

# Longitudinal Relationships Between Family Routines and Biological Profiles Among Youth With Asthma

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**Objective:** To investigate whether longitudinal trajectories of inflammatory markers of asthma can be predicted by levels of family routines in youth with asthma. **Design:** Family routines were assessed through parent questionnaires and peripheral blood samples obtained from youth every 6 months throughout the 18-month study period. Longitudinal relationships were evaluated using hierarchical linear modeling. **Main Outcome Measures:** Mitogen-stimulated production of cytokines implicated in asthma, specifically IL-4, IL-5, and IL-13. **Results:** Youth with more family routines in their home environment showed decreases in IL-13 (but not IL-4 or IL-5) over the course of the study period. In turn, within-person analyses indicated that at times when stimulated production of IL-13 was high, asthma symptoms were also high, pointing to the clinical relevance of changes in IL-13 over time. A variety of child and parent psychosocial as well as child behavioral characteristics could not explain these effects. However, medication use eliminated the relationship between family routines and stimulated production of IL-13. **Conclusion:** Our study suggests that family routines predict asthma outcomes at the biological level, possibly through influencing medication use. Considering daily family behaviors when treating asthma may help improve both biological and clinical profiles in youth with asthma.

**Keywords:** family routines, IL-13, asthma, children, adolescents

Asthma is one of the most common chronic illnesses among North American youth, and its overall prevalence has been rising in recent years. In 2005, about 2.25 million Canadians over the age of 12 were reported to have asthma, up from about 1.78 million in 1996–1997, representing an increase from 7.2% to 8.3% of the Canadian population (Statistics Canada, 2007). Similarly, about 9 million American youth under the age of 18 (12.5%) have had asthma at some point in their lives (Dey & Bloom, 2005). What is more, about 4 million American youth under the age of 18 (6%) experienced an acute asthma attack during the past 12 months (Dey & Bloom, 2005). Asthma also has important consequences for youth's daily life functioning. In the United States, asthma led to 12.8 million missed school days in 2003 and close to 200,000 hospitalizations among youth with asthma (Akinbami, 2006).

## The Impact of Psychological Factors on Asthma

Many factors are believed to influence asthma, with psychological factors often cited as important contributors, including stress, anxiety, and depression, which have been associated with nonadherence to medication, greater exposure to asthma triggers, and more frequent hospitalizations and emergency room visits for asthma (Lehrer, Feldman, Giardino, Song, & Schmalzing, 2002).

Much of this previous research has focused on individual-level factors, such as stress or depression.

Fewer studies have investigated how the larger social context (e.g., social support, family) might play a role among patients, particularly children, with asthma. Some exceptions include studies that have shown that people with both low social support and more negative life events were the most likely to experience asthma exacerbations (Smith & Nicholson, 2001); some studies have found that parental depression is linked to a greater likelihood of children requiring unscheduled physician visits, hospitalizations, and emergency room visits because of asthma (Bartlett et al., 2001; Brown et al., 2006; Shalowitz, Berry, Quinn, & Wolf, 2001), as well as experiencing more asthma attacks (Ortega, Goodwin, McQuaid, & Canino, 2004). Other research has highlighted the relevance of the family response to asthma symptoms (McQuaid et al., 2007), indicating that the family's response to a child's asthma symptoms may connect youth's symptom perception and morbidity, such that poor estimates of asthma severity on the part of youth is often linked to inadequate family plans for dealing with asthma exacerbations.

## Family Routines

Few studies, however, have looked past parent characteristics and considered asthma within the framework of the entire family as a whole. This may be particularly important for pediatric asthma, as children are connected to a larger family system that may play an important role in shaping health. One factor at the family level that may be important to asthma is family routines. Fiese and Wamboldt (2000) define *family routines* as an indicator of the degree to which organized roles and routines are part of family practices. Family routines are characterized by direct and

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instrumental communication and behaviors, aiming to effectively deal with tasks that require more immediate attention (Fiese, Foley, & Spagnola, 2006). Examples of family routines include eating meals at the same time each night and children doing regular household chores.

### Family Routines and Asthma

Family routines have been shown to have protective effects on clinical outcomes among youth with asthma. For example, Gustafsson, Kjellman, and Bjørksten (2002) reported that recovery from atopic illness during the first 3 years of life was 4 times more likely in children whose families had more functional interactions during behavioral observations. In another study, the presence of more clearly defined roles and routines within the family was related to youth reporting being less bothered by their asthma symptoms (Sawyer et al., 2000). In addition, Fiese et al. (2006) have shown that youth with asthma from families that regularly ate together and used common mealtimes as opportunities to engage in direct communication were less likely to report internalizing symptoms. Finally, the implementation of routines more generally has recently been implicated as a promising tool for treating other illnesses such as bipolar disorder (e.g., Frank, Swartz, & Boland, 2007), cyclothymia (Shen et al., 2008), and Type I diabetes (Greening, Stoppelbein, Konishi, Jordan, & Moll, 2007).

### Routines and Biological Markers of Health

The above studies have focused on how family routines affect mental and physical health outcomes, but little is known about the biological pathways through which routines might come to be associated with health. However, there are a number of studies that suggest that social routines may be able to alter biological rhythms in healthy individuals. For example, Stetler, Dickerson, and Miller (2004) found that in healthy young women there was a relationship between social rhythms—that is, the extent to which various daily social activities were performed regularly—and daily cortisol responses, such that on days during which women engaged in more social routines they showed evidence of more normative declines in their cortisol levels throughout the day. Similarly, McClintock (1971) showed that the menstrual cycles of women living in the same space (dormitories) become synchronized over time.

Other phenomena that have been shown to affect daily biological profiles include socially derived triggers of daily routines. For example, individuals who participate in Ramadan, with its different patterns of eating for a prescribed period of time, show changes in the secretion of a number of hormones, such as cortisol, testosterone, and growth hormone, among others (Bogdan, Bouchareb, & Touitou, 2001). Similarly, daily cortisol has been found to be affected by time of awakening, such that an earlier time of awakening has been connected with greater cortisol awakening responses (Edwards, Evans, Hucklebridge, & Clow, 2001; Stetler & Miller, 2005). Lastly, other behaviors such as long-distance travel and shift work have been shown to disrupt the circadian rhythm (Boivin, Tremblay, & James, 2007; Rudiger, 2004). These studies have begun to address the extent to which social factors can affect individuals at the biological level. To date, however, we have no knowledge of whether social or family routines are associated with

biological markers in the context of a chronic medical illness such as asthma.

### Pathophysiology of Asthma

Asthma involves chronic airway inflammation brought about by a number of cytokines, which are chemical messengers of the immune system. These cytokines initiate inflammatory cascades, which ultimately result in increased inflammation, airway constriction, and mucus production. Specifically, this involves two major pathways. In both cases, T helper cells, known as Th2 cells, become activated and release inflammatory markers. One pathway involves Th2 cells promoting B cell proliferation, which in turn results in a humoral response that brings about antibody synthesis. That is, Th2 cytokines such as IL-4 and IL-13 bind to B cells, resulting in the release of immunoglobulin E (IgE) antibodies. IgE then binds to mast cells in the airways, causing them to degranulate and to release allergic mediators in the process. Another pathway involves the release of IL-5 by Th2 cells, which recruits eosinophils to the airways. In both cases, increased airway obstruction and inflammation result.

Existing research has shown that psychosocial stressors are related to increases in inflammatory markers of asthma. For example, a study by Kang and Fox (2001) evaluated the impact of academic stress on immunological outcomes among youth with asthma. They found that as a result of exam stress, students showed increases in the level of a Th2 cytokine, IL-6. In addition, students with a history of childhood asthma had relatively greater increases in levels of Th2 cytokines in response to academic stress than their healthy counterparts. Similarly, chronic caregiver stress in early childhood was associated with higher levels of immune markers involved in asthma, for example, higher levels of total IgE (Wright et al., 2004). Another study found that family factors, such as family support, were related to increased inflammatory markers, such as stimulated IL-4 production, which in turn were related to poorer clinical indicators, such as more frequent symptoms (Chen, Chim, Strunk, & Miller, 2007).

Most previous research has used cross-sectional designs. Hence, it is unclear whether relationships exist because family routines affect asthma outcomes, or whether worsening asthma disrupts family life and routines. In addition, although associations have been demonstrated between family routines and clinical outcomes in the context of asthma, it remains unclear through which biological pathways family routines come to affect childhood asthma, and there is a shortage of studies investigating these links using longitudinal study designs (for an exception, see Gustafsson et al., 2002).

### The Current Study

The overall objectives of the current study were to investigate how family routines in the home environment of youth with asthma “get under the skin” to affect youth asthma. To this end, we followed youth with asthma for 18 months, allowing us to measure inflammatory markers of asthma at four separate time points during the study period, and to test whether family routines could predict longitudinal trajectories of asthma-relevant inflammatory markers. Our second goal was to test whether associations between family routines and inflammatory markers could be explained by

other social or behavioral factors, such as parents' psychological characteristics or child behaviors.

For example, one of the most important components of proper asthma management relates to daily medication use. Hence, family routines may be associated with asthma biological profiles because they help to shape behaviors related to taking medications. In addition, other child health behaviors, such as smoking or exercise, may account for associations between routines and asthma inflammatory markers. Alternatively, it is possible that parent characteristics, such as parental depression, or general family functioning at large are responsible for the extent to which routines are implemented in a given family and in turn shape asthma outcomes. Consequently, we assessed whether these variables altered the association between family routines and inflammatory markers of asthma.

## Method

### Participants

Fifty-nine youth (78% boys,  $n = 46$ ) between the ages of 9 and 16 years ( $M = 12.68$  years,  $SD = 2.55$ ) from the larger Vancouver, BC, area were recruited through advertisements at schools, physician offices, and local newspapers as part of a larger ongoing study. All youth were English speaking, had physician-diagnosed asthma, were free of any other chronic illnesses, and were free of acute respiratory illness at the time of their visits. Participants represented the full range of asthma severity. Twenty percent of youth ( $n = 12$ ) had mild intermittent asthma, 34% ( $n = 20$ ) mild persistent asthma, 36% ( $n = 21$ ) moderate persistent asthma, and 10% ( $n = 6$ ) severe persistent asthma. Asthma severity was classified according to a standardized algorithm from the National Asthma Education and Prevention Program/Expert Panel Report 2 Guidelines based on the higher of symptom frequency and medication use, paralleling the approach of previous researchers (Bacharier et al., 2004). The majority of participants (83.1%,  $n = 49$ ) had allergic asthma. At study entry, 38 of 59 children (64%) had been prescribed an inhaled corticosteroid. Furthermore, all participants had been prescribed a rescue inhaler for emergencies, but only 30 participants (51%) reported having used their rescue inhaler during the 2 weeks prior to the first study visit. Lastly, only six of the 59 participants (10%) had been prescribed leukotriene modifiers, and all of these children had also been prescribed inhaled corticosteroids at the same time; hence, we did not code leukotriene modifiers separately, given the small numbers and given that no children were prescribed only this medication. Time since diagnosis varied from 0 to 15 years in this sample ( $M = 8.0$  years). See Table 1 for a summary of demographic information on our participants.

### Procedure

Written assent and consent were obtained from participating youth and their parents, respectively. Participating youth visited the laboratory 4 times over 1.5 years, on average once every 6 months, together with a parent. At each visit, youth underwent a peripheral blood draw and during their first visit also completed a number of computer questionnaires (younger participants were given the option of having questions read to them by their research

Table 1  
*Participant Characteristics (N = 59)*

Variable	Statistic
Gender, $n$ (%)	
Male	46 (78)
Female	13 (22)
Mean ( $SD$ ) age (years)	12.68 (2.55)
Asthma severity $n$ (%)	
Mild intermittent	12 (20.3)
Mild persistent	20 (33.9)
Moderate persistent	21 (35.6)
Severe persistent	6 (10.2)
Mean ( $SD$ ) medication use <sup>a</sup>	
Inhaled corticosteroids ( $n = 38$ )	7.1 (6.1)
Beta-agonists	4.1 (5.6)
Mean ( $SD$ ) parent questionnaire score	
Family routines	40.25 (5.24)
Parent depression	10.14 (8.23)
Parent perceived stress	15.50 (6.94)
General family functioning	24.43 (4.40)
Mean ( $SD$ ) child questionnaire score	
Perceived parent support	21.44 (2.45)
Activity level	7.04 (4.39)
Smoke exposure	11.96 (29.22)
Sleep quality	1.77 (0.35)

