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 (FEV₁). 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, FEV₁, 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.

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).

IL = interleukin; IFN = interferon; PEFR = peak expiratory flow rate; FVC = forced vital capacity; FEV₁ = forced expiratory volume; PBMC = peripheral blood mononuclear cells; PMA = phorbol myristate acetate; INO = ionomycin; CHLC = Children’s Health Locus of Control.
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 (FEV₁)% 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>
<thead>
<tr>
<th>TABLE 1. Sample Descriptive Information (N = 40)*</th>
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<td>Variable</td>
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<td>Ethnicity</td>
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<td>Asian</td>
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<td>Other</td>
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<td>Antileukotriene</td>
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<td>Biological outcome measures</td>
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<td>Eosinophil count (&lt;10⁶ cells/l)</td>
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<td>IL-4 (pg/ml)</td>
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<td>IL-13 (pg/ml)</td>
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<td>IFN-γ (pg/ml)</td>
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PEF = peak expiratory flow (percent variability from morning to night); FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second. *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/chaos (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/chaos 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/chaos items were reverse scored, and then a total score was created by summing the internal control items and the reverse-scored external/chaos 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 FEV₁, 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. FEV₁ and FVC values are expressed as a percent of

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predicted values, based on child age, gender, ethnicity, and height. Lower FEV₁ 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 x 10⁶ 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 (1 µg/ml) for a period of 48 hours at 37°C in 5% CO₂. This PMA/IONO 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 IFNγ 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 a 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 FEV₁ 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 FEV₁ or peak flow variability. Greater asthma symptoms were associated with lower FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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
between locus of control and IFN-γ for illustrative purposes. There was no significant association in IL-4 between children low and high on perceived control.

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 ($r = -0.54, p < .01$).

**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 symptoms.

**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.

**TABLE 2. Associations Between Children’s Health Locus of Control and Immune and Pulmonary Measures (N = 40)**

<table>
<thead>
<tr>
<th>Biological Measure</th>
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<tr>
<td>IL-4</td>
<td>-0.44**</td>
</tr>
<tr>
<td>IL-5</td>
<td>-0.44**</td>
</tr>
<tr>
<td>IL-13</td>
<td>-0.42*</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>0.04</td>
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<tr>
<td>Eosinophil count</td>
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<tr>
<td>FEV$_1$ %</td>
<td>0.50**</td>
</tr>
<tr>
<td>FVC %</td>
<td>0.46**</td>
</tr>
<tr>
<td>PEF % variability</td>
<td>-0.42*</td>
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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.
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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 deter-
mine 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

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