore stratified the sample into 4 groups ranging from low (1) to high (4). This variable was normally distributed.

#### Glucocorticoid sensitivity

When participants arrived, a topical anesthetic (Eutectic Mixture of Local Anesthetics, APP Pharmaceuticals, Schaumburg, Ill) was applied to minimize discomfort from venipuncture. One hour later, 10 mL of blood was drawn from the antecubital vein into Cell Preparation Tubes (Becton Dickinson, Franklin Lakes, NJ). PBMCs were then isolated and resuspended in RPMI-1640 medium with HEPES supplemented with 10% FCS (Sigma-Aldrich, St Louis, Mo) at a concentration of 3 × 10^6 cells/mL. PBMCs were then incubated at 37°C and 5% CO₂ with 25 ng/mL phorbol 12-myristate 13-acetate and 1 μg/mL ionomycin calcium salt and either 0 or 10 ng/mL hydrocortisone (all from Sigma-Aldrich). The final in-well concentration of hydrocortisone was 28 nmol/L. (In pilot studies we experimented with hydrocortisone doses ranging from 0.3 to 300 nmol/L. Because cytokine responses were strongly correlated across doses, with r values ranging from 0.79 for IL-13 to 0.91 for IFN-γ, we opted to use a single 28 nmol/L administration in the final study. This dose is roughly similar to the values in human blood during mild psychologic stress.) After 48 hours of culture, cell suspensions were centrifuged, and supernatants were collected and frozen at −80°C.

Concentrations of IL-5, IL-13, and IFN-γ were quantified by means of ELISA (R&D Systems, Minneapolis, Minn). Coefficients of variation averaged less than 8%. For each cytokine, we later computed a variable reflecting “percent-age resistance to glucocorticoid inhibition” by dividing values in hydrocortisone-treated wells by those in saline-treated wells.

To evaluate the reproducibility of these procedures, we drew blood from 3 technicians on 3 consecutive days and then divided each sample into 3 aliquots. The assay was then run on 9 samples. Analyses revealed that within-person coefficients of variation averaged 9.7%, 11.4%, and 16.6% for IL-5, IL-13, and IFN-γ, respectively. These data suggest that our procedures are reproducible and that patient responses are fairly stable over short timeframes.

#### Eosinophil counts and activation

Eosinophil counts were measured as part of a 5-part blood count and differential with a Bayer Advia 70 hematology analyzer (Diamond Diagnostics, Holiston, Mass). ECP levels were measured by using the ImmunoCAP system (PhadiaAB, Uppsala, Sweden) with reagents from Somagen (Edmonton, Alberta, Canada). Ten milliliters of blood was drawn into Serum Separator Tubes (BD, Franklin Lakes, NJ) and incubated at room temperature for 90 minutes. During this interval, activated eosinophils released ECP. The tubes were then centrifuged. After serum had been aspirated, it was stored at −80°C.

#### Potential confounders

To determine whether behavioral and biomedical characteristics might be acting as confounders, we collected information regarding the children’s age, sex, family income, cigarette exposure, pulmonary function, and medication use. Each of these factors has been linked to family support, cytokine production in past work, or both. Demographic information was collected during parental interviews. Personal use of cigarettes and secondhand exposure were ascertained by means of a questionnaire. Because only 1 child was a regular smoker, we used hours per week of exposure to secondhand smoke as a covariate in analyses. Pulmonary function was indexed by FEV₁ during a spirometric examination.Spirometry was conducted at least 4 hours after the last use of a short-acting bronchodilator and performed according to guidelines used in large multisite clinical trials in patients with asthma.

FEV₁ values were calculated as a percentage of predicted value based on child age, sex, ethnicity, and height. Medication use was assessed by having parents bring all of their child’s medications to the research center. The name and dosage of each medication was recorded directly from the label, and the frequency of use in the past 2 weeks was ascertained. In analyses we included variables reflecting days of treatment with inhaled corticosteroids and β-agonists as covariates.

#### Statistical analyses

Hypotheses were evaluated in a series of regression equations. Each biologic outcome was predicted from 3 blocks of variables entered consecutively. They consisted of (1) potential confounders, (2) indicators of parental support and asthma status, and (3) a product term representing the interaction of the latter factors. When a statistically significant interaction emerged, it was decomposed according to standard procedures. Simple slopes within each group were computed. Percentage resistance was then estimated at low, medium, and high levels of support (defined as 1 SD below, the sample mean, and 1 SD above, respectively) and then plotted separately for the asthmatic and healthy children. For all statistical analyses, α was set to .05, and 2-tailed tests of significance were performed.

### RESULTS

#### Preliminary analyses

Table I displays the sample characteristics. The children with asthma and medically healthy children were similar in terms of age, ethnic background, family income, and cigarette exposure (P > .35). However, there was a greater proportion of male subjects in the asthmatic sample ($χ^2 = 5.74, P = .03$).
The same patterns emerged in wells treated with hydrocortisone.

Eosinophil mobilization and activation

To evaluate potential downstream consequences of the glucocorticoid resistance, we examined relations between parental support and eosinophil mobilization and activation. As Table III shows, eosinophil counts were higher among children with asthma and those using regular medications but unrelated to familial support. ECP levels were higher in asthmatic patients and showed a significant medical status-by-family support interaction similar to IL-5 and IFN-γ (Fig 3). Thus in children with asthma, low parental support emerged as a significant predictor of glucocorticoid sensitivity.

**TABLE I. Characteristics of the sample**

<table>
<thead>
<tr>
<th></th>
<th>Asthmatic subjects (n = 67)</th>
<th>Healthy subjects (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>13.3 ± 0.4</td>
<td>13.4 ± 0.3</td>
</tr>
<tr>
<td>Sex (male)*</td>
<td>49 (73.2%)</td>
<td>40 (52.6%)</td>
</tr>
<tr>
<td>Descent (European)</td>
<td>39 (58.2%)</td>
<td>43 (57.3%)</td>
</tr>
<tr>
<td>Descent (Asian)</td>
<td>22 (32.8%)</td>
<td>20 (26.3%)</td>
</tr>
<tr>
<td>Annual family income (thousands)</td>
<td>68.7 ± 2.7</td>
<td>68.8 ± 2.6</td>
</tr>
<tr>
<td>Low income (&lt;$35,000 annually)</td>
<td>9 (13.4%)</td>
<td>13 (17.1%)</td>
</tr>
<tr>
<td>FEV1 (% predicted)*</td>
<td>97.1 ± 1.0</td>
<td>103.2 ± 1.9</td>
</tr>
<tr>
<td>Cigarette exposure (h/wk)</td>
<td>1.2 ± 0.2</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Inhaled corticosteroids (last 2 wk)</td>
<td>25 (37.3%)</td>
<td>—</td>
</tr>
<tr>
<td>Bronchodilator (last 2 wk)</td>
<td>28 (41.8%)</td>
<td>—</td>
</tr>
<tr>
<td>Asthma severity (moderate or severe)</td>
<td>33 (49.3%)</td>
<td>—</td>
</tr>
<tr>
<td>Family support (1-4)</td>
<td>2.5 ± 1.1</td>
<td>2.5 ± 0.1</td>
</tr>
<tr>
<td>IL-5 production, saline (pg/mL)</td>
<td>73.3 ± 91.1</td>
<td>72.9 ± 7.6</td>
</tr>
<tr>
<td>IL-13 production, saline (pg/mL)</td>
<td>259.6 ± 27.3</td>
<td>311.9 ± 21.2</td>
</tr>
<tr>
<td>IFN-γ production, saline (pg/mL)</td>
<td>6,392.9 ± 962.9</td>
<td>16,523.3 ± 1,519.9</td>
</tr>
<tr>
<td>IL-5 production, hydrocortisone (pg/mL)</td>
<td>46.8 ± 5.5</td>
<td>49.7 ± 5.3</td>
</tr>
<tr>
<td>IL-13 production, hydrocortisone (pg/mL)</td>
<td>219.7 ± 21.8</td>
<td>267.1 ± 19.6</td>
</tr>
<tr>
<td>IFN-γ production, hydrocortisone (pg/mL)</td>
<td>6,385.8 ± 1,004.7</td>
<td>13,215.1 ± 1,268.6</td>
</tr>
<tr>
<td>Circulating eosinophils (× 10⁷ cells/L)†</td>
<td>0.35 ± 0.04</td>
<td>0.17 ± 0.02</td>
</tr>
<tr>
<td>ECP (µg/L)†</td>
<td>16.2 ± 1.5</td>
<td>11.5 ± 1.0</td>
</tr>
</tbody>
</table>

Values are presented as means ± SE or numbers (percentages). Symbols indicate that the asthmatic and healthy groups differ.