<sup>a</sup> Medication use represents the average number of days during the 2 weeks preceding the first study visit that participants reported having taken their medication. Use of inhaled corticosteroids is reported for the 38 participants who were prescribed such medication.

assistant). Youth also kept daily diaries of their sleep quality on diary cards for 2 weeks following the study visit. At the same time, parents completed computer questionnaires and reported on their children's asthma symptoms over the past 2 weeks as part of a semistructured interview conducted by a trained research assistant. Participants were reimbursed for their time as well as transportation to the study site. The study was approved by the Research Ethics Board of the University of British Columbia.

### Parent Questionnaires

**Family routines.** Fourteen items from the Family Routines Inventory (FRI; Jensen, James, Boyce, & Hartnett, 1983) were answered by the parent on a 1 to 4 Likert scale with anchors of 1 = *always; every day* to 4 = *almost never* at the second visit to the research site. The FRI aims to investigate the degree to which daily family life follows set routines and guidelines that have been established within the family. Items include statements such as "Our family eats dinner together every night" and "My children do the same things each morning as soon as they wake up." Items from the original FRI that did not pertain to child routines (e.g., "Parent talks to his or her parents regularly") and that would not be relevant to the entire age range of this study (e.g., "Parent reads stories to the child almost every day") were excluded. All answers were reverse scored, and higher scores indicate the presence of more family routines, that is, a more structured family life. Thirty-day test-retest reliability has previously been found to be good at  $r = .74$  (Jensen et al., 1983). Validity was established by comparing the FRI to a related measure, the Family Environment Scale (Moos, Insel, & Humphrey, 1974), and was found to be good given that scores on the FRI were a significant predictor of the Family

Environment Scale. Internal consistency in our sample was found to be acceptable at Cronbach's  $\alpha = .71$ . In our analyses, routines were treated as a stable Level 2 variable.

**Psychosocial parental and general family characteristics.** A number of psychosocial parent and general family characteristics that could provide alternative explanations for associations between routines and asthma biological markers were assessed through self-report questionnaires.

**Parental depression.** Parental depression was assessed through the Center for Epidemiological Studies Depression scale (CES-D; Radloff, 1977), a widely used depression scale consisting of 20 items assessing the frequency of a number of behaviors, such as feeling hopeful, lonely, or sad, over the past week (from 0 = *less than one day* to 3 = *5–7 days*). It has been tested in clinical as well as general populations and been shown to have an excellent internal consistency of  $\alpha = .85$  in the general population. Parents completed the CES-D as part of every study visit.

**Parental perceived stress.** Parental perceived stress was assessed through the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983). The PSS is a 14-item scale asking people about their feelings and thoughts during the past month, such as feeling "on top of things." It is answered on a 0–4 scale, ranging from 0 = *never* to 4 = *very often*. Internal reliability has been found to be very good, with alphas between .84 and .86 (Cohen et al., 1983). Parents completed the PSS during every study visit.

**General family functioning.** Parents completed the General Functioning Scale (GFS) of the Family Assessment Device (FAD). The GFS of the FAD (Epstein, Baldwin, & Bishop, 1983) consists of 13 items answered on a 4-point Likert scale ranging from 1 = *strongly agree* to 4 = *strongly disagree*. This measure discriminates between nonclinical and psychiatric families (Byles, Byrne, Boyle, & Offord, 1988). The reliability of the GFS was previously found to be  $\alpha = .86$  (Byles et al., 1988). Moreover, the GFS was significantly correlated with variables such as family structure (single-parent vs. two-parent family), marital violence and disharmony, socioeconomic status, and whether the parent had been arrested at any point in time (Byles et al., 1988). Parents completed the GFS as part of their first study visit.

## Child Questionnaires

**Child health behaviors.** Child smoke exposure was assessed by summing all six questions of the smoking questionnaire (Childhood Asthma Management Program Research Group, 1999), which inquires about first- and second-hand smoke exposure during the past 6 months as well as weekly and daily smoke exposure. Higher scores indicate greater smoke exposure. Previous research suggests that self-reported smoke exposure provides information that is consistent with biochemical markers of smoke exposure (Assaf, Parker, Lapane, McKenney, & Carleton, 2002).

Youth's exercise levels were assessed using the Child Physical Activity and Exercise questionnaire (Aaron et al., 1993). Responses to the first question—on how many days during the past 2 weeks youth had performed hard exercise (including sports such as basketball, jogging, and cycling for at least 20 min)—were used. Higher scores indicate higher activity levels.

Youth noted their sleep quality during the previous night's sleep each morning on a diary card for 2 weeks following the first laboratory visit. They rated their sleep quality from 1 to 4 as

ranging from *very good* to *very poor*. The average sleep quality for each participant over the 2 weeks was computed and used in the analyses. Higher values represent poorer sleep quality across the 2-week period. Youth completed their daily diary an average of  $12.42 \pm 3.8$  of 14 days. Sleep was only measured once as it was part of a substudy conducted for other purposes.

**Harter Social Support Scale.** Youth also completed the Parent subscale of the Harter Social Support Scale (Harter, 1986) consisting of six questions asking youth whether they felt they received support from their parents. Scores were summed to create a single score. Higher scores indicate greater social support.

## Clinical Outcomes

**Child symptoms.** At each visit, parents were asked about the number of days over the past 2 weeks on which their children experienced daytime, nighttime, or exertional asthma symptoms, defined as coughing, wheezing, shortness of breath, and chest tightness. Responses to these three questions were summed to create a single symptom score for each child for each visit. Average symptom scores for the visits ranged from 3.78 ( $SD = 5.81$ ) to 4.25 ( $SD = 1.82$ ) points. Note that asthma symptoms across the four study visits were person-centered in our statistical model to allow us to look at our participants' changes in asthma symptoms across time, relative to their own mean on asthma symptoms.

