Perceived Control and Immune and Pulmonary Outcomes in Children With Asthma

MELISSA JOY GRIFFIN, BSC, AND EDITH CHEN, PHD

Objective: This study tested the relationships between perceived control and biological processes relevant to asthma in children. **Methods:** Forty children diagnosed with asthma completed the Children's Health Locus of Control (CHLC) scale. Participants also completed pulmonary function testing, measuring forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV_1). Blood was drawn to assess immune markers associated with asthma. Specifically, stimulated production of the cytokines interleukin 4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), interferon-γ (IFN-γ), as well as eosinophil count, was measured. At home, participants completed peak expiratory flow rate (PEFR) measures to monitor their daily pulmonary function. **Results:** Higher levels of perceived control were associated with significantly better FVC, FEV_1, and PEFR variability. Higher levels of perceived control were also associated with decreased production of asthma-related cytokines, including IL-4, IL-5, and IL-13. **Conclusion:** These results suggest that psychological processes such as perceived control may play an important role in asthma-related biological processes among children with asthma. **Key words:** asthma, immune, pulmonary, perceived control.

IL = interleukin; **IFN** = interferon; **PEFR** = peak expiratory flow rate; **FVC** = forced vital capacity; **FEV** = forced expiratory volume; **PBMC** = peripheral blood mononuclear cells; **PMA** = phorbol myristate acetate; **INO** = ionomycin; **CHLC** = Children's Health Locus of Control.

INTRODUCTION

Asthma is the most common chronic illness in childhood, affecting approximately 13% of US children under the age of 18 (1). Moreover, childhood asthma is on the rise: asthma cases among US children ages 0 to 17 increased by an average of 4.3% per year from 1980 to 1996 (2). Children with asthma use substantially more health care services and have more school absences than children without asthma (2–4). In addition, the burden of asthma on health care costs has been found to have increased over the past 2 decades (2,5). These epidemiologic patterns highlight the importance of understanding factors that contribute to asthma morbidity in order to begin to reduce the burden of childhood asthma on our society. The present study represents a first step toward this goal of better understanding factors related to asthma by empirically testing links between psychological and immune measures implicated in childhood asthma.

One psychological factor that is commonly linked to health outcomes is perceived control. Perceived control refers to beliefs about the extent to which individuals have control over their lives, either generally or in specific domains such as work or health (also known as internal locus of control). In general, lower levels of perceived control are associated with poorer health outcomes, such as higher mortality rates (6), increased likelihood of illnesses, physical symptoms, and poor physical functioning (7–12). Interventions that provide individuals with control over aspects of their daily lives are associated with better health outcomes, such as fewer medications and lower mortality rates (13–16).

Within the psychoneuroimmunology literature, previous research has aimed to explain relationships between perceived control and health by examining immune measures associated with perceived control. Numerous animal studies exist (e.g., (17,18)), with fewer studies having been conducted in humans. Adult human studies have revealed that lower levels of perceived control were associated with decreased numbers of T cells, typically in response to an acute stressor (19–21). Uncontrollable stressors resulted in lower levels of natural killer cell activity and decreased production of the cytokine interleukin (IL)-6 in adults (22,23), although in one study, an uncontrollable stressor did not produce change in lymphocyte proliferation (24). Finally, in adults, lower levels of perceived work-related control were associated with higher levels of plasma fibrinogen, a risk factor for coronary heart disease (25).

In addition, psychological constructs similar to perceived control have been associated with immune measures in adult human studies. For example, pessimistic attributions for the cause of negative events were associated with lower lymphocyte proliferation in a sample of older adults (26) and with faster CD4 cell decline in adult patients who were human immunodeficiency virus (HIV)+ (27). Similarly, HIV+ adult women who were more pessimistic had lower natural killer cell cytotoxicity, as well as lower percentages of CD8+ T cells (28).

All of the above studies were conducted in adults. In children, the psychoneuroimmunology literature has documented immune effects related to similar constructs, such as depression and stress. For example, depression in children ages 8 to 12 was associated with higher lymphocyte proliferation, whereas depression in adolescents and adults was associated with lower lymphocyte proliferation (29–31). In healthy children, higher levels of stress were associated with lowered mucosal immunity (32). Higher levels of stress also were associated with higher rates of respiratory illness among children who were stress reactive (33). In young children predisposed to atopy, higher levels of caregiver stress have been associated with increased production of the cytokine TNF-α and increased allergen-induced lymphocyte proliferation (34). In adolescents diagnosed with asthma, life stress explained the relationship between socioeconomic status and production of the cytokine IL-5 (35).

However, as far as we are aware, no studies to date have

Received for publication August 16, 2005; revision received January 24, 2006. From the University of British Columbia, Vancouver, British Columbia, Canada.

Address correspondence and reprint requests to Edith Chen, University of British Columbia, Department of Psychology, 2136 West Mall, Vancouver, BC V6T 1Z4 Canada. E-mail: echen@psych.ubc.ca

This research was supported by the NIH Grant HL073975, the Canadian Institutes of Health Research, and the William T. Grant Foundation.

DOI: 10.1097/01.psy.0000221367.96439.da

0033-3174/06/6803-0493

tested whether the psychological construct of perceived control is associated with immune measures in children with asthma, despite the fact that perceived control is linked to asthma outcomes such as quality of life and treatment adherence (36,37). Thus the goal of the present study was to test associations of perceived control with asthma-relevant immune measures in children diagnosed with asthma.

The immune measures we chose for this study were based on current understanding of the biology of asthma. Asthma is marked by allergic inflammation leading to bronchial hyperresponsiveness, airway constriction and increased mucus production (38,39). Research has highlighted the role of cytokines in this inflammatory cascade. Cytokines are extracellular signaling proteins that act on target cells in a variety of ways including cell activation, proliferation, and differentiation (40). In asthma, airborne allergens can enter the body and initiate T helper cells to differentiate into Th-1 or Th-2 cells. Th-2 activation has been shown to trigger the production of the cytokines IL-4, IL-5, and IL-13. These cytokines initiate the inflammatory response in the airways that is characteristic of asthma (40). For example, IL-5 is known to activate eosinophils, a type of leukocyte considered to be one of the principal inflammatory cells in the pathogenesis of asthma. When activated, eosinophils secrete proteins that damage the bronchial epithelium, increase mucous secretion, and cause vasodilation in the airways (41). IL-4 and IL-13 induce B cells to produce IgE antibodies, which initiate an inflammatory cascade leading to airway constriction and mucus production (42). In contrast to Th-2 cytokines, Th-1 cytokines such as interferon γ (IFN-γ) are thought to have an inhibitory effect on Th-2 cells, decreasing the amount of IL-4, IL-5, and IL-13 when present (40).

Thus, the overall aim of this study was to investigate the relationship between perceived health control and specific biological and pulmonary markers related to asthma in a sample of children with asthma. It was hypothesized that higher levels of perceived control would be associated with beneficial profiles in the context of asthma inflammatory markers, as indicated by lower levels of IL-4, IL-5, IL-13, and eosinophils, but higher IFN-γ. It was also hypothesized that higher levels of perceived control would be associated with better pulmonary function, including higher forced expiratory volume (FEV_1)%, higher forced vital capacity (FVC)%, and lower at-home daily peak flow variability.

METHODS

Participants

The sample consisted of 40 children and adolescents with asthma from Vancouver, BC. Families were recruited from the Vancouver community through physician offices, public schools, newspaper ads, and community flyers between June of 2004 and March of 2005. Children were eligible for participation if 1) they had been physician-diagnosed with asthma; 2) they were between the ages of 9 and 18; 3) they had no other chronic medical illnesses; 4) they were English speaking; and 5) they had not had an acute respiratory illness in the previous 4 weeks (if they had, they were rescheduled outside of the 4-week window). Participants had a mean age of 13.4 (SD = 2.8); 68% of the sample was male, and 61% were Caucasian, 24% Asian, and 15% other (primarily mixed race). See Table 1. This study was approved by the research ethics board of the University of British Columbia.

TABLE 1. Sample Descriptive Information ($N = 40$)[a]

Variable	%	M	SD	Range
Gender				
Male	68			
Female	32			
Ethnicity				
Caucasian	61			
Asian	24			
Other	15			
Child age		13.39	2.76	9–18
Medications				
β-2 Agonist	75			
Inhaled glucocorticoid	58			
Antileukotriene	8			
Asthma symptoms		2.59	3.31	0–14
Biological outcome measures				
PEF % variability		10.82	7.93	3–42
FVC %		103.85	15.57	81–142
FEV_1 %		97.17	13.69	80–126
Eosinophil count ($\times 10^9$ cells/l)		0.34	0.30	0–1.5
IL-4 (pg/ml)		24.27	31.74	0–131
IL-5 (pg/ml)		131.71	88.36	7–452
IL-13 (pg/ml)		600.79	383.61	62–1782
IFN-γ (pg/ml)		30,616.21	22,710.73	210–98,828

PEF = peak expiratory flow (percent variability from morning to night); FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second.
[a] Medications refer to the percentage of children who used each type of medication. Asthma symptoms refers to the average number of days in the past 2 weeks that the child experienced symptoms.

Psychological Measure

The Children's Health Locus of Control (CHLC) scale was used to measure perceived control. This questionnaire contains items in an agree/disagree format (43). Subscales include internal control (the degree to which a child believes that s/he exerts influence over his/her own health), external/chance (the degree to which a child believes that his/her health is controlled by external or outside factors), and powerful others (the degree to which a child believes that his/her health is controlled by people such as a parent, teacher, etc.). In this study, we focused on the internal and external/chance scales, given that these represent the original conceptualization of locus of control (44) and that the powerful others scale contained questions not applicable to asthma (e.g., "Only the dentist can take care of my teeth"). All external/chance items were reverse scored, and then a total score was created by summing the internal control items and the reverse-scored external/chance items, as has been done in other studies (44,45). Thus, higher total scores indicate greater beliefs that a child controls his/her own health. Adequate internal consistency (0.75), test-retest reliability (0.62), and construct validity (0.50 correlation with a general control scale) were demonstrated in a sample of children grades 2 to 6 representing Caucasian, African American, and Hispanic backgrounds (43). This scale is widely used in children (46,47) and has been validated in children as young as 7 (43).

Physiological Measures

Pulmonary Function

Pulmonary function was measured in the laboratory using spirometry (Vmax/Spectra, SensorMedics, Yorba Linda, CA). Measurements included FEV_1, the amount of air forced from the lung during the first second of a forced expiratory maneuver that is started from full lung capacity (maximal inspiration), and FVC, the total amount of air forcefully exhaled following a maximal inspiration. FEV_1 and FVC values are expressed as a percent of predicted values, based on child age, gender, ethnicity, and height. Lower FEV_1 and FVC percentiles indicate poorer pulmonary function.

Daily variability in pulmonary function was monitored at home using an electronic peak flow monitor (Quadromed, Hoechberg, Germany). This monitor measures peak expiratory flow rate (PEFR), which is the maximal exhalation rate achieved during a forced expiratory maneuver, expressed as liters per second. Daily variability in peak flow was calculated as the difference between morning and night peak flow divided by morning peak flow. Variability was averaged over the 14-day monitoring period. Greater variability indicates poorer lung functioning.

Immune Measures

White blood cells' cytokine secretion in response to mitogen stimulation was measured as an in vitro model of allergen exposure, as has been done in previous studies on stress and cytokines in asthma (48,49). 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 (50–52). Twenty milliliters of peripheral blood was drawn into two BD Vacutainer Cell Preparation Tubes containing sodium heparin, and 3×10^6 fresh peripheral blood mononuclear cells (PBMCs) were isolated through density-gradient centrifugation. PBMCs were then resuspended in culture medium consisting of RPMI plus 10% fetal calf serum and stimulated with phorbol myristate acetate (PMA; 25 ng/ml) and ionomycin (INO; 1 μg/ml) for a period of 48 hours at 37°C in 5% CO_2. This PMA/INO combination has been used to stimulate cells in other asthma studies (53,54). Cultures were centrifuged, and then supernatants were aspirated and frozen at −20°C until the end of the study. Supernatants were then assayed to determine levels of IL-4, IL-5, IL-13, and IFN γ using enzyme-linked immunosorbent assays (ELISA) (R&D System, Minneapolis, MN). Previous studies have reported that age is positively correlated with IL-4, IL-5, and IFN-g production in atopic children and adolescents (55); thus, we tested for age as a potential confound in statistical analyses below. Intra-assay CVs ranged from 3.68% to 4.76%.

Another 3 ml of peripheral blood was drawn into an ethylenediaminetetraacetic acid (EDTA) tube for eosinophil counts. A complete blood count with differential (Bayer ADVIA 70 hematology system, Holiston, MA) was performed to enumerate eosinophil count.

Potential Covariates

We measured a set of demographic and medical variables that could be associated with perceived control or immune and pulmonary outcomes. Demographic variables included child age, gender, and ethnicity. Medical variables included asthma symptoms in the past 2 weeks (number of days the child had coughing, wheezing, shortness of breath, or chest tightness during the day; number of days the child was awakened at night with one or more of these symptoms; and number of days the child experienced one or more of these symptoms while playing or exercising), use of inhaled corticosteroid medication, use of β agonist medication, use of antileukotriene medication, and child body mass index (BMI).

Procedure

Families who were interested contacted the laboratory and underwent a screening interview to determine eligibility. Eligible families were then scheduled for a laboratory appointment. Laboratory sessions were scheduled in the afternoon, typically after school hours. Families were mailed written consent forms for the parents and written assent forms for the child to review before their visit. On arrival at the laboratory, the study procedures were reviewed, and any questions from parents and children were answered. Parents and children signed the written consent and assent forms, respectively. A local anesthetic cream (EMLA) was applied to the child's arm in preparation for the blood draw. Height and weight were taken on a standard medical-grade balance beam scale. Pulmonary function was conducted using a spirometer. Children were coached in appropriate blowing techniques, and six to eight trials were done for each child to obtain a laboratory best FEV_1 and FVC, following the spirometry protocols of other large, multisite clinical asthma trials (56). Measures were taken at least 4 hours after the last use of a β agonist. After spirometry, children completed the CHLC on the computer (younger children were given the option of having questions read to them). Then a sample of the child's blood was drawn. Parents were asked to bring in their child's current asthma medications. Medication names were recorded directly from the bottles or inhalers.

At the end of the visit, children were instructed to collect PEFR measures on awakening and before bedtime every day for a 2-week period. The best of three efforts was digitally recorded and stamped for date and time to ensure measures were taken at appropriate times. After completing the 2-week assessment period, children returned the monitors in a prestamped envelope. Participants received an honorarium for their laboratory visit and home monitoring.

Data Analysis

To test associations of locus of control with immune and pulmonary outcomes, bivariate Pearson correlations were conducted. Based on preliminary analyses with demographic and medical variables (see first paragraph of Results section), we included demographic and medical variables as covariates when these variables were significantly associated with primary study variables. Where covariates were included, partial correlations were conducted. Two-tailed tests of significance were utilized for all correlational analyses.

RESULTS

Descriptive information about the sample and variables is presented in Table 1. To identify potential confounders, correlations were first computed between children's demographic and medical characteristics and both the independent variable (locus of control) and dependent variables (immune and pulmonary outcomes). Child gender and use of asthma medications were not associated with locus of control or any immune or pulmonary measures. Child age was inversely associated with eosinophil count ($p <.05$) but was not associated with locus of control, cytokines, or pulmonary measures. Child ethnicity was associated with FVC (Asians having lower FVC than Caucasians or "other," $p < .05$), and child BMI was positively associated with FVC ($p < .05$). Neither ethnicity nor BMI was associated with locus of control, immune outcomes, or FEV_1 or peak flow variability. Greater asthma symptoms were associated with lower FEV_1 and higher IL-4 (p values $<.05$) but were not associated with locus of control or other immune or pulmonary outcomes. Thus, child age was included as a covariate in analyses involving eosinophil count; child ethnicity and BMI as a covariate in analyses involving FVC, and asthma symptoms as a covariate in analyses with FEV_1 and IL-4.

CHLC and Pulmonary Function

CHLC scores were positively associated with FVC percentile after controlling for child ethnicity and BMI ($r = 0.37$, $p < .05$), indicating that higher beliefs of internal control were associated with greater total lung capacity. Locus of control was positively associated with FEV_1 percentile after controlling for asthma symptoms ($r = 0.50$, $p < .01$), indicating that children who perceived greater internal control also exhibited greater forced expiratory volume in the first second. Figure 1 shows the difference in FEV_1 between children low and high on perceived control for illustrative purposes.

With respect to home measures, higher locus of control scores were associated with decreased variability in PEFR

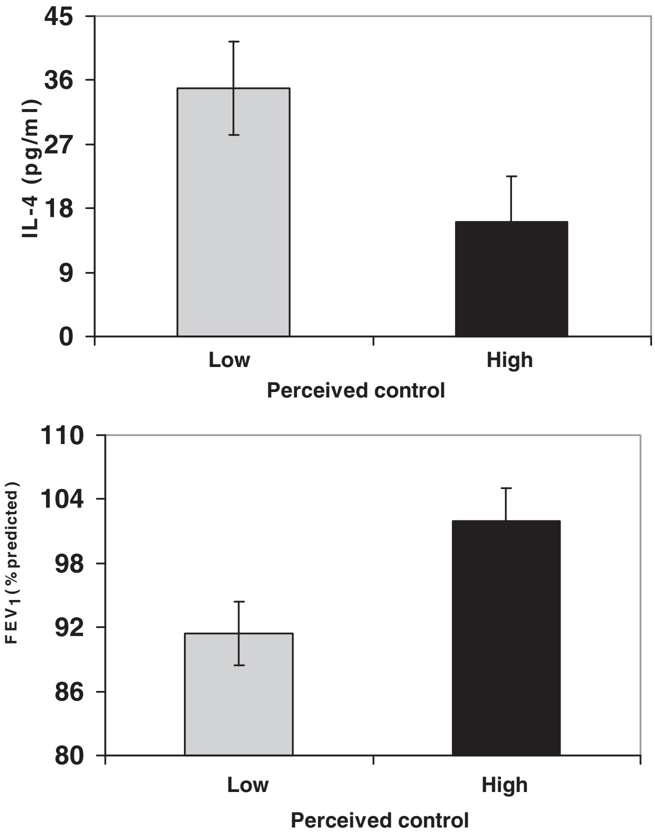

Figure 1. Top panel: Differences in IL-4 production by perceived control. Bottom panel: Differences in FEV_1 by perceived control. These figures provide a graphical illustration of some of the associations reported in Table 2. For illustrative purposes, children were divided using a median split into low and high perceived control. The error bars represent standard error of the mean.

across the 2 weeks ($r = -0.41$, $p < .05$), indicating that children who perceived greater internal control exhibited less variability across the day in their pulmonary function scores.

We also tested whether locus of control was associated with a composite pulmonary function score. This composite measure was calculated by standardizing and then averaging the three pulmonary function variables (FEV_1, FVC, PEFR variability; note that PEFR variability was reverse scored for this composite such that higher scores would indicate better pulmonary function, consistent with FEV_1 and FVC). Higher locus of control scores were associated with a higher pulmonary function composite score ($r = 0.53$; $p < .001$).

CHLC and Immune Outcomes

Intercorrelations among the four cytokines ranged from 0.11 to 0.56. Locus of control scores were negatively associated with stimulated production of cytokines relevant to asthma, including IL-4 ($r = -0.44$, $p < .01$), IL-5 ($r = -0.39$, $p < .05$), and IL-13 ($r = -0.36$, $p < .05$). These findings indicate that higher beliefs of internal control were associated with reduced Th-2 inflammatory response to mitogen stimulation. Figure 1 shows the difference in IL-4 between children low and high on perceived control for illustrative purposes. There was no significant association between locus of control and IFN-γ or eosinophil count.

We also tested whether locus of control was associated with a composite score reflecting Th-2 cytokine production. This composite measure was calculated by standardizing and then averaging the three Th-2 cytokine production variables (IL-4, IL-5, IL-13). Higher locus of control scores were associated with a lower Th-2 composite score ($r = -0.45$, $p < .01$).

Role of Asthma Symptoms

Given that one of the major alternative explanations for our findings could be that children who experience more asthma symptoms both have poorer pulmonary function and perceive less control over their asthma, we recomputed all analyses using partial correlations, controlling for asthma symptoms in order to address this hypothesis. Greater perceived control remained significantly associated with higher FVC ($r = 0.46$, $p < .01$), higher FEV_1 ($r = 0.50$, $p < .01$), and lower peak flow variability ($r = -0.42$, $p < .05$) independent of asthma symptoms. In addition, greater perceived control remained significantly associated with lower IL-4 ($r = -0.44$, $p < .01$), IL-5 ($r = -0.44$, $p < .01$), and IL-13 ($r = -0.42$, $p < .05$) independent of asthma symptoms. As well, the association with eosinophil count independent of asthma symptoms became marginally significant ($r = -0.29$, $p < .10$). See Table 2.

In addition, independent of asthma symptoms, greater perceived control was associated with a higher pulmonary function composite score ($r = 0.59$, $p < .001$), and a lower Th-2 composite score ($r = -.54$, $p < .01$).

DISCUSSION

The results from this study suggest that higher levels of perceived control are associated with better pulmonary and immune outcomes in a sample of children with asthma. More specifically, higher levels of perceived control were associated with greater FVC and FEV_1 in the laboratory, and with less day-to-day variability in peak flow at home. Higher levels of perceived control also were associated with lower levels of stimulated Th-2 cytokine production, including lower IL-4, IL-5, and IL-13. These findings were independent of asthma

TABLE 2. Associations Between Children's Health Locus of Control and Immune and Pulmonary Measures ($N = 40$)[a]

Biological Measure	r
IL-4	−0.44**
IL-5	−0.44**
IL-13	−0.42*
IFN-γ	0.04
Eosinophil count	−0.29†
FEV_1 %	0.50**
FVC %	0.46**
PEF % variability	−0.42*

FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; PEF = peak expiratory flow (percent variability from morning to night);
* $p < .05$; ** $p < .01$; † $p < .10$.
[a] These values represent partial correlations between locus of control (higher values indicating greater internal control) and immune and pulmonary measures, controlling for asthma symptoms.

symptoms and any medical (medication, BMI) and demographic (age, gender, ethnicity) variables associated with outcome variables.

The present study is consistent with previous research on other psychosocial factors and immune measures related to asthma. This research has documented that higher levels of psychosocial stress (as measured via the caregiver) were associated with increased lymphocyte proliferation in response to cockroach and dust mite allergens and higher total IgE levels among young children at risk for atopy (34) and that higher adolescent stress levels explained associations of low SES with greater stimulated production of IL-5 in adolescents with asthma (35). Thus, in addition to high levels of stress, low levels of perceived control appear to be associated with a pattern of heightened inflammatory responses that could be detrimental for childhood asthma.

It should be noted that previous studies in healthy adults have typically found that lower levels of control are associated with down-regulation of immune responses (19,22,23). In contrast, in children related constructs such as depression have been associated with heightened immune responses, such as greater lymphocyte proliferation (30). The present study found that lower levels of perceived control in children were associated with heightened production of asthma-related cytokines. These differences across studies may be due to the fact that many of these previous studies investigated immune responses to acute laboratory stressors (rather than real-life stress), differences in medical status (e.g., children with a chronic illness versus healthy adults), or differences by age in cells' responses to mitogen stimulation (55). Thus, perceived control may have differential immune effects, depending on medical status or age.

Why might higher levels of perceived control be associated with better pulmonary and immune function in children with asthma? One obvious explanation is that children who experience more asthma symptoms have poorer biological profiles (poorer pulmonary function and heightened inflammatory markers) and that experiencing more asthma symptoms leads these children to perceive less control over their health. We tested this possibility by statistically controlling for self-reported asthma symptoms in all analyses and found significant associations of perceived control with pulmonary and immune measures over and above children's level of asthma symptomatology. This suggests that asthma symptoms are not the primary explanation for why perceived control was associated with pulmonary and immune outcomes in this study.

A second possibility is that children with greater adherence to asthma medications have better pulmonary function and reduced inflammatory markers and that these children also perceive greater control over their health. We explored this possibility by testing associations of pulmonary, inflammatory, and perceived control measures with medication use in terms of inhaled corticosteroids, β agonists, and antileukotrienes. No evidence was found that use of these medications was associated with perceived control or pulmonary and immune outcomes in this study, suggesting that relationships between perceived control and biological asthma outcomes cannot be explained solely by adherence to these types of medications.

Another possibility is that health behaviors not measured in this study explain the association between perceived control and pulmonary/immune measures. Aside from medication use, more general health practices (such as smoking, exercising, etc.) and/or better self-management of asthma could account for this relationship. Previous research has shown a relationship between greater internal control and health behaviors, as well as self-management of asthma (57,58). Thus, future studies that explore the ability of these variables to account for relationships between perceived control and biological indicators of disease would be important to conduct.

Finally, it is possible that children who exerted greater effort during testing had higher pulmonary function values and were the same children who were likely to endorse high levels of perceived control. However, this explanation makes less sense with respect to the immune results. Given that findings were robust across peak flow, spirometry, and immune markers, this lends credibility to the associations with perceived control.

In terms of pathways explaining why perceived control is associated with immune and pulmonary measures, one possibility is the endocrine system. For example, perceived control may affect the hypothalamic-pituitary-adrenal axis, as well as the sympathetic-adrenal-medullary axis, which regulates output of hormones such as cortisol, epinephrine, and norepinephrine. Previous research has shown that adults with lower levels of perceived control have a higher cortisol response to laboratory stressors (59,60). In turn, such hormones are implicated in asthma and have been proposed as biological mechanisms for psychological variables affecting asthma (61,62). For example, there is some evidence that high physiologic levels of cortisol can induce a shift toward a Th-2 cytokine response profile (63,64). Future research is needed to empirically test whether endocrine pathways provide a viable explanation for associations between perceived control and immune/pulmonary measures in asthma.

Limitations to the present study include the correlational design. This design makes it difficult to infer directionality from the findings. Although perceived control may lead to improved pulmonary and immune outcomes, it is also possible that better biological profiles among children with asthma lead them to perceive greater control over their health. Longitudinal studies would help clarify the directionality of these findings, an approach our research group is currently undertaking. In addition, the sample size in this study was small. It should be noted, however, that this sample size is fairly typical of other studies of psychological variables and cytokine production in chronically ill populations (35,48,65,66). Future studies with larger samples are necessary to clarify the reliability of associations of perceived control with pulmonary and immune measures. Finally, future studies should include a broad array of psychosocial and biological characteristics to determine the relative importance of perceived control in relation to other child variables.

In conclusion, this study provides evidence that perceived control is associated with pulmonary and immune markers implicated in asthma in a sample of children with asthma. Given the societal burden of childhood asthma, understanding factors that have implications for asthma morbidity could have important public health ramifications. If the directionality were such that perceived control influenced asthma pulmonary and immune outcomes, this would suggest that developing interventions aimed at enhancing perceptions of control could have beneficial effects on asthma morbidity. In addition, if perceptions of control could be altered earlier in life, this might allow children to develop healthier trajectories into adulthood with respect to asthma. Together with an understanding of the role of genetic, environmental, and health care factors, incorporating psychosocial characteristics such as perceived control may help researchers and practitioners develop a fuller understanding of childhood asthma.

REFERENCES

1. Dey AN, Bloom B. Summary Health Statistics for U.S. children: National Health Interview Survey, 2003. In: National Center for Health Statistics, ed. Vital and Health Statistics 2005;223:1–78.
2. Akinbami LJ, Schoendorf KC. Trends in childhood asthma: prevalence, health care utilization, and mortality. Pediatrics 2002;110:315–22.
3. Parcel GS, Gilman SC, Nader PR, Bunce H. A comparison of absentee rates of elementary schoolchildren with asthma and nonasthmatic schoolmates. Pediatrics 1979;64:878–81.
4. Fowler MG, Davenport MG, Garg R. School functioning of US children with asthma. Pediatrics 1992;90:939–44.
5. Asthma: United States, 1980–1987. MMWR Morb Mortal Wkly Rep 1990;39:493–7.
6. Bosma H, Schrijvers C, Mackenbach JP. Socioeconomic inequalities in mortality and importance of perceived control: cohort study. BMJ 1999; 319:1469–70.
7. Seeman M, Seeman TE. Health behavior and personal autonomy: a longitudinal study of the sense of control in illness. J Health Soc Behav 1983;24:144–60.
8. Feldman PJ, Steptoe A. How neighborhoods and physical functioning are related: the roles of neighborhood socioeconomic status, perceived neighborhood strain, and individual health risk factors. Ann Behav Med 2004;27:91–9.
9. Lachman ME, Weaver SL. The sense of control as a moderator of social class differences in health and well-being. J Pers Soc Psychol 1998;74: 763–73.
10. Bosma H, Marmot MG, Hemingway H, Nicholson AC, Brunner E, Stansfeld S. Low job control and risk of coronary heart disease in Whitehall II (prospective cohort) study. BMJ 1997;314:558–65.
11. Marmot MG, Bosma H, Hemingway H, Brunner E, Stansfeld S. Contribution of job control and other risk factors to social variations in coronary heart disease incidence. Lancet 1997;350:235–9.
12. Hemingway H, Marmot M. Psychosocial factors in the aetiology and prognosis of coronary heart disease: systematic review of prospective cohort studies. BMJ 1999;318:1460–7.
13. Rodin J. Aging and health: effects of the sense of control. Science 1986;233:1271–6.
14. Langer EJ, Rodin J. The effects of choice and enhanced personal responsibility for the aged: a field experiment in an institutional setting. J Pers Soc Psychol 1976;34:191–8.
15. Rodin J, Langer EJ. Long-term effects of a control-relevant intervention with institutionalized aged. J Pers Soc Psychol 1977;35:897–902.
16. Schulz R. Effects of control and predictability on physical and psychological well-being of institutionalized aged. J Pers Soc Psychol 1976;33: 563–73.
17. Laudenslager ML, Ryan SM, Drugan RC, Hyson RL, Maier S. Coping and immunosuppression: inescapable but not escapable shock suppresses lymphocyte proliferation. Science 1983;221:568–70.
18. Visintainer MA, Volpicelli JR, Seligman MEP. Tumor rejection in rats after inescapable or escapable shock. Science 1982;216:437–9.
19. Brosschot JF, Godaert GL, Benschop RJ, Olff M, Ballieux RE, Heijnen CJ. Experimental stress and immunological reactivity: a closer look at perceived uncontrollability. Psychosom Med 1998;60:359–61.
20. Brosschot JF, Benschop RJ, Godaert GL, Olff M, De Smet M, Heijnen CJ, Ballieuk RE. Influence of life stress on immunological reactivity to mild psychological stress. Psychosom Med 1994;56:216–24.
21. Wiedenfeld SA, O'Leary A, Bandura A, Brown S, Levine S, Raska K. Impact of perceived self-efficacy in coping with stressors on components of the immune system. J Pers Soc Psychol 1990;59:1082–94.
22. Sieber WJ, Rodin J, Larson L, Ortega S, Cummings N. Modulation of human natural killer cell activity by exposure to uncontrollable stress. Brain Behav Immun 1992;6:141–56.
23. Peters ML, Godaert GL, Ballieux RE, Brosschot JF, Sweep FC, Swinkels LM, et al. Immune responses to experimental stress: effects of mental effort and uncontrollability. Psychosom Med 1999;61:513–24.
24. Weisse CS, Pato CN, McAllister CG, Littman R, Breier A, Paul SM, et al. Differential effects of controllable and uncontrollable acute stress on lymphocyte proliferation and leukocyte percentages in humans. Brain Behav Immun 1990;4:339–51.
25. Brunner E, Smith GD, Marmot M, Canner R, Beksinska M, O'Brien J. Childhood social circumstances and psychosocial and behavioural factors as determinants of plasma fibrinogen. Lancet 1996;347:1008–13.
26. Kamensiegel L, Rodin J, Seligman MEP, Dwyer J. Explanatory style and cell-mediated-immunity in elderly men and women. Health Psychol 1991;10:229–35.
27. Segerstrom SC, Taylor SE, Kemeny ME, Reed GM, Visscher BR. Causal attributions predict rate of immune decline in HIV-seropositive gay men. Health Psychol 1996;15:485–93.
28. Byrnes DM, Antoni MH, Goodkin K, Efantis-Potter J, Asthana D, Simon T, et al. Stressful events, pessimism, natural killer cell cytotoxicity, and cytotoxic/suppressor T cells in HIV+ black women at risk for cervical cancer. Psychosom Med 1998;60:714–22.
29. Kronfol Z. Immune dysregulation in major depression: a critical review of existing evidence. Int J Neuropsychopharmacol 2002;5:333–43.
30. Bartlett JA, Schleifer SJ, Demetrikopoulos MK, Keller SE. Immune differences in children with and without depression. Biol Psychiatry 1995;38:771–4.
31. Schleifer SJ, Bartlett JA, Keller SE, Eckholdt HM, Shiflett SC, Delaney BR. Immunity in adolescents with major depression. J Am Acad Child Adolesc Psychiatry 2002;41:1054–60.
32. Drummond PD, Hewson Bower B. Increased psychosocial stress and decreased mucosal immunity in children with recurrent upper respiratory tract infections. J Psychosom Res 1997;43:271–8.
33. Boyce WT, Chesney M, Alkon A, Tschann JM, Adams S, Chesterman B, et al. Psychobiologic reactivity to stress and childhood respiratory illnesses: results of two prospective studies. Psychosom Med 1995;57: 411–22.
34. Wright RJ, Finn P, Contreras JP, Cohen S, Wright RO, Staudenmayer J, et al. Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy. J Allergy Clin Immunol 2004;113:1051–7.
35. Chen E, Fisher EB Jr, Bacharier LB, Strunk RC. Socioeconomic status, stress, and immune markers in adolescents with asthma. Psychosom Med 2003;65:984–92.
36. Katz PP, Yelin EH, Eisner MD, Blanc PD. Perceived control of asthma and quality of life among adults with asthma. Ann Allergy Asthma Immunol 2002;89:251–8.
37. Scherer YK, Bruce S. Knowledge, attitudes, and self-efficacy and compliance with medical regimen, number of emergency department visits, and hospitalizations in adults with asthma. Heart Lung 2001;30:250–7.
38. Busse WW, Lemanske RF. Advances in immunology: asthma. N Engl J Med 2001;344:350–62.
39. Stirling RG, Chung KF. New immunological approaches and cytokine targets in asthma and allergy. Eur Respir J 2000;16:1158–74.
40. Chung KF, Barnes PJ. Cytokines in asthma. Thorax 1999;54:825–57.
41. Huan-Zhong S. Eosinophils in asthma. Chin Med J 2004;117:792–4.
42. Bacharier LB, Geha RS. Molecular mechanisms of IgE regulation. J Allergy Clin Immunol 2000;105:S547–8.

43. Parcel GS, Meyer MP. Development of an instrument to measure children's health locus of control. Health Educ Monogr 1978;6:149–59.
44. Rotter JB. Generalized expectancies for internal versus external control of reinforcement. Psychol Monogr Gen Appl 1966;80:1–28.
45. Wallston BS, Wallston KA, Kaplean GD, Maides SA. Development and validation of the health locus of control (HLC) scale. J Consult Clin Psychol 1976;44:580–5.
46. Kulby LS, McClellan MS. Effects of self-care instruction on asthmatic children. Issues Pediatr Nurs 1984;7:121–30.
47. Goertzel L, Goertzel T. Health locus of control, self-concept, and anxiety in pediatric cancer patients. Psychol Rep 1991;68:531–40.
48. Kang D, Coe C, McCarthy DO, Jarjour NN, Kelly EA, Rodriguez RR, et al. Cytokine profiles of stimulated blood lymphocytes in asthmatic and healthy adolescents across the school year. J Interferon Cytokine Res 1997;17:481–7.
49. Marshall GD, Agarwal SK, Lloyd C, Cohen L, Henninger EM, Morris GJ. Cytokine dysregulation associated with exam stress in healthy medical students. Brain Behav Immun 1998;12:297–307.
50. Gemou-Engesæth V, Kay AB, Bush A, Corrigan CJ. Activated peripheral blood CD4 and CD8 T-lymphocytes in child asthma: correlation with eosinophilia and disease severity. Pediatr Allergy Immunol 1994;5:170–7.
51. Corrigan CJ, Hamid Q, North J, Barkans J, Moqbel R, Durham S, et al. Peripheral blood CD4 but not CD8 T-lymphocytes in patients with exacerbation of asthma transcribe and translate messenger RNA encoding cytokines which prolong eosinophil survival in the context of Th2-type pattern: effect of glucocorticoid therapy. Am J Respir Cell Mol Biol 1995;12:567–78.
52. Corrigan CJ, Haczku A, Gemou-Engesæth V, Doi S, Kikuchi S, Takatsu K, et al. CD4 T-lymphocyte activation in asthma is accompanied by increase serum concentrations of interleukin-5. Am Rev Respir Dis 1993;147:540–7.
53. Schuerwegh AJ, De Clerck LS, De Schutter L, Bridts CH, Verbruggen A, Stevens WJ. Flow cytometric detection of type 1 (IL-2, IFN-γ) and type 2 (IL-4, IL-5) cytokines in T-helper and T-suppressor/cytotoxic cells in rheumatoid arthritis, allergic asthma and atopic dermatitis. Cytokine 1999;11:783–8.
54. Magnan AO, Mely LG, Camilla CA, Badier MM, Montero-Julian FA, Guillot CM, et al. Assessment of the Th1/Th2 paradigm in whole blood in atopy and asthma: increased IFN-γ-producing $CD8^+$ T cells in asthma. Am J Respir Crit Care Med 2000;161:1790–6.
55. Smart JM, Kemp AS. Ontongeny of T-helper 1 and T-helper 2 cytokine production in childhood. Pediatr Allergy Immunol 2001;12:181–7.
56. Childhood Asthma Management Program Research Group. The Childhood Asthma Management Program (CAMP): design, rationale, and methods. Control Clin Trials 1999;20:91–120.
57. Guevara JP, Wolf FM, Grum CM, Clark NM. Effects of educational interventions for self management of asthma in children and adolescents. Br J Med 2003;326:1308–9.
58. Steptoe A, Wardle J. Locus of control and health behaviour revisited: a multivariate analysis of young adults from 18 countries. Br J Psychol 2001;92:659–72.
59. Pruessner JC, Gaab J, Hellhammer DH, Lintz D, Schommer N, Kirschbaum C. Increasing correlations between personality traits and cortisol stress responses obtained by data aggregation. Psychoneuroendocrinology 1997;22:615–25.
60. Bollini AM, Walker EF, Hamann S, Kestler L. The influence of perceived control and locus of control on the cortisol and subjective responses to stress. Biol Psychol 2004;67:245–60.
61. Wright RJ, Rodriguez M, Cohen S. Review of psychosocial stress and asthma: an integrated biopsychosocial approach. Thorax 1998;53:1066–74.
62. Cohen S, Rodriguez M. Stress, viral respiratory infections, and asthma. In: Skoner DP, ed. Asthma and Respiratory Infection. New York, NY: Marcel Decker; 1999.
63. Snijdewint FGM, Kapsenberg ML, Wauben-Penris PJJ, Bos JD. Corticosteroids class-dependently inhibit in vitro Th1- and Th2-type cytokine production. Immunopharmacology 1995;29:93–101.
64. Wu CY, Sarfati M, Heusser C, Fournier S, Rubio-Trujillo M, Peleman R, et al. Glucocorticoids increase the synthesis of immunoglobulin E by interleukin 4-stimulated human lymphocytes. J Clin Invest 1991;87:870–7.
65. Liu LY, Coe CL, Swenson CA, Kelly EA, Kita H, Busse WW. School examinations enhance airway inflammation to antigen challenge. Am J Respir Crit Care Med 2002;165:1062–7.
66. Ackerman KD, Martino M, Heyman R, Moyna NM, Rabin BS. Stress-induced alteration of cytokine production in multiple sclerosis patients and controls. Psychosom Med 1998;60:484–91.