*P < .05.
†P < .01.

Children with asthma had lower FEV1 percentiles than healthy control subjects (t = 2.82, P = .007). About 40% of them had used inhaled corticosteroids and β-agonists in the past 2 weeks. Using guidelines from the National Asthma Education and Prevention Program’s Expert Panel Report 2, based on the higher of symptom frequency and medication use,31 11 (7.6%) of the children with asthma had mild intermittent disease, and the others had persistent disease that was classified as mild (23 [15.9%]), moderate (22 [15.2%]), or severe (11 [7.6%]). Fifty-seven (85.1%) of the children with asthma (85.1%), and 32 (42.1%) of the healthy children (76) who had not used them in the last 2 weeks. The results were identical to those presented above. For both IL-5 and IFN-γ, there were interactions between asthma status and parental support (for IL-5 interaction: B = −0.14, SE = 0.07, P = .05; for IFN-γ interaction: B = −0.16, SE = 0.08, P = .05). In both cases lower support was associated with greater resistance to hydrocortisone inhibition among children with asthma. In the healthy control subjects family support was unrelated to IL-5 hydrocortisone sensitivity but showed a weak positive relation with IFN-γ, which was not significant (P for simple slope = .61). These findings are displayed in Fig 2. There was no interaction for IL-13.

Seven asthmatic patients had taken a course of oral steroids within the last 6 months. The pattern of results was similar when they were removed from the analyses (for IL-5 interaction: B = −0.13, SE = 0.05, P = .02; for IFN-γ interaction: B = −0.14, SE = 0.07, P = .04), suggesting that use of these medications was not contributing to the findings.

**Parental support and glucocorticoid sensitivity**

Table II presents regression analyses for each cytokine. For IL-5, subjects from lower-income families were more resistant to the inhibitory properties of hydrocortisone, but none of other covariates emerged as significant predictors. There were also no main effects of asthma status or parental support. However, a significant interaction between these variables emerged (P = .03; Fig 1, upper panel). Asthmatic patients with less family support were more resistant to hydrocortisone inhibition of IL-5 production, but there was no association between these factors among the healthy children.

For IFN-γ, none of the covariates was a predictor of glucocorticoid sensitivity, and asthmatic patients displayed greater resistance to inhibition than healthy children. There was also a significant interaction between asthma status and parental support (P = .03) that was similar to the IL-5 effect (Fig 1, lower panel); that is, among children with asthma, low parental support was associated with more resistance to hydrocortisone inhibition, whereas these factors were unrelated in healthy children.

For IL-13, the only variable to predict glucocorticoid sensitivity was FEV1 percentage: children with lower pulmonary function were more resistant to hydrocortisone. The main effects of asthma status and parental support and their interaction were nonsignificant.

To further evaluate the role of inhaled corticosteroids in these associations, we redid analyses in the subgroup of asthmatic patients (n = 42) and healthy control subjects (n = 76) who had not used them in the last 2 weeks. The results were identical to those presented above. For both IL-5 and IFN-γ, there were interactions between asthma and support (for IL-5 interaction: B = −0.14, SE = 0.07, P = .05; for IFN-γ interaction: B = −0.16, SE = 0.08, P = .05). In both cases lower support was associated with greater resistance to hydrocortisone inhibition among children with asthma. In the healthy control subjects family support was unrelated to IL-5 hydrocortisone sensitivity but showed a weak positive relation with IFN-γ, which was not significant (P for simple slope = .61). These findings are displayed in Fig 2. There was no interaction for IL-13.

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support was associated with higher ECP concentrations, whereas in healthy children these variables were unrelated.

**DISCUSSION**

Researchers focusing on stress and asthma have long struggled to resolve a paradox: How can stress worsen the disease if it also triggers secretion of cortisol, a hormone that potently suppresses inflammation and is used clinically to ameliorate symptoms? The data from this study suggest that glucocorticoid insensitivity might be one of the mechanisms. We found that to the extent that children with asthma perceived low support from their parents, they were more resistant to hydrocortisone’s anti-inflammatory effects on production of IL-5 and IFN-γ. These factors were unrelated in healthy control subjects.

**TABLE II.** Regression analyses relating family support to cytokine production

<table>
<thead>
<tr>
<th>Predictor</th>
<th>IL-5</th>
<th>IFN-γ</th>
<th>IL-13</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td>β</td>
</tr>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.01</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Sex</td>
<td>−0.04</td>
<td>0.06</td>
<td>−0.05</td>
</tr>
<tr>
<td>Income</td>
<td>−0.03</td>
<td>0.02</td>
<td>−0.17</td>
</tr>
<tr>
<td>Smoke exposure</td>
<td>−0.01</td>
<td>0.02</td>
<td>−0.01</td>
</tr>
<tr>
<td>FEV1</td>
<td>−0.01</td>
<td>0.01</td>
<td>−0.07</td>
</tr>
<tr>
<td>Steroids</td>
<td>−0.23</td>
<td>0.16</td>
<td>−0.21</td>
</tr>
<tr>
<td>β-Agonists</td>
<td>0.16</td>
<td>0.16</td>
<td>0.15</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>−0.06</td>
<td>0.07</td>
<td>−0.09</td>
</tr>
<tr>
<td>Support</td>
<td>−0.01</td>
<td>0.04</td>
<td>−0.02</td>
</tr>
<tr>
<td>Step 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma × support</td>
<td>−0.13</td>
<td>0.06</td>
<td>−0.27</td>
</tr>
</tbody>
</table>

In the IL-5 equation the cumulative percentage variance explained (100 × R²) at steps 1, 2, and 3 was 4.3, 9.4, and 13.7. The parallel figures for the IFN-γ and IL-13 equations were 7.8, 10.6, and 13.9 and 9.6, 10.7, and 11.2, respectively.

*B* , Unstandardized regression coefficient; *SE B*, standard error of regression coefficient; *β*, standardized regression coefficient.

**FIG 1.** Cytokine production as a function of family support. To the extent that they perceived low support from their parents, children with asthma were more resistant to hydrocortisone’s anti-inflammatory effects on production of IL-5 and IFN-γ. These factors were unrelated in healthy control subjects.

**FIG 2.** Cytokine production as a function of family support in children who do not use inhaled corticosteroids regularly. To the extent that they perceived low support from their parents, inhaled corticosteroid–free children with asthma were more resistant to hydrocortisone’s anti-inflammatory effects on production of IL-5 and IFN-γ. These factors were unrelated in healthy control subjects.
parent-child relations, and perhaps stress more generally, worsens asthma by diminishing cortisol’s ability to regulate IL-5 activity and subsequent eosinophilic inflammation.

IFN-γ’s role in this chain of events is unclear. We found that among children with low parental support, hydrocortisone was less able to suppress IFN-γ production. If this dynamic increases levels of IFN-γ in the airways, it might be expected to positively influence disease because this molecule is a potent inhibitor of Th2 cytokines, such as IL-5, that promote eosinophilic inflammation. However, recent evidence indicates that IFN-γ is often present at fairly high levels in the airways of asthmatic patients, and some have argued that it even contributes to asthma pathogenesis by coordinating epithelial responses to viral infection.\(^3\) Another possibility is that by diminishing cortisol’s ability to regulate IL-5 activity could amplify the antiviral immune response and thereby contribute to inflammation and obstruction of the airways. Consistent with this reasoning, studies indicate that stress accentuates the proinflammatory cytokine response to respiratory pathogens.\(^4\) These data highlight the importance of family relationships in asthma. Parental support has long been viewed as an essential component of childhood asthma management, but the prevailing assumption has been that its benefits are primarily attributable to improved compliance with medication and avoidance of asthma triggers. However, these data add to growing evidence that familial relations also have a more direct influence on the biologic processes that drive asthma pathogenesis.\(^7\) For example, other studies have shown that in children with asthma, impaired family functioning is related to higher levels of IgE, greater lymphocyte proliferative responses to allergic triggers, and heightened production of Th2 cytokines, as well as to clinical outcomes, such as the onset of wheezing and asthma and the expression of symptoms in daily life.\(^8\) A lack of parental support might be one of the critical mechanisms underlying these associations because of its importance in facilitating effective coping, emotional adjustment, and treatment adherence.\(^3\)

These data also converge with research indicating that stress alters cortisol-signaling dynamics in children with asthma. For example, asthmatic children display blunted cortisol responses to acute psychologic stress and, when they are exposed to familial turmoil and other life events, express markedly less GR mRNA in leukocytes.\(^24\) In animal models stress-induced blunting of cortisol output has been linked with greater bronchial reactivity and more cellular infiltration of the airways.\(^40\) Collectively, these findings suggest that stress has the capacity to broadly impair cortisol-related signaling in asthma, not only by reducing the expression of relevant ligands and receptors but also by impairing lymphocytes’ ability to register and respond to signals from cortisol.

Thus our findings might have implications for understanding why some asthmatic patients have suboptimal responses to glucocorticoid therapy.\(^2\) Most of these patients have an acquired form of glucocorticoid resistance thought to arise from heavy exposure to allergens, infection with microbial superantigens, or genetic predisposition.\(^41\) Our data suggest that unsupportive parental relationships could play a role in the response to glucocorticoid therapy as well. The mechanisms underlying such an effect are not clear but could include poor medication compliance or stress-related downregulation of GR.\(^24\) It is also interesting to note that interpersonal difficulties are associated with increased activation of nuclear factor κB–dependent genes in monocytes, a pattern that is also seen in the bronchoalveolar lavage fluid of glucocorticoid-resistant asthmatic patients.\(^45\) Thus upregulation of the classical macrophage activation pathway is another potential mechanism contributing to the findings herein.
Our data also suggest that familial dynamics relate to cytokine activity differently in healthy children and asthmatic patients. Although low parental support was associated with hydrocortisone resistance in the asthmatic sample, these factors were unrelated in control subjects. This pattern of findings was unexpected. Other studies have found linkages between difficult family situations and resistance to glucocorticoids in healthy subjects. However, in these projects the stressors were severe and chronic; for example, the subjects had spouses or children with cancer. Thus it might be that healthy subjects have a relatively high threshold for stress-related changes in glucocorticoid sensitivity compared with asthmatic patients.

This study has several limitations. First, it is based on a small group of children who generally had well-controlled asthma and good family functioning, and as such, its generalizability might be limited.

Second, it focused on support from parents, which is just one of several important dimensions of family functioning in asthma, along with family conflict, parenting difficulties, and mental health status. Future work will need to explore the relative contributions of these processes and pay more careful attention to issues such as chronicity of exposure and variation across demographic groups.

Third, the assays used to index glucocorticoid sensitivity were carried out in vitro and made use of a nonspecific mitogen cocktail. Future research will need to substantiate these findings in conditions that more closely approximate the airway milieu.

Finally, because the project’s design was cross-sectional, it is impossible to make causal inferences from the data. We have ruled out some of the most plausible alternative explanations for the observed patterns, including differences in socioeconomic conditions, cigarette exposure, disease severity, and medication use. Nonetheless, other (unmeasured) confounders could have contributed to the associations.

Despite these limitations, the study begins to shed light on a long-standing paradox about the role of cortisol in linking stress to asthma and in doing so provides some clues about how the social world might affect airway disease. Of course, there are likely to be additional mechanisms involved, such as stress-related shifts in the balance of T-helper 1/T-helper 2 cytokines, and changes in medication adherence, health behavior, and symptom perception, and future research will need to evaluate the relative importance of these pathways. Such work will provide a deeper understanding of potential mechanisms and might inform the development of interventions to improve patient outcomes.

Clinical implications: These findings suggest that strained familial relations diminish cortisol’s ability to regulate cytokines that orchestrate inflammation. By assessing the familial environment and making necessary referrals, clinicians might be able to improve patient outcomes.

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