**Medication use.** Medication use was controlled for by including the number of times youth used inhaled corticosteroids during the 2-week period preceding each of the visits. Families brought medications to the laboratory, and children and parents were queried separately about the number of times over the past 14 days the child had taken the controller medication. If discrepant information was provided by the parent and child, they were queried further, asked to discuss which answer was likely to be more accurate, and a consensus response was agreed on. However, inclusion of beta-agonist use did not change any of the results reported here. Youth reported having used their controller medication an average of  $7.1 \pm 6.1$  times over the past 2 weeks and their rescue inhalers an average of  $4.1 \pm 5.6$  times. Beta-agonist use over the same time period was also assessed. Note that medication use across the four study visits was person-centered in our model for the same reason as asthma symptoms.

**Inflammatory markers.** As individuals with asthma typically experience a shift toward Th2 cytokines, these cytokines, including IL-4, IL-5, and IL-13, formed the focus of the current study. Measuring stimulated cytokine production in vitro provides a marker of the magnitude of the inflammatory response the immune system is capable of mounting when presented with a foreign stimulus.

At each visit, participants underwent a blood draw during which peripheral blood was drawn into cell-preparation tubes (Becton-Dickinson, Franklin Lakes, NJ) containing sodium heparin. Stimulated production of IL-4, IL-5, and IL-13 was measured in vitro. Within 2 hr of the blood draw, all tubes were spun using density-gradient centrifugation. Peripheral mononuclear blood cells were isolated after three subsequent wash steps and resuspended in complete culture medium (RPMI 1640 with Hepes, L-glutamine, 10% fetal calf serum, 1% penicillin-streptomycin; all reagents: Sigma-Aldrich Canada Ltd., Oakville, ON) in a concentration of

$3 \times 10^6$  cells/ml. Cells were immediately incubated for 48 hr with phorbol 12-myristate 13-acetate (25 ng/ml f.c.) and ionomycin (1  $\mu$ g/ml f.c.) at 37 °C, 5% CO<sub>2</sub> in six well plates (Sarstedt, Newton, NC). After incubation, plates were centrifuged and supernatants stored at -80 °C. Stimulated production of IL-5 and L-13 was determined using commercially available enzyme-linked immunosorbent assay, and stimulated IL-4 production using commercially available high-sensitivity enzyme-linked immunosorbent assays (R&D System, Minneapolis, MN). All assay coefficients of variation were < 10%.

## Covariates

Asthma severity was entered as a covariate in all analyses and classified as mild intermittent, mild persistent, moderate persistent, or severe persistent, as determined from the National Asthma Education and Prevention Program/Expert Panel Report 2 Guidelines based on the higher of symptom frequency and medication use, paralleling the approach of previous researchers (Bacharier et al., 2004).

## Statistical Analyses

Hierarchical linear modeling was used to predict trajectories of immunological outcomes of asthma over the 1.5-year study period from the level of present family routines. Hierarchical linear modeling is a multilevel modeling technique that can be used to assess both within-person and between-persons factors predicting changes in a dependent variable (e.g., stimulated cytokine production) over time.

We began by examining the within-person (Level 1) model only to first estimate stimulated cytokine production as a function of time. This resulted in a series of person-specific slopes and intercepts. Next, we added the between-persons model (Level 2) to estimate the slopes and intercepts at Level 1 as a function of factors varying across people. In this second step, we first added asthma severity into our model and then family routines as a third step. We also investigated the effect of a number of alternative explanations, each of which was entered independently to assess its impact on the relationship between family routines and stimulated cytokine production. Medication use, parent perceived stress, and parent depression were entered at Level 1 because of their within-person nature. All other covariates, including a number of psychosocial characteristics (overall family functioning and child-reported parent support) and behavioral characteristics (child exercise, child smoke exposure, and child sleep quality), were entered as between-persons variables at Level 2. Hence, in this set of analyses, trajectories of stimulated cytokine production were predicted from asthma severity, one of the above psychosocial and behavioral potential explanations, and family routines.

We also tested whether reported asthma symptoms were related to stimulated cytokine production, that is, whether within-person levels of reported symptoms and stimulated cytokine production varied together. To do this, we predicted stimulated cytokine production from youths' asthma symptoms, which, given that they varied from visit to visit, were entered at Level 1 (within-person). This within-person model allowed us to estimate stimulated cytokine production as a function of reported symptoms, which also varied across time. These analyses resulted in person-specific

slopes reflecting differential cytokine production at times during which youth are reported to have fewer or more symptoms.

All relationships were estimated using full maximum likelihood and robust standard errors. Cytokine data were standardized to account for any potential nonsystematic variation due to laboratory procedures. All analyses were performed controlling for asthma severity. We also tested the influence of demographic variables by repeating the analyses controlling for age and gender. However, neither variable affected our results; thus, these additional analyses are not detailed below. Seventy-six percent of participants had Level 1 data available for three or more visits.

## Results

### Preliminary Analyses

Our first model estimated stimulated cytokine production as a function of time. Over the 18-month study period, levels of stimulated IL-4, IL-5, and IL-13 production did not change significantly ( $B = .0463$ ,  $SE = .0688$ ,  $p > .50$ ;  $B = -.0229$ ,  $SE = .0594$ ,  $p > .50$ ; and  $B = -.0430$ ,  $SE = .0474$ ,  $p > .30$ , respectively).

In our second model, we added our covariate of asthma severity at Level 2. Asthma severity was not a significant predictor of stimulated IL-4, IL-5, and IL-13 production over time ( $B = -.0038$ ,  $SE = .0817$ ,  $p > .50$ ;  $B = -.0215$ ,  $SE = .0519$ ,  $p > .50$ ;  $B = -.0061$ ,  $SE = .0425$ ,  $p > .50$ , respectively).

