LONGITUDINAL RELATIONSHIPS BETWEEN FAMILY ROUTINES AND BIOLOGICAL PROFILES IN YOUTH WITH ASTHMA

by

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B.A.Hon., McGill University, 2006

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF ARTS

in

THE FACULTY OF GRADUATE STUDIES

(Psychology)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

AUGUST 2008

ABSTRACT

While numerous studies have linked family routines to pediatric asthma outcomes, it remains unclear how family routines come to be associated with these outcomes on a biological level. The current study investigated whether longitudinal trajectories of inflammatory markers of asthma could be predicted by levels of family routines in youth with asthma. Family routines were assessed at baseline through parent questionnaires and peripheral blood samples obtained from youth every 6 months (total number of assessments = 4) over the course of an 18 month study period. Youth with more family routines in their home environment showed decreases in mitogen-stimulated production of a cytokine implicated in asthma, IL-13, 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 potential explanations for this effect were probed. Parental depression, stress, and general family functioning could not explain these effects, suggesting that family routines are not just a proxy for parent psychological traits or family relationship quality. However, medication use eliminated the relationship between family routines and stimulated production of IL-13. This suggests that family routines do impact asthma outcomes at the biological level, possibly through influencing medication adherence. Considering daily family behaviors when treating asthma may help improve both biological and clinical profiles in youth with asthma.

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CO-AUTHORSHIP STATEMENT

Hannah M. C. Schreier has made significant contributions to all parts of this study, in particular the data collection, data analysis, and manuscript preparation.

CHAPTER ONE[1]

Asthma is one of the most common chronic illnesses among Canadian 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 1996/7, representing an increase from 7.2% to 8.3% of the Canadian population. (Statistics Canada, 2007). Asthma also has important consequences for youth's daily life functioning. In Canada, asthma contributed to 12% and 10% of hospitalizations among 0-4 year olds and 5-14 year olds in 1997, respectively (Health Canada, 2001) and is the leading cause for school absenteeism (Asthma Society of Canada, 2005).

The Impact of Psychological Factors on Asthma

Many factors are believed to influence asthma, with psychological factors often being 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, & Schmaling, 2002).

Most of the research on psychological factors and asthma has focused on studying asthma at the individual level, with fewer studies investigating how the larger social context might play a role among patients, particularly children, with asthma. Some previous studies have investigated whether social networks, for example social support from friends (e.g. Smith & Nicholson, 2001; Wainwright, Surtees, Wareham, & Harrison, 2007) or the psychosocial characteristics of close others, such as parents

[1] A version of this chapter will be submitted for publication. Schreier, H. M. C. and Chen, E. Longitudinal Relationships Between Family Routines and Biological Profiles in Youth With Asthma.

(e.g. Bartlett et al., 2001; Brown et al., 2006; Horwood, Fergusson, & Shannon, 1985; Shalowitz, Berry, Quinn, & Wolf, 2001), impact childhood asthma. These studies found that social support from friends can act as a buffering factor against cold-induced asthma exacerbations. For example, Smith & Nicholson (2001) showed that people with both low social support and more negative life events were the most likely to experience asthma exacerbations. In terms of parent psychosocial characteristics, research has linked traits such as high levels of parental depression 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 et al., 2001). Research to date also suggests that these parent characteristics more strongly predict morbidity in youth already diagnosed with asthma, rather than asthma onset (Horwood et al., 1985).

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, in other words, observable behaviors. Family routines are characterized by direct and instrumental communication and commitment, aiming to effectively deal with tasks that require more immediate attention (Fiese, Foley, & Spagnola, 2006).

Furthermore, family routines form one aspect of family functioning, or the degree to which a family is able to master different situations together as a team (Fiese et al., 2006).

Family Routines and Asthma

Adaptive family functioning in the form of family routines has been shown to have protective effects on youth with asthma. For example, Gustafsson, Kjellman, and Bjørksten (2002) investigated family functioning in children with atopic illness at 18 months and followed them until age 3. They reported that recovery from atopic illness during this time period was four times more likely in children whose families had more functional interactions, defined as the family's ability to adapt to demands of a situation and family cohesion as assessed from videotapes. Furthermore, 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). Another important family routine concerns common mealtimes. In general, healthy youth eating more frequently together with their parents show less evidence of problem behaviors, including less drinking and smoking, and have better mental health (Compan, Moreno, Ruiz, & Pascual, 2002; Eisenberg, Olson, Neumark-Sztainer, Story, & Bearinger, 2004). This also translates to youth with asthma, as Fiese et al. (2006) have shown that the presence of mealtime family routines impacted the mental health of youth with asthma. Youth 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 prom-

ising 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).

Family Routines and Biological Markers of Health

The above studies have all focused on how family routines affect mental and physical health outcomes. However, little is known about the biological pathways through which routines might come to be associated with health. In healthy individuals, there is some evidence that routines are associated with biological markers such as cortisol. 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. 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.

Linking Family Routines to Asthma and Addressing Research Gaps

As mentioned above, 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 impact childhood 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. These inflammatory processes in turn manifest clinically as asthma symptoms, such as wheezing and shortness of breath. Further research is needed about whether family routines can be linked to inflammatory processes relevant

to asthma. Secondly, most previous research has utilized cross-sectional designs. Hence it is unclear whether relationships exist because family routines impact asthma outcomes, or whether worsening asthma disrupts family life and routines. 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 impact youth's 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 medication adherence.

For example, one of the most important components of proper asthma management relates to daily medication adherence. Hence, if family routines are associated with asthma biological profiles, one reason could be that routines help to shape adherence to asthma medications. 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 variables such as medication adher-

ence, or parental depression or stress, altered the association between family routines and inflammatory markers of asthma.

BIBLIOGRAPHY

Asthma Society of Canada (2005). *Asthma facts & statistics*. Retrieved March 20th, 2007, from http://www.asthma.ca/adults/community/pdf/Booklets/ASC_Fact_Sheet_Asthma Statistics.pdf.

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*(3), 347-353.

Brown, E. S., Gan, V., Jeffress, J., Mullen-Gingrich, K., Khan, D. A., Wood, B. L., et al. (2006). Psychiatric symptomatology and disorders in caregivers of children with asthma. *Pediatrics, 118*(6), e1715-1720.

Compan, E., Moreno, J., Ruiz, M. T., & Pascual, E. (2002). Doing things together: adolescent health and family rituals. *Journal of Epidemiology & Community Health, 56*(2), 89-94.

Eisenberg, M. E., Olson, R. E., Neumark-Sztainer, D., Story, M., & Bearinger, L. H. (2004). Correlations between family meals and psychosocial well-being among adolescents. *Archives of Pediatrics & Adolescent Medicine, 158*(8), 792-796.

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 & 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*(4), 405-418.

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*(3), 325-332.

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*(4), 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 & Immunology, 13*(1), 51-57.

Health Canada (2001). *Respiratory Disease in Canada*. Ottawa, Canada: Health Canada.

Horwood, L. J., Fergusson, D. M., & Shannon, F. T. (1985). Social and familial factors in the development of early childhood asthma. *Pediatrics, 75*(5), 859-868.

Lehrer, P., Feldman, J., Giardino, N., Song, H.-S., & Schmaling, K. (2002). Psychological aspects of asthma. *Journal of Consulting and Clinical Psychology, 70*(3), 691-711.

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: An*

International Journal of Quality of Life Aspects of Treatment, Care & Rehabilitation, 9(10), 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*(4), 185-193.

Shen, G. H. C., Sylvia, L. G., Alloy, L. B., Barrett, F., Kohner, M., Iacoviello, B., et al. (2008). Lifestyle regularity and cyclothymic symptomatology. *Journal of Clinical Psychology, 64*(4), 482-500.

Smith, A., & Nicholson, K. (2001). Psychosocial factors, respiratory viruses and exacerbation of asthma. *Psychoneuroendocrinology, 26*(4), 411-420.

Statistics Canada (2007). *Persons with asthma, by age and sex (%)*. Retrieved March 20th, 2007, from http://www40.statcan.ca/l01/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*(10), 1250-1259.

Wainwright, N. W. J., Surtees, P. G., Wareham, N. J., & Harrison, B. D. W. (2007). Psychosocial factors and asthma in a community sample of older adults. *Journal of Psychosomatic Research, 62*(3), 357-361.

CHAPTER TWO[2]

METHODS

Participants

Fifty-nine youth (78% male, n = 46) between the ages of 8-17 years (M = 12.68, 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 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.

Measures

Parent Questionnaires

Family Routines

14 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

[2] A version of this chapter will be submitted for publication. Schreier, H. M. C. and Chen, E. Longitudinal Relationships Between Family Routines and Biological Profiles in Youth With Asthma.

to child routines (e.g., 'Parent talks to his/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, i.e. a more structured family life. Thirty day test-retest reliability has previously been found to be good, with a raw score correlation of r = 0.74. Validity was established by comparing the FRI to a related measure, the Family Environment Scale (Moos, Insel, & Humphrey, 1974) and found to be good as scores on the FRI were a significant predictor of the Family Environment Scale. Since family routines are a relatively stable family trait, family routines were entered as a between-person factor (level two) in our Hierarchical Linear Modeling (HLM) model in order to predict trajectories of immune outcomes.

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. Responses to these questionnaires were entered as between-person factors at level 2 in our HLM model in order to test whether they too predict trajectories of inflammatory cytokines over time and could present possible mechanisms through which routines come to influence biological asthma outcomes.

Parental depression. Parental depression was assessed through the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977). The CES-D is a widely used depression scale consisting of 20 items assessing the frequency of the oc-

currence 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 shown to have an excellent internal consistency of α = .85 in the general population. Parents completed the CES-D as part of their first study visit.

Parental Perceived Stress. Parental perceived stress was assessed through the perceived stress scale (PSS; Cohen, Kamarck, & Mermelstein, 1983). The PSS is a brief 14-item scale asking people to provide information on 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, between α = .84 - .86 in the three samples the PSS was originally validated in. All parents completed the PSS during their first study visit.

General family functioning. Parents completed the general functioning scale of the Family Assessment Device (FAD). The general functioning scale (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 subscale is related to all items in the family assessment device and can be considered a short version of the full scale, which discriminates between nonclinical and psychiatric families (Byles, Byrne, Boyle, & Offord, 1988). The reliability of the general functioning scale was established in a previous large scale study and was found to be α = .86. Moreover, the GFS was significantly correlated with variables such as family structure (single parent versus 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.

Clinical Outcomes

Child Symptoms

At each visit parents were asked about the number of days over the past two 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 M = 3.78 (SD = 5.81) to M = 4.25 (SD = 1.82) points.

Medication Use

Medication use was controlled for by including the number of times youth used inhaled corticosteroids or beta antagonists during the two week period preceding each one of the visits. Each type of medication was coded separately.

Inflammatory markers

Inflammatory cytokines involved in asthma are produced by two types of functionally different T-helper cells and referred to as Th1 and Th2 cytokines. While Th1 cytokines are primarily involved in cell-mediated immunity, Th2 cytokines are involved in humoral immunity, that is, extra-cellular immunity. Th2 cytokines include cytokines such as IL-4, IL-5, and IL-13. As individuals with asthma typically experience a shift towards Th2 cytokines, these cytokines formed the focus of the current study. IL-4 and IL-13, for example, induce the production and proliferation of B cells, which in turn produce immunoglobulin E (IgE). IgE binds to mast cells in the airways, causing them to degranulate and release histamines and leukotrienes, ultimately resulