Socioeconomic Status, Stress, and Immune Markers in Adolescents With Asthma

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Objective: Previous research has demonstrated links between low socioeconomic status (SES) and clinical asthma outcomes, as well as links between stress and asthma. The objective of this study was to test whether adolescents with asthma from different SES backgrounds differed in biological profiles relevant to asthma, including immune and cortisol measures. The second objective was to test whether psychological stress and control beliefs could explain these differences. **Materials and Methods:** Adolescents with persistent asthma from either low ($N = 18$) or high ($N = 12$) SES neighborhoods were interviewed about their stress experiences (chronic stress, acute life events, interpretations of ambiguous life events) and control beliefs. Blood was drawn to assess immune (cytokines, eosinophils, IgE) and neuroendocrine (cortisol) markers associated with asthma. **Results:** Adolescents in the low SES group had significantly higher levels of a stimulated cytokine associated with a Th-2 immune response (IL-5), higher levels of a stimulated cytokine associated with a Th-1 immune response (IFN-γ), and marginally lower morning cortisol values compared with the high SES group. Low SES adolescents also had greater stress experiences and lower beliefs about control over their health. Statistical mediational analyses revealed that stress and control beliefs partially explained the relationship between SES and IL-5/IFN-γ. **Conclusion:** Our finding that low SES was associated with elevations in certain immune responses (IL-5/IFN-γ) in adolescents with asthma suggests the importance of further exploration into relationships between SES and Th-2/Th-1 responses in asthma. Our findings also suggest that psychological stress and control beliefs may provide one explanation for links between SES and immune responses in childhood asthma. **Key words:** socioeconomic status, stress, asthma, cytokine production.

SES = socioeconomic status.

INTRODUCTION

Asthma is a disease involving inflammation of the airways. Some researchers have argued that cytokines play a critical role in coordinating the events related to airway inflammation (1). For example, exposure to antigens (eg, environmental allergens) provokes activation of certain types of T helper (Th) cells. Th-1 cells are essential for cellular immunity, whereas Th-2 cells promote B cell production and differentiation (humoral immunity). T cell secretion of certain cytokines (eg, IL-4) induces B cells to switch to producing IgE antibodies. IgE initiates an inflammatory cascade leading to airway constriction and mucus production. The longer-lasting inflammatory response involves recruitment of eosinophils to the airways, which also promotes airway inflammation and obstruction. T cell secretion of IL-5 increases eosinophil production. Thus some researchers have argued that the inflammatory response in asthma involves a Th-2 mechanism (eg, IL4, IL-5 cytokines) (1–3).

Research has demonstrated that patients with asthma differ from healthy individuals in cytokine profiles. Patients with asthma have cells that produce higher levels of cytokines such as IL-4 and IL-5 (4–6), as well as greater expression of mRNA for IL-4 and IL-5 (7–9) compared with healthy individuals. Within samples of patients with asthma, cytokines have been linked to clinically relevant variables. For example, allergen challenge produces greater expression of IL-4 and IL-5 mRNA (10), and symptomatic patients with asthma have higher levels of IL-5 compared with nonsymptomatic patients (5). Administration of IL-4 or IL-5 causes an increase in eosinophils and bronchial responsiveness in patients with asthma (11,12). In addition, expression of IL-5 mRNA is greater in patients with more severe disease (8).

This previous research has demonstrated variability in cytokines within patients with asthma. Our interest was in whether social and psychological factors can be linked to the variability in immune profiles among adolescents with asthma. In the present study, we focused on two social environment factors that have been commonly linked to asthma: socioeconomic status (SES) and stress. In particular, we tested whether adolescents with asthma from low SES versus high SES neighborhoods differed in their immune profiles, and if so, whether psychological stress could explain this association.

Clinical Evidence for SES, Stress, and Asthma Relationships

Lower SES has a profound effect on physical health throughout the lifespan (17–19). Previous research has demonstrated associations of SES with clinical indicators of asthma. For example, epidemiological studies have documented that lower SES children have more severe cases of asthma (13–16). In addition, lower SES has been associated with poorer psychological profiles (20). In healthy children, low SES has been associated with more frequent exposure to stressful life events (21–23), and children who live in low SES neighborhoods are more likely to report witnessing incidents of violence (24). Low SES also has been associated with greater threat interpretations during ambiguous life situations. That is, when presented with the same ambiguous event, low-SES adolescents are more likely than high-SES adolescents to interpret it as threatening (25,26), indicating that not only are low-SES children experiencing life stressors more frequently, but that the same event can have greater impact on low SES children.

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Received for publication August 30, 2002; revision received May 2, 2003.
DOI: 10.1097/01.PSY.0000097340.54195.3C

0033-3174/03/6506-0984

Clinical research has demonstrated that stress in turn is associated with asthma outcomes. Among a sample of children with moderate to severe asthma, experiencing an acute negative life event increased children's risk for an asthma attack 4 to 6 weeks after the event (27). Moreover, of children with ongoing chronic stress, those experiencing an acute life event had greater risk for an asthma attack within 2 weeks of the acute event (27). In daily diary studies of patients with asthma, life stressors have been associated with same-day lower peak expiratory flow rate and greater self-report of asthma symptoms (28). Additionally, number of asthma exacerbations induced by colds was found to be higher in adults with asthma who had high numbers of negative life events and low social support (29). Finally, perceived stress has been linked to development of asthma-related symptoms. Parental reports of stress have been prospectively associated with risk of wheezing among children during the first 2 years of life (30).

The present study seeks to elaborate on previous clinical findings by testing associations of SES with immune variables relevant to asthma. In addition, given that lower SES has been associated with lower control beliefs (33), and that greater beliefs about asthma self-efficacy have been associated with better asthma status and better asthma management practices (34), the present study will test the roles of both psychological control beliefs and stress in the relationship between SES and asthma-related immune measures.

Immunological Evidence for Stress and Cytokines

A variety of studies have shown effects of stress on immune markers of the type that have been implicated in asthma (31,32). In healthy individuals, periods of stress (eg, examinations performed by medical students) are associated with a shift toward increased stimulated Th-2 cytokine (IL-10) production and away from Th1 cytokine (IFN-γ) production, as evidenced by a decreased IFN-γ-to-IL-10 ratio immediately after the examination compared with the ratio at the beginning of the semester (35). This type of shift toward a Th-2 profile during stress could be important in asthma because it could enhance the humoral response to allergens in a way that would promote airway inflammation and obstruction. Indeed, taking a school examination was associated with greater stimulated Th-2 cytokine production (IL-5) in adolescents with asthma compared with healthy control adolescents (36). In addition, even 2 to 3 weeks after the examination, IL-5 levels remained elevated in adolescents with asthma compared with control adolescents (36). School examination among participants with asthma also was associated with greater eosinophil and Th-2 cytokine production (IL-5) in response to an antigen challenge compared with responses of the same students to antigen challenge during a low stress period (no examination) (37). These previous studies have focused specifically on stress effects on cytokine production; the present study is the first that we know of to also consider the effects of the larger social environment (SES) on cytokine profiles.

Role of Cortisol

Cortisol is a hormone secreted by the hypothalamic-pituitary-adrenal (HPA) axis in a diurnal fashion. Different types of stress are thought to produce different effects on cortisol patterns. While earlier reviews suggested that stress was associated with heightened cortisol secretion (38), more recent evidence suggests that the HPA axis habituates quickly to stress, and that cortisol levels can sometimes rebound below normal (39). For example, various types of chronic stressors have been associated with either blunted cortisol levels or flatter cortisol rhythms throughout the day. High levels of work-related burnout are associated with lower levels of cortisol in the morning (40), and high work stress is associated with both lower morning cortisols and flatter cortisol rhythms (41). Posttraumatic stress disorder is associated with lower cortisol levels (42). Women with asthma who have high levels of chronic stress and few resources to cope with stress have the lowest levels of morning cortisol compared with women with low stress or many resources (43). Other evidence suggests different patterns of cortisol secretion in healthy versus chronically ill children. Children with atopic dermatitis had lower cortisol responses to an acute stressor than healthy children (44).

Cortisol in turn has an inhibitory effect on the immune system, signaling immune cells to stop inflammatory processes. Conversely, inadequate HPA axis activity is thought to be associated with an immune system that is overactive (45). Empirical evidence for this link has been demonstrated in genetically altered Lewis rats, who are highly susceptible to inflammatory diseases, and who have been shown to have reduced cortisol responses during stress (46). Thus, one possible mechanism is that children with asthma who experience high levels of chronic life stress will have lower cortisol levels and/or flatter cortisol rhythms, which could result in the inflammatory processes related to asthma flourishing unchecked.

The Present Study

The goals of the present study were: (1) to test whether adolescents with asthma from different SES groups differed in their immune and cortisol profiles and (2) to test whether stress and control beliefs could explain these differences. Through this design, we are testing the question of what factors are associated with variability within childhood asthma. In addition, because our primary question of interest is whether variations in asthma biological markers can be attributed to SES, it was important to recruit a sample that differed in SES, but not on other variables. Thus we kept clinical severity level of asthma equivalent across SES groups; otherwise, it would be difficult to determine whether biological differences were caused by severity differences or caused by SES differences. This approach is similar to other studies that have examined stress and peak flow rates or antigen challenge responses among patients within restricted categories of severity (14,27).

We tested three hypotheses about relationships among SES, psychological stress and beliefs, and immune and neu-

roendocrine markers in adolescents with persistent asthma: (1) low SES adolescents will have greater stress experiences (greater acute life stress, greater chronic life stress, and greater threat interpretations during ambiguous situations) and lower control beliefs (believing that they have less control over their asthma than others do); (2) low-SES adolescents will have higher levels of inflammatory markers (eg, higher stimulated Th-2 cytokines) as well as lower levels of cortisol; and (3) low SES will be associated with this inflammatory/neuroendocrine pattern because of adolescents' stress experiences and control beliefs (ie, stress/control beliefs will mediate the relationship between SES and immune/neuroendocrine responses).

PATIENTS AND METHODS

Participants

Participants were 30 adolescents, ages 13 to 18, with persistent asthma (ie, required regular use of antiinflammatory medications to maintain control over asthma symptoms). Participants were recruited from St. Louis Children's Hospital Division of Allergy and Pulmonary Medicine, and all were undergoing the care of one of two physicians in the Division (to minimize physician variability in asthma diagnosis or management). Fifty three percent were black (47% white) and 60% were male. Participants were recruited if they had persistent asthma but had no other chronic illnesses. To test our hypotheses about SES, we recruited a group of low-SES and a group of high-SES adolescents. Eligibility criteria included families coming from either a low-SES neighborhood (>20% of people in the neighborhood living below poverty level, based on 1990 United States Census tract data) or a high-SES neighborhood (<5% of people living below poverty level). Eighteen low-SES and 12 high-SES adolescents participated in the study.

Measures of Stress

CAUSE Videos

As a measure of interpretations of potentially stressful ambiguous events, the Cognitive Appraisal and Understanding of Social Events (CAUSE) videos were designed to present adolescents with life situations that are either ambiguous or negative in outcome (26). The videos are used to investigate differences in adolescents' interpretations when the situations (videos) are kept constant across all participants. One ambiguous and one negative CAUSE video were used in the present study. The ambiguous video "shopping" depicts a teenager browsing in a department store with a potentially suspicious saleswoman and security guard nearby. The negative video "Caught in the Act" depicts a high school student being teased in class, reacting to the other students, and then being reprimanded by the teacher. Each video is slightly more than 3 minutes in length. Instructions state that participants should experience the video as if it were happening to them. After each video, participants were asked open-ended questions about their interpretations of the videos (eg, "Why do you think the teacher has asked to speak with you?"). Responses were audio taped and coded for threat interpretations on a 5-point scale, ranging from -2 (very benign) to $^{+}2$ (very threatening). Previous work demonstrated that responses can be reliably coded, with two raters agreeing within 1 point 89% to 94% of the time (26,47). Raters were kept blind to the SES of the participant.

UCLA Life Stress Interview

Adolescents were interviewed about chronic and acute stress experiences over the previous 6 months. This interview was modeled after the UCLA Life Stress Interview (LSI) (48), with age-appropriate modifications (the original interview was designed for adults). This semi-structured interview asked about stresses in six different domains (friends, family, school, finances, health, neighborhood). Events were coded as either chronic (no discrete onset/offset, lasting longer than 3 months) or acute. Chronic stress was rated in each domain on a 5-point scale, with higher numbers reflecting more stress. Average chronic stress was calculated as the mean rating across all domains except health (so as not to confound asthma health status with stress). Severity of episodic events was rated by the interviewer, based on the nature of the event and the context in which it occurred (eg, car breaking down is rated as a higher severity event for a single working mother with two children and no other mode of transportation compared with a married woman who is a homemaker and whose family owns three cars). Severe events were defined as those receiving a rating of 4 or 5 points on a 1-to-5 scale (eg, death of a family member). Good reliability for this interview has been demonstrated, and evidence for validity has been provided through associations of stress ratings with depression (48). Raters were kept blind to the SES of the participant.

Measures of Beliefs

Health Locus of Control Scale (HLOC) (49) is an 11-item measure with subscales referring to internal (eg, "If I take care of myself, I can avoid illness") versus external (eg, "Good health is largely a matter of good fortune") beliefs about control. Items are rated on a 6-point scale, with higher scores indicating greater external locus of control. Discriminant validity and test-retest reliability have been demonstrated for this scale (49).

Asthma-specific beliefs were also assessed using two open-ended questions related to asthma care. Adolescents were asked about the person they believed knew best about their asthma and about their attitudes toward using the emergency department (ED) for their asthma.

Immune and Neuroendocrine Measures

To assess white blood cells' capacity to produce cytokines involved in asthma pathogenesis, Th-1 and Th-2 cytokine secretion in response to mitogen stimulation were measured as an in vitro model similar to antigen exposure in patients with asthma. Our protocol of testing stimulated peripheral blood mononuclear cells (PBMCs) was similar to previous studies on stress and cytokines in asthma (35,36). Studies have demonstrated that peripheral blood measures in asthma are similar to measures taken via bronchoalveolar lavage, and correlate with eosinophil count and disease severity (7,50,51). Heparizined whole blood samples were centrifuged using the Ficoll-histopaque procedure to isolate PBMCs. PBMCs were then incubated with phorbol myristate acetate (PMA 25 ng/ml) ionomycin (INO 1 M/ml) for a period of 48 hours at 37°C in 5% CO_2. This dose was determined to be the optimal concentration in previous testing by the Clinical Immunology Laboratory. The use of a single-dose stimulation parallels the techniques used in other studies of stimulated cytokines inpatient and healthy samples (35,36,52,53), and analyses on optimal dose concentration have been reported to be equivalent to repeated measures analyses conducted on multiple concentrations (54). After the samples were removed from the incubator, they were centrifuged for 10 minutes at 1400 rpm. The supernatants were harvested and stored at -70°C until they were assayed for IL-4, IL-5, and IFN-γ concentrations using commercially available ELISAs (Amersham Life Science, Arlington Heights, IL). Cytokine values are expressed as stimulated minus unstimulated values, as recommended by other researchers (54). The intraassay and interassay coefficients of variance are less than 10%. In addition, blood from a healthy control participant (a member of the laboratory) was drawn each day that an asthma participant was studied, within 1 hour of the patient's blood being drawn, and immune values for the healthy subject were used as a statistical control for day-to-day assay variability, as recommended by Schleifer et al. (55).

A complete blood count with differential (Sysmex XE2100; Roche, Basel, Switzerland) was performed to enumerate eosinophil count. Total circulating IgE levels were enumerated using standard commercially available nephelometry (Dade Behring, Chicago, IL). The St. Louis Children's Hospital Clinical Immunology Laboratory performed all immunologic assays. Blood draw was unable to be completed on one low-SES participant; otherwise, all immune and neuroendocrine data are complete.

Salivary cortisol samples were taken by subjects, as described. Samples were spun at 3000 rpm for 5 minutes, and then frozen at -70°C until assay. The assay involved time-resolved immunoassay with fluorescence detection using a biotin-CORT conjugate as a tracer and a streptavidin europium label. This assay has a sensitivity of 0.43 nM and assay CVs of less than 10%. Samples were shipped on dry ice to Dr. Clemens Kirschbaum at the Univer-

sity of Dusseldorf, Germany, where assays were performed. Cortisol values were log-transformed, following procedures in previous studies (56). To measure area under the curve (the total volume of cortisol secretion over the day), the trapezoidal method was used such that higher values reflect greater cortisol release.

Asthma steroid medication was assessed by asking participants what types of medications they were currently using for their asthma and asking them to bring these medications to their laboratory visit. All asthma medication names were recorded directly from the bottles or inhalers (to maximize accuracy of reporting of medications). Medications were classified as inhaled corticosteroids, oral steroids, nonsteroidal antiinflammatory medications, or bronchodilators.

Procedures

This study was approved by the Washington University School of Medicine Institutional Review Board. Families were informed about the study by their physician. Interested families were contacted for detailed discussion of the study. If eligible, they were scheduled for an appointment at the Psychobiology of Health Laboratory. Informed consent was obtained from the parent and assent from the child at the beginning of the laboratory visit. Adolescents were interviewed with the UCLA LSI. They then watched the CAUSE videos (order counterbalanced across all participants) and discussed their interpretations of each video. After the interviews, a certified phlebotomist drew approximately 50 ml of blood through antecubital venipuncture. Adolescents then completed the beliefs questionnaires.

Adolescents were given eight salivettes and a beeper to take home. Participants were asked about their anticipated waking time during the 2 days of saliva collection, and beepers were programmed to sound at 1, 4, 9, and 11 hours after waking over the following 2 days to prompt participants to collect a saliva sample. This schedule yields a robust estimate of diurnal cortisol secretion, as evidenced by previous research demonstrating that using cortisol at these four time points had a reliability of 0.70 with cortisol samples taken every 15 minutes during waking hours on 2 consecutive days (57). Each time participants were beeped, they were instructed to place a cotton roll in their mouth for approximately 1 minute and then put the cotton roll into a salivette tube for storage. Participants were also beeped with a code that they were instructed to write down on the salivette tube, which allowed us to assess compliance with the timing of the salivary cortisol collections. Participants correctly noted an average of 7.15 (SD = 1.10) out of 8 codes. After completing 2 days of saliva collection, participants mailed in the salivettes and beeper in a prestamped envelope and received $75 compensation for their study participation.

Data Analyses

All analyses were conducted comparing the low-SES group with the high-SES group on psychological and biological outcome variables. Most analyses used *t* tests. However, in some cases in which it was necessary to include covariates (described), ANCOVAs were used. In addition, for cytokine measures, immune values for the healthy subject measured on the same day were used as a control for day-to-day assay variations. Thus all immune analyses were conducted as ANCOVAs, covarying the healthy participant's immune values. Race, age, and gender were not associated with immune or neuroendocrine outcomes ($p > 0.10$), and thus were not included as controls in analyses reported.

RESULTS

Descriptive Information

Patients from the low-SES group did not differ from patients in the high-SES group in terms of age or gender (M = 15.4 and 14.8, respectively, for age; 67% and 50% male, respectively; $p > 0.10$). As expected, patients from the low-SES group were more likely to be black (72%) compared with patients from the high-SES group (17%, $\chi^2 = 10.87$, $p < 0.01$). However, race was not associated with any of the immune or cortisol variables ($p > 0.10$).

Most patients (80%) had severe persistent asthma, as defined by the National Heart, Lung, and Blood Institute's Guidelines for the Diagnosis and Management of Asthma (58). There was no difference by SES group in asthma severity level ($p > 0.10$), and asthma severity category was not related to immune markers or cortisol levels ($p > 0.10$). In terms of medications, most patients were on inhaled corticosteroids (93%) and were not using oral corticosteroids (prednisone) (90%). There was no difference by SES group in likelihood of taking inhaled steroids, oral steroids, nonsteroidal antiinflammatory medications, or bronchodilators ($p > 0.10$). Use of inhaled steroids, oral steroids, nonsteroidal antiinflammatory medications, and bronchodilators was not related to any immune markers ($p > 0.10$), but there was a relationship with cortisol area-under-the-curve levels [t (28) = 2.04, $p = 0.05$], with those using oral steroids having higher cortisol output. The higher cortisol level is likely caused by cross reaction in the assay; thus, all analyses with cortisol reported were conducted controlling for steroid use.

SES and Immune/Neuroendocrine Markers

See Table 1 for descriptives regarding stimulated and unstimulated cytokine values. The low-SES group had greater stimulated IL-5 (Th-2) production [F (1, 26) = 4.53, $p < 0.05$], and greater stimulated IFN-γ (Th-1) production compared with the high-SES group [F (1, 26) = 4.52, $p < 0.05$]. No significant differences were found for IL-4 (low-SES group: M = 9.33 pg/ml, SD = 12.36; high-SES group: M = 5.62 pg/ml, SD = 8.04) [F (1, 26) = 2.46, $p = 0.13$], IgE (low-SES group: M = 382.53 IU/ml, SD = 468.26; high-SES group: M = 231.50 IU/ml, SD = 266.10) [t (27) = 1.00, not significant], or numbers of peripheral blood eosinophils (low-SES group: M = 0.35 K/cumm, SD = 0.27; high-SES group: M = 0.35 K/cumm, SD = 0.19) [t (27) = 0.04, not significant].

The low-SES group had marginally lower morning cortisol levels (first sample of the day: M = 0.85 nmol/L, SD = 0.35) compared with the high-SES group (M = 1.01 nmol/L, SD =

TABLE 1. Stimulated and Unstimulated Values for Cytokine Assays[a]

	Low SES (n = 17)		High SES (n = 12)	
	M	SD	M	SD
IL-4				
Stimulated	9.42	12.46	5.78	8.18
Unstimulated	0.09	0.29	0.16	0.37
IL-5				
Stimulated[b]	1764.64	1174.90	831.16	754.65
Unstimulated	42.57	70.80	14.79	41.96
IFN-γ				
Stimulated[b]	13628.52	11390.12	6413.42	4647.64
Unstimulated	39.41	112.39	79.75	145.85

[a] All values are expressed as pg/ml.

[b] $p < .05$ for the difference between low and high SES adolescents for stimulated minus unstimulated cytokine values. Unstimulated values do not differ between low and high SES participants for any cytokine.

0.25) [F (1, 26) = 3.03, $p < 0.10$]. No differences were found for area-under-the-curve cortisol concentrations [F (1, 26) = 0.29, not significant].

SES and Stress

Low-SES adolescents were rated as having greater chronic stress (LSI measure) in their lives (M = 2.92, SD = 0.57) [t (28) = 6.63, $p < 0.001$], as well as being more likely to experience a severe acute event (LSI measure) in the previous 6 months (72%) [$\chi^2 = 6.5, p < 0.025$] compared with high-SES adolescents (M = 1.70, SD = 0.36, and 25%, respectively).

Consistent with previous work (25,26), low-SES adolescents also reported greater threat interpretations (low-SES group: M = 0.50, SD = 0.29) during the ambiguous CAUSE video compared with high-SES adolescents (M = −0.83, SD = 0.32) [t (28) = 2.99, $p < 0.01$]. In contrast, no differences emerged in interpretations for the negative video [t (28) = 0.25, not significant].

SES and Control Beliefs

Low-SES adolescents' scores on the HLOC measure of external locus of control were significantly higher (M = 24.17, SD = 5.22) than those of high-SES adolescents (M = 17.18, SD = 3.54) [t (27) = 3.91, $p < 0.01$]. With respect to asthma-specific beliefs, high-SES adolescents were more likely to report that they were the person who knew best about their asthma, whereas low-SES adolescents were more likely to report that others (eg, their doctor) knew best about their asthma [$\chi^2 = 6.4, p < 0.05$]. In addition, low-SES adolescents were more likely to indicate that the ED was there to help them during times when their asthma got out of control, whereas high-SES adolescents were more likely to indicate that the ED was a place that could be avoided if they were taking good care of their asthma [$\chi^2 = 3.9, p < 0.05$] (Figure 1).

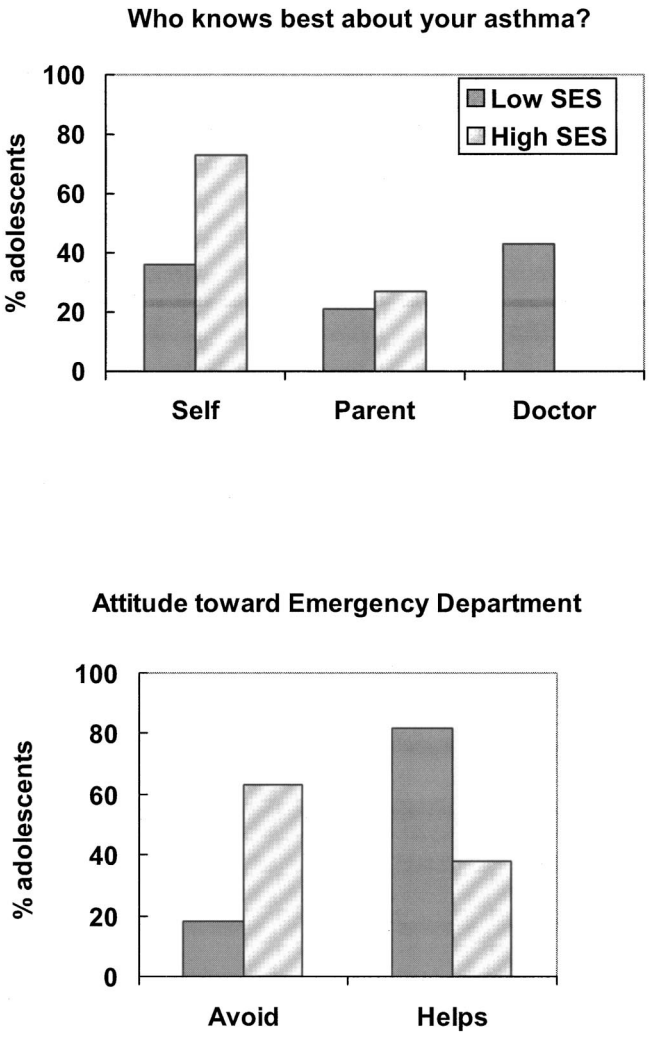

Figure 1. Differences in beliefs for low- and high-SES adolescents. Avoid = belief that emergency department can be avoided if you take good care of your asthma. Helps = belief that emergency department is there to help you during times when asthma gets out of control. In the top graph, the percentage for high-SES children in the "Doctor" column = 0.

Mediational Analyses

To assess whether stress/beliefs operated as a pathway through which SES is associated with cytokine measures (we did not test mediators of cortisol, given the marginal effects), we followed Stone's recommendations for testing statistical mediation (59). Three criteria must be met for data to be consistent with a mediational model: (1) the predictor variable must be associated with the proposed mediator; (2) the predictor variable must be associated with the outcome variable; and (3) the magnitude of the association between the predictor and outcome variables must be reduced when the proposed mediator is statistically controlled.

Step 1 (SES and stress/control beliefs) was reported earlier. To test step 2, we regressed immune measures onto SES (controlling for the healthy control participant's immune values). To test step 3, we conducted analyses in which immune measures were regressed onto healthy control immune values and stress or control beliefs in the first step, and then SES was entered in the second step. The difference between the estimates of variance attributable to SES in the regression analyses for step 2 versus step 3 indicates the extent to which stress or control beliefs mediate the SES-immune relationships. See Table 2 for a summary of the mediational findings.

SES accounts for 14.0% of the variance in IL-5 [R^2 = 0.140, beta = −0.38, t = 2.13, $p < 0.05$]. A stress score was calculated by combining the two stress measures. The CAUSE video score and LSI stress score were each standardized and then the two standardized scores were summed. When stress is partialled out, SES accounts for only 3.4% of the variance in IL-5, representing a decrease of 76%. In addition, SES is no longer a significant predictor of IL-5 when stress is controlled.

SES accounts for 14.8% of the variance in IFN-γ [R^2 = 0.148, beta = −0.38, t = 2.12, $p < 0.05$]. When stress is partialled out, SES accounts for only 9.1% of the variance in IFN-γ, representing a decrease of 38%. In addition, SES is no longer a significant predictor of IFN- γ when stress is controlled.

Turning to the mediational role of control beliefs, SES accounts for 14.0% of the variance in IL-5, as reported. When

TABLE 2. Mediational Analyses Investigating the Role of Psychological Variables in Explaining SES-Immune Relationships[a]

	R^2 (% Variance SES Accounts for in Immune Measure)	Regression Coefficient	*t*	*p*
IL-5	14.0	–0.38	2.13	<.05
Controlling for stress	3.4	–0.18	1.03	ns
Controlling for beliefs	3.4	–0.18	1.01	ns
IFN-γ	14.8	–0.38	2.12	<.05
Controlling for stress	9.1	–0.30	1.64	ns
Controlling for beliefs	7.4	–0.27	1.44	ns

[a] *t* and *p* values indicate the statistical significance of SES in predicting immune values.

beliefs (only HLOC score used, given that the other belief questions contained nominal categories of responses that could not be aggregated) are partialled out, SES accounts for only 3.4% of the variance in IL-5, which represents a decrease of 76%. In addition, SES is no longer a predictor of IL-5 when beliefs are controlled.

SES accounts for 14.8% of the variance in IFN- γ, as reported. When beliefs are partialled out, SES accounts for only 7.4% of the variance in IFN- γ, which is a decrease of 50%. In addition, SES is no longer a significant predictor of IFN- γ when beliefs are controlled.

Additional Analyses

Although asthma severity and steroid use were not associated with either SES or immune variables, we repeated the aforementioned analyses controlling for both factors as a more conservative approach to analyses. After including severity and steroid use as additional controls, the same patterns of significant and nonsignificant differences between SES group in immune/neuroendocrine measures emerged, with the SES differences in morning cortisol becoming slightly stronger [$F(1, 25) = 3.72$, $p = 0.06$] compared with analyses performed without control variables. In mediational analyses, the psychological variables (stress, control beliefs) still reduced the variance in immune measures accounted for by SES even after controlling for severity and steroid use.

Separating out the stress components (exposure to chronic stress vs. appraisals of stress) produced similar patterns of mediational findings, suggesting that the effects are not due to one specific component of stress. In addition, stress and control beliefs were moderately correlated [$r(29) = 0.45$, $p < 0.025$], suggesting that although they share variance, the mediational effects of stress are not identical to the mediational effects of control beliefs. When stress and control beliefs are both controlled, SES accounts for only 0.4% of the variance in IL-5 (a 97% reduction) and only 5.8% of the variance in IFN-γ (a 61% reduction). In both cases, SES is no longer a significant predictor of IL-5 or IFN- γ ($p > 0.10$). Overall, the results of this study are consistent with our hypotheses that SES would be associated with asthma-related immune measures and that psychological stress and control beliefs would each play roles in explaining the relationship between SES and immune measures.

DISCUSSION

The results from this study advance previous research by highlighting possible biological pathways for explaining links among SES, stress, and asthma. We found that low-SES children had increased numbers of cytokines from peripheral blood lymphocytes stimulated in vitro (IL-5 and IFN-γ) compared with high-SES children. Moreover, the effect sizes for these findings are considered large by Cohen's standards (60), with *d* values ranging from 0.74 to 0.83. This pattern is consistent with the possibility that lower-SES children may respond to exacerbating factors with greater activation of both the Th-1 and Th-2 components of the immune system. However, given the nonspecific mitogen stimulation in this study, these results warrant further exploration and conclusions are speculative. Previous research on SES and asthma draws heavily from the epidemiological literature in demonstrating links between SES and asthma outcomes such as hospitalization rates (13–16,61). The present study is the first that we are aware of to demonstrate a link between SES and immune markers implicated in asthma.

Low-SES adolescents also displayed marginally lower levels of morning cortisol compared with high-SES adolescents. Although only a marginal difference, the effect size was a medium one ($d = 0.50$). This finding is consistent with research that has documented other types of chronic stressors (having a child with a chronic illness, job burnout, work stress) being associated with lower morning cortisol levels (40,41,62). Low levels of morning cortisol may indicate a less active HPA system. In asthma, having a less-active HPA system may mean greater difficulty controlling inflammation, which may result in increased chronic disease severity as well as heightened frequency and severity of exacerbations.

Psychologically, low-SES adolescents with asthma were rated by interviewers as having higher levels of chronic stress, were more likely to report a severe acute life event during the previous 6 months, and were more likely to interpret an ambiguous life situation in a threatening manner. These findings indicate that SES affects multiple dimensions of stress in adolescents, including both stress exposure (more ongoing burdens, events of greater severity) as well as stress appraisals (perceiving the same event in a more threatening fashion). These patterns of associations are similar to ones found in

healthy children (26) and suggest that these psychological characteristics may have more to do with SES background than with the impact of having a chronic illness (21,23).

In addition, the control beliefs of low- and high-SES adolescents with asthma differed. Low-SES children were more likely to believe in the power that others had over their illness, whereas high-SES adolescents were more likely to believe in the control they had over their illness (believing that they are the person that knows best about their asthma, and believing that the ED is a place that can be avoided if one is taking care of one's asthma). These relationships have important potential implications for asthma outcomes, given that they may affect not only biological systems but also behavioral pathways such as asthma self-care management practices (34,63).

Finally, the psychological characteristics of stress and control beliefs accounted for a substantial portion of the variability in SES and cytokine relationships. Both stress and beliefs independently reduced the percentage of variance in IL-5/IFN- γ that SES accounted for by 38% to 76%, and after controlling for these mediators, the relationships between SES and IL-5/IFN-γ were no longer statistically significant. This suggests that stress and control beliefs operate as partial pathways through which low SES comes to be associated with heightened immune responses. Previous research has focused on links between stress and cytokines (36,37). The present study puts these previous findings into a broader context by demonstrating that stress and control beliefs may also help to explain how the larger social environment (low SES) affects cytokine production in adolescents with asthma.

Although asthma is often thought to involve predominantly a Th-2 response, the present study found that SES was associated with the production of stimulated cytokines that have been associated with both the Th-2 response (IL-5) and the Th-1 response (IFN-γ). Some researchers have argued that the Th-2 model is too simplistic, and that IFN-γ also likely contributes to the asthma inflammatory response, given some evidence that both stimulated and serum IFN-γ levels are elevated in patients with asthma (64,65). One interpretation of our findings, then, is that asthma is associated with elevations in inflammatory markers that have been associated with both a Th-2 and Th-1 response (rather than an imbalance between Th-2 and Th-1), and that low-SES adolescents may display multiple types of heightened inflammatory responses to antigens. In addition, the findings with stress in the present study could be considered consistent with previous research demonstrating that stress is associated with elevated IFN-γ in patients with other inflammatory conditions (atopic dermatitis, multiple sclerosis) (66,67). Again, our study findings must be interpreted with caution, given the nonspecific mitogen stimulation and cross-sectional nature of the study.

In the present study, no differences by SES group were found for numbers of peripheral blood eosinophils or IgE levels. The majority of study patients were homogenous in their clinical profile, in terms of having severe asthma and not using oral steroids (factors that can influence levels of these markers). However, unlike the cytokines, which were measured after stimulation with a mitogen, eosinophils and IgE were measured in peripheral blood (basal levels, not in response to stimulation). Given that these immune markers promote responses to antigens, it is possible that differences might have been more marked in contexts where the immune system has been challenged, ie, during periods of asthma exacerbations. In support of this possibility, previous research that used an in vivo antigen challenge paradigm found differences by stress in eosinophil count in response to antigen (37).

Limitations to the present study include the small sample size. It should be noted, however, that this sample size is fairly typical of studies of stress and cytokine production in chronically ill populations (36,37,67). Future replication studies with large samples would help to determine the reliability of associations of SES with cytokines in patients with asthma. Interpretations of the present study also must be cautious because not all biological markers tested in this study varied by SES. In addition, this study measured stimulated cytokines in vitro, which may or may not reflect the in vivo environment and the levels found in the airways. Finally, this study was limited by its ability to assay blood samples only once. Repeated blood draws would provide greater reliability for immune assays, and are warranted in future studies.

The present study addresses the question of whether SES is associated with asthma biological markers in a sample of adolescents who already have asthma. The cross-sectional nature of this study allowed us a preliminary test of associations; however, future studies should use longitudinal designs to track whether SES is associated with patterns of stress over time, whether changes in stress are associated with changes in asthma biological markers, and, lastly, whether changes in these biological markers over time are reflected in changes in clinical asthma indicators over time (eg, changes in severity over time). Thus future longitudinal studies that enroll patients from a wide range of severity levels and that include clinical outcomes (eg, pulmonary function tests, symptom measures, health care use patterns) will allow for a more complete picture of the links among SES, stress, immune/neuroendocrine pathways, and clinical outcomes in asthma.

An additional important question for future studies is whether SES and stress play a role in the development of asthma. Studies that compare samples of healthy children to samples of children with asthma, as well as studies that track healthy children over time to determine whether certain biological responses to stress are associated with greater risk of onset of asthma would contribute important information about the role of SES and stress in triggering asthma. Research in this domain has already been conducted in terms of examining psychosocial predictors of onset of asthma episodes (68–70); further research incorporating biological factors such as cytokine profiles would strengthen our understanding of contributors to childhood asthma.

In sum, we found that low-SES children with persistent asthma had elevated IL-5 and IFN-γ stimulated cytokine levels and marginally blunted morning cortisol levels. Low-SES children also reported greater stress and lower beliefs of

control over their health. Moreover, these stress experiences and beliefs partially mediated the association of SES with IL-5/IFN-γ. A previous review found that in chronically stressed adult populations, stress management intervention was beneficial for producing changes in immune functioning (71). Among the many possible mechanisms linking socioeconomic disadvantage with disease, the path through individually encountered stressors, interpretations of stress, and immune markers is an important one. Clearly, reducing socioeconomic disadvantage is a good health policy. Short of substantially reducing such disadvantage, and mindful of assuming casual relationships from correlational data, our findings suggest the intriguing possibility that interventions aimed at reducing stress experiences (perhaps by modifying interpretations and coping strategies during stressful events), as well as enhancing beliefs about control over one's health, may shift low SES adolescents' immune and cortisol profiles in a direction that could produce beneficial effects for their asthma.

The authors thank Elizabeth Glass and Yvonne Raphaelson for assistance with data collection. The authors also thank Sharon Bader at the Clinical Immunology Laboratory at St. Louis Children's Hospital for performing the immune assays, and Dr. Clemens Kirschbaum at the University of Dusseldorf for performing salivary cortisol assays.

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