### Family Routines Predicting Trajectories of Stimulated Cytokine Production

In the third model, we entered family routines at Level 2. Family routines significantly predicted changes in youth's stimulated IL-13 production over time after controlling for asthma severity ( $B = -.0200$ ,  $SE = .0067$ ,  $p < .01$ ). The negative coefficient indicates that as levels of family routines increased, youth showed decreased stimulated production of IL-13 over time. There was no significant effect of routines on the IL-13 intercept ( $B = .0386$ ,  $SE = .0238$ ,  $p > .10$ ), meaning that participants' levels of stimulated IL-13 production at study entry did not differ by family routines. See Figure 1 for a graphical representation of these results. Family routines did not predict slopes or intercepts for IL-4 or IL-5 ( $ps > .20$ ).

### Relationship Between Reported Child Asthma Symptoms and Stimulated Cytokine Production

To assess the clinical relevance of these longitudinal changes in youth's cytokine production, we investigated whether changes in our outcome variable were also associated with changes in youth's asthma symptoms. Within-person analyses showed that youth's asthma symptoms over time were related to their stimulated IL-13 production ( $B = .0510$ ,  $SE = .0245$ ,  $p < .05$ ) such that within an individual, at times when children were reported to experience more asthma symptoms, they also exhibited greater stimulated production of IL-13.

### Medication Use as a Pathway?

We next tested whether youth's medication use could explain the associations between family routines and stimulated cytokine

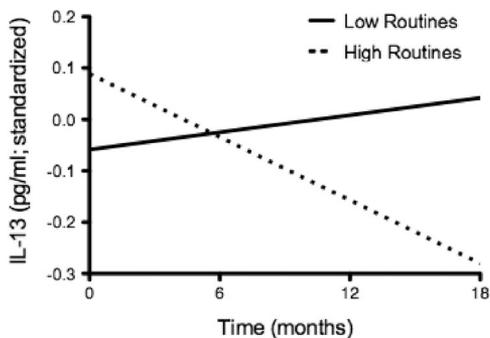


Figure 1. Family routines predicting trajectories of stimulated IL-13 production across the 18-month study period. Trajectories of stimulated IL-13 production over the course of 18 months among youth with asthma growing up in home environments marked by either high or low levels of family routines. Levels of family routines depicted here represent the 25th and 75th percentile. The intercept effect is nonsignificant.

production trajectories by controlling for inhaled corticosteroid use. After controlling for medication and asthma severity, family routines did not significantly predict changes in youth’s stimulated IL-13 production over time ( $B = .0081, SE = .0117, p > .40$ ), suggesting that one possible behavioral pathway through which family routines affect childhood asthma is through medication use. The effect size for the relationship between family routines and trajectories of stimulated IL-13 production dropped from Cohen’s  $d = 0.78$  to  $d = 0.18$ , a 60% reduction, when medication use was included. In contrast, child asthma symptoms were still associated with stimulated production of IL-13 over time when controlling for both asthma severity and medication ( $B = .0909, SE = .0354, p < .05$ ), suggesting that the relationship between stimulated IL-13 production and asthma symptoms over time persists, even independent of medication use. Inclusion of beta-agonist use did not alter these results.

**Other Psychosocial and Behavioral Characteristics as Pathways?**

We next tested whether other psychosocial or behavioral factors might explain relationships between family routines and IL-13 trajectories over time. With parental depression entered, family routines remained a significant predictor of trajectories of stimulated production of IL-13 ( $B = -.0219, SE = .0069, p < .01$ ). With parental stress entered, family routines remained a significant predictor of IL-13 trajectories ( $B = -.0212, SE = .0069, p < .01$ ). When family functioning was entered, family routines remained a significant predictor of IL-13 trajectories ( $B = -.0180, SE = .0086, p < .05$ ). Finally, with youth-reported parent support entered, family routines also remained a significant predictor of IL-13 trajectories ( $B = -.0193, SE = .0069, p < .01$ ). Parental depression and stress were measured at each time point; however, including these as time-varying variables did not change our results.

Similar patterns emerged when entering child health behaviors. Family routines remained significant predictors of IL-13 trajectories after youth exercise ( $B = -.0249, SE = .0059, p < .001$ ), youth smoke exposure ( $B = -.0194, SE = .0072, p = .01$ ), and

youth sleep quality ( $B = -.0177, SE = .0077, p < .05$ ) were entered.

These results indicate that the relationship between family routines and youths’ stimulated cytokine production is independent of the effect of commonly implicated psychosocial parent and child characteristics, general family functioning, and child behavioral characteristics.

See Table 2 for a more detailed overview of our main results.

**Discussion**

The present study showed that levels of family routines in the homes of youth with asthma predict changes in stimulated production of the asthma inflammatory cytokine IL-13, but not IL-4 and IL-5, over an 18-month time period, independent of youth’s asthma severity. As levels of family routines increased, youth exhibited decreased production of IL-13 over an 18-month period.

Table 2  
Family Routines Predicting Trajectories of Stimulated IL-13 Production

Variable	B	SE	p
<b>Model 1</b>			
Severity	-.0007	.0374	.99
Family routines	-.0196	.0067	.005
<b>Model 2</b>			
Severity	-.0535	.1337	.69
Inhaled corticosteroids	-.0026	.0207	.90
Family routines	.0081	.0117	.49
<b>Model 3</b>			
Severity	.0037	.0400	.93
Parental depression	.0011	.0094	.90
Family routines	-.0219	.0069	.003
<b>Model 4</b>			
Severity	.0134	.0447	.77
Parental stress	-.0093	.0183	.61
Family routines	-.0212	.0069	.004
<b>Model 5</b>			
Severity	-.0003	.0382	.99
General family functioning	.0046	.0148	.76
Family routines	-.0180	.0086	.04
<b>Model 6</b>			
Severity	.0042	.0397	.92
Child-perceived parent support	.0113	.0212	.60
Family routines	-.0193	.0070	.008
<b>Model 7</b>			
Severity	.0017	.0397	.97
Youth exercise	.0035	.0018	.77
Family routines	-.0249	.0059	.000
<b>Model 8</b>			
Severity	.0081	.0438	.85
Youth smoke exposure	.0009	.0011	.43
Family routines	-.0194	.0072	.01
<b>Model 9</b>			
Severity	-.0006	.04812	.99
Youth sleep quality	-.0018	.1771	.99
Family routines	-.0177	.0077	.03

Note. Each of the nine sets of analyses shown here represents a different model. The first model is the basic one, in which family routines predicts trajectories of IL-13 production over time, after controlling for asthma severity. The next eight models test whether family routines remain a significant predictor of IL-13 trajectories after controlling for each of a variety of psychosocial and behavioral variables.

Furthermore, these differences in stimulated IL-13 production have clinical relevance as within-person changes in IL-13 over the study period were associated with within-person changes in child asthma symptoms, such that within any given individual, stimulated IL-13 production tended to be higher at times of greater asthma symptoms. Our results represent a first step in shedding light on biological pathways linking family routines and asthma outcomes by implicating an inflammatory pathway involving one of the key cytokines implicated in asthma.

Our findings suggest that family routines predict changes in inflammatory profiles in youth with asthma, an association that has implications clinically. Increased stimulated IL-13 production may fuel an inflammatory cascade in the airways of youth with asthma, eventually resulting in greater airway inflammation and constriction and, subsequently, worsened asthma morbidity. The fact that greater asthma symptoms were related with greater stimulated production of IL-13 in this study testifies to the likelihood and plausibility of this pathway.

In addition, our study examined several possible psychological and behavioral pathways through which family routines could predict youth's stimulated IL-13 production over time. One possibility was that family routines would affect asthma through effects on daily medication use. Research suggests that controller medication use among youth with asthma is generally poor, with only 30–50% of youth with persistent asthma adhering to their prescribed twice daily dose of medication as they should (Bender, Milgrom, Rand, & Ackerson, 1998). In the present study, we found that when controlling for daily use of inhaled corticosteroids, level of family routines no longer predicted stimulated IL-13 production. The presence of family routines may be one factor explaining why youth in some families more reliably use their prescribed daily medication. Fiese, Wamboldt, and Anbar (2005) reported that specific medication routines were related to clinical asthma outcomes in youth, in particular, the amount of medication actually taken on a regular basis and needed in case of asthma exacerbations.

One reason that family routines may facilitate the use of asthma medications is that families who are proficient at solving problems as a team and have good family functioning likely benefit from these preexisting structures and the organization already in place; hence, it may be easier for families that already have strong routines to successfully integrate any additional routines relating to asthma management. In contrast, families that are not used to working as a team and do not have a working system of routines in place may find it more challenging to create practicable and salient routines and to maintain and adapt these in order to engage in good asthma management.

We further found that a number of other psychosocial and behavioral characteristics were not able to explain the relationship between family routines and IL-13 trajectories. In particular, we tested individual parent characteristics, such as parental depression and stress, family factors, such as perceived parental support and overall family functioning, and individual child behaviors, such as smoking, exercise, and sleep, and found that none of these accounted for the relationship between family routines and trajectories over time of stimulated IL-13 production. This suggests that there is something unique to family routines that is not captured by key psychosocial parent characteristics or overall family functioning. Although this may seem somewhat surprising given previous

research documenting that parental psychosocial characteristics are associated with child asthma outcomes (e.g., Shalowitz et al., 2001; Weil et al., 1999), these studies typically have not linked biological pathways to these types of psychosocial characteristics.

There are a number of strengths to this study. First, we followed our participants longitudinally for 18 months, during which we were able to get four assessments of inflammatory markers, allowing us to predict changes over time in inflammatory cytokine production as a function of family factors. As a result of these four assessment times, we were also able to take advantage of a more powerful statistical technique, hierarchical linear modeling, to model trajectories of change over time in biological variables.

There are also a number of limitations to the current study. First is the wide age range present in our participants, including both older children as well as adolescents. Including age as a covariate did not alter our results. However, future research should investigate whether there indeed are differences in the relationship between family routines and biological asthma outcomes in youth from different age groups. It is possible, for example, that family routines are particularly important for younger youth in terms of shaping long-term trajectories of biological and clinical asthma indicators. It is also possible that family routines change throughout the various developmental stages of children and youth; hence, we will be collecting longitudinal data on family routines in future studies.

Second, different medications may work through different mechanisms to affect inflammatory markers in a number of ways. For example, regular use of inhaled corticosteroids has been shown to reduce asthma exacerbations in the long run while also reducing the number of inflammatory cells in the airways (Koopmanns, Lutter, Jansen, & van der Zee, 2006). Hence, the results from our study suggest that greater family routines may encourage more regular use of inhaled corticosteroid medications, which may in turn reduce airway inflammation. Future research should conduct more sophisticated analyses of how the details of the medication regimens, such as dosages and specific types of medications, may affect both biological and clinical outcomes among youth with asthma. We also note that the large majority of our participants had been prescribed inhaled corticosteroids as their controller medication. Hence, these findings may not generalize to youth on different medication regimens.

Third, we were only able to assess medication adherence through self-report, which some studies suggest may result in inflated adherence rates (e.g., Bender et al., 2000). It is possible that a more detailed evaluation of youth's asthma treatment adherence, for example, through electronic monitoring, may have altered our findings regarding medication adherence as a mechanism through which family routines may affect youth inflammatory profiles. More accurate assessments of medication adherence are needed in the future.

Fourth, better long-term data concerning the stability of family routines are needed. Although the original validation of the FRI together with an examination of its face validity suggest that family routines are relatively stable across time, this study did not include longitudinal data on family routines. Future studies should ensure collection of data on family routines at multiple times across at least 1 year to determine the stability of family routines with greater certainty.

Finally, although we have investigated a number of psychological and behavioral factors through which family routines may affect biological asthma outcomes in youth, there remains a possibility that other factors not evaluated in this study could be important. For example, conscientiousness has been linked to greater longevity (Friedman et al., 1995), health behaviors (Bogg & Roberts, 2004), and being more invested in one's family (Lodi-Smith & Roberts, 2007). Hence, one could imagine that parental conscientiousness may influence the relationship between family routines and biological asthma outcomes. Future research should continue to investigate other factors that may provide potential links between family routines and biological asthma outcomes.

Another possibility that needs to be investigated in the future is whether family routines affect the immune profiles of youth with allergic asthma differently from those of youth who do not have allergic asthma. Of our participants, 83.1% had allergic asthma, and IL-13 is directly implicated in allergic asthma. Hence, the possibility remains that different associations would be found in youth who do not have allergic asthma. In addition, the majority of youth in our study had mild to moderate asthma, and it is unclear whether family routines would have similar effects in a sample of youth with severe asthma.

Future research should explore whether there are certain types of families for which family routines are more important than others. Identifying such families would allow us to more specifically target families that could benefit the most from integrating family routines into their child's asthma treatment plan.

We would also like to call attention to the fact that family routines predicted trajectories over time of stimulated IL-13 production but not of stimulated IL-4 and IL-5 production. IL-5 contributes to the inflammatory process of asthma through a different pathway than IL-13 (one involving eosinophil production), which may explain the lack of association for IL-5. However, IL-4 and IL-13 both activate the same pathway (production of IgE); hence, it is unclear why the effects found in this study were not seen for stimulated production of IL-4. One possible explanation may be assay sensitivity. IL-4 is typically present at much lower levels than many other cytokines, which has led to the creation of high-sensitivity assays specifically for measuring IL-4. Hence, it is possible that IL-4 production occurred at levels too low to accurately model changes in cytokine production over multiple time points.

Furthermore, the intercepts for IL-13 did not differ by routines. The participants in this study had a wide range in terms of years since diagnosis (0–15 years,  $M = 8.0$  years), and this may have obscured intercept differences. Alternatively, it is possible that the effects of family routines have to accumulate for some time before one sees effects on inflammatory markers.

In sum, our study demonstrated that family routines predict clinical asthma outcomes through biological pathways, in this case through stimulated IL-13 (but not IL-4 and IL-5) production, and that these changes in IL-13 are clinically relevant. Youth coming from families implementing more routines may find it easier to integrate asthma into their daily lives and hence show decreasing inflammatory cytokine profiles over time, possibly because they are better managing their prescribed medication regimen. We have also shown that although there appears to be a relationship between family routines and stimulated IL-13 production, this relationship is not explained by other psychosocial characteristics,

including parental psychological characteristics, family functioning, or child health behaviors, pointing to a unique relevance of family routines. Future research should investigate in more detail which families could benefit most from a focus on family routines as part of asthma treatment regimens. This research suggests that taking into account the family at large when dealing with pediatric and adolescent asthma instead of focusing exclusively on either the parent or the child alone may prove beneficial and may result in improved profiles, both biologically and clinically, in youth with asthma.

## References

- Aaron, D. J., Kriska, A. M., Dearwater, S. R., Anderson, R. L., Olsen, T. L., Cauley, J. A., & LaPorte, R. E. (1993). The epidemiology of leisure physical activity in an adolescent population. *Medicine & Science in Sports & Exercise*, 25, 847–853.
- Akinbami, L. (2006). *Asthma prevalence, health care use and mortality: United States, 2003–05*. Retrieved from <http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma03–05/asthma03–05.htm>
- Assaf, A. R., Parker, D., Lapane, K. L., McKenney, J. L., & Carleton, R. A. (2002). Are there gender differences in self-reported smoking practices? Correlation with thiocyanate and cotinine levels in smokers and non-smokers from the Pawtucket Heart Health Program. *Journal of Women's Health*, 11, 899–906.
- Bacharier, L. B., Strunk, R. C., Mauger, D., White, D., Lemanske, R. F., Jr., & Sorkness, C. A. (2004). Classifying asthma severity in children: Mismatch between symptoms, medication use, and lung function. *American Journal of Respiratory and Critical Care Medicine*, 170, 426–432.
- Bartlett, S. J., Kolodner, K., Butz, A. M., Eggleston, P., Malveaux, F. J., & Rand, C. S. (2001). Maternal depressive symptoms and emergency department use among inner-city children with asthma. *Archives of Pediatrics & Adolescent Medicine*, 155, 347–353.
- Bender, B., Milgrom, H., Rand, C., & Ackerson, L. (1998). Psychological factors associated with medication nonadherence in asthmatic children. *Journal of Asthma*, 35, 347–353.
- Bender, B., Wamboldt, F. S., O'Connor, S. L., Szeffler, S., Milgram, H., & Wamboldt, M. Z. (2000). Measurement of children's asthma medication adherence by self-report, mother report, canister weight, and Doser CT. *Annals of Allergy, Asthma, & Immunology*, 85, 416–421.
- Bogdan, A., Bouchareb, B., & Touitou, Y. (2001). Ramadan fasting alters endocrine and neuroendocrine circadian patterns. Meal-time as a synchronizer in humans? *Life Sciences*, 68, 1607–1615.
- Bogg, T., & Roberts, B. W. (2004). Conscientiousness and health-related behaviors: A meta-analysis of the leading behavioral contributors to mortality. *Psychological Bulletin*, 130, 887–919.
- Boivin, D. B., Tremblay, G. M., & James, F. O. (2007). Working on atypical schedules. *Sleep Medicine*, 8, 578–589.
- Brown, E. S., Gan, V., Jeffress, J., Mullen-Gingrich, K., Khan, D. A., Wood, B. L., . . . Rush, A. J. (2006). Psychiatric symptomatology and disorders in caregivers of children with asthma. *Pediatrics*, 118, e1715–e1720.
- Byles, J., Byrne, C., Boyle, M. H., & Offord, D. R. (1988). Ontario Child Health Study: Reliability and validity of the General Functioning subscale of the McMaster Family Assessment Device. *Family Process*, 27, 97–104.
- Chen, E., Chim, L. S., Strunk, R. S., & Miller, G. E. (2007). The role of the social environment in children and adolescents with asthma. *American Journal of Respiratory and Critical Care Medicine*, 176, 644–649.
- Childhood Asthma Management Program Research Group. (1999). The Childhood Asthma Management Program (CAMP): Design, rationale, and methods. *Controlled Clinical Trials*, 20, 91–120.
- Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, 24, 385–396.

- Dey, A. N., & Bloom, B. (2005, March). Summary health statistics for U.S. children: National Health Interview Survey, 2003. National Center for Health Statistics. *Vital Health and Statistics* 10(223), 1–78.
- Edwards, S., Evans, P., Hucklebridge, F., & Clow, A. (2001). Association between time of awakening and diurnal cortisol secretory activity. *Psychoneuroendocrinology*, 26, 613–622.
- Epstein, N. B., Baldwin, L. M., & Bishop, D. S. (1983). The McMaster Family Assessment Device. *Journal of Marital and Family Therapy*, 9, 171–180.
- Fiese, B. H., Foley, K. P., & Spagnola, M. (2006). Routine and ritual elements in family mealtimes: Contexts for child well-being and family identity. *New Directions for Child and Adolescent Development*, (111), 67–89.
- Fiese, B. H., & Wamboldt, F. S. (2000). Family routines, rituals, and asthma management: A proposal for family-based strategies to increase treatment adherence. *Families, Systems, & Health*, 18, 405–418.
- Fiese, B. H., Wamboldt, F. S., & Anbar, R. D. (2005). Family asthma management routines: Connections to medical adherence and quality of life [see Comment]. *Journal of Pediatrics*, 146, 171–176.
- Frank, E., Swartz, H. A., & Boland, E. (2007). Interpersonal and social rhythm therapy: An intervention addressing rhythm dysregulation in bipolar disorder. *Dialogues in Clinical Neuroscience*, 9, 325–332.
- Friedman, H. S., Tucker, J. S., Schwartz, J. E., Martin, L. R., Tomlinson-Keasey, C., Wingard, D. L., & Criqui, M. H. (1995). Childhood conscientiousness and longevity: Health behaviors and cause of death. *Journal of Personality and Social Psychology*, 68, 696–703.
- Greening, L., Stoppelbein, L., Konishi, C., Jordan, S. S., & Moll, G. (2007). Child routines and youths' adherence to treatment for Type 1 diabetes. *Journal of Pediatric Psychology*, 32, 437–447.
- Gustafsson, P. A., Kjellman, N. I. M., & Bjorksten, B. (2002). Family interaction and a supportive social network as salutogenic factors in childhood atopic illness. *Pediatric Allergy and Immunology*, 13, 51–57.
- Harter, S. (1986). *Manual for social support for children*. Denver: University of Colorado.
- Jensen, E. W., James, S. A., Boyce, W. T., & Hartnett, S. A. (1983). The Family Routines Inventory: Development and validation. *Social Science & Medicine*, 17, 201–211.
- Kang, D. H., & Fox, C. (2001). Th1 and Th2 cytokine responses to academic stress. *Research in Nursing and Health*, 24, 245–257.
- Koopmanns, J. G., Lutter, R., Jansen, H. M., & van der Zee, J. S. (2006). Adding salmeterol to an inhaled corticosteroid: Long-term effects on bronchial inflammation in asthma. *Thorax*, 61, 306–312.
- Lehrer, P., Feldman, J., Giardino, N., Song, H.-S., & Schmalting, K. (2002). Psychological aspects of asthma. *Journal of Consulting and Clinical Psychology*, 70, 691–711.
- Lodi-Smith, J., & Roberts, B. W. (2007). Social investment and personality: A meta-analysis of the relationship of personality traits to investment in work, family, religion, and volunteerism. *Personality and Social Psychology Review*, 11, 68–86.
- McClintock, M. K. (1971, January 22). Menstrual synchrony and suppression [Erratum appears in *Nature* (1971, February 26), 229, 643]. *Nature*, 229, 244–245.
- McQuaid, E. L., Mitchell, D. K., Walders, N., Nassau, J. H., Kopel, S. J., Klein, R. B., . . . Fritz, G. K. (2007). Pediatric asthma morbidity: The importance of symptom perception and family response to symptoms. *Journal of Pediatric Psychology*, 32, 167–177.
- Moos, R. H., Insel, P., & Humphrey, B. (1974). *Family Environment Scale: Preliminary manual*. Palo Alto, CA: Consulting Psychologists Press.
- Ortega, A. N., Goodwin, R. D., McQuaid, E. L., & Canino, G. (2004). Parental mental health, childhood psychiatric disorders, and asthma attacks in island Puerto Rican youth. *Ambulatory Pediatrics*, 4, 308–315.
- Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, 1, 385–401.
- Rudiger, H. W. (2004). Health problems due to night shift work and jetlag. *Internist*, 45, 1021–1025.
- Sawyer, M. G., Spurrier, N., Whaites, L., Kennedy, D., Martin, A. J., & Baghurst, P. (2000). The relationship between asthma severity, family functioning and the health-related quality of life of children with asthma. *Quality of Life Research*, 9, 1105–1115.
- Shalowitz, M. U., Berry, C. A., Quinn, K. A., & Wolf, R. L. (2001). The relationship of life stressors and maternal depression to pediatric asthma morbidity in a subspecialty practice. *Ambulatory Pediatrics*, 1, 185–193.
- Shen, G. H. C., Sylvia, L. G., Alloy, L. B., Barrett, F., Kohner, M., Iacoviello, B., & Mills, A. (2008). Lifestyle regularity and cyclothymic symptomatology. *Journal of Clinical Psychology*, 64, 482–500.
- Smith, A., & Nicholson, K. (2001). Psychosocial factors, respiratory viruses and exacerbation of asthma. *Psychoneuroendocrinology*, 26, 411–420.
- Statistics Canada. (2007). *Persons with asthma, by age and sex (%)*. Retrieved from <http://www40.statcan.ca/101/cst01/health49b.htm>
- Stetler, C., Dickerson, S. S., & Miller, G. E. (2004). Uncoupling of social zeitgebers and diurnal cortisol secretion in clinical depression. *Psychoneuroendocrinology*, 29, 1250–1259.
- Stetler, C., & Miller, G. E. (2005). Blunted cortisol response to awakening in mild to moderate depression: Regulatory influences of sleep patterns and social contacts. *Journal of Abnormal Psychology*, 114, 697–705.
- Weil, C. M., Wade, S. L., Bauman, L. J., Lynn, H., Mitchell, H., & Lavigne, J. (1999). The relationship between psychosocial factors and asthma morbidity in inner-city children with asthma. *Pediatrics*, 104, 1274–1280.
- Wright, R. J., Finn, P., Contreras, J. P., Cohen, S., Wright, R. O., Staudenmayer, J., . . . Gold, D. R. (2004). Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy. *Journal of Allergy and Clinical Immunology*, 113, 1051–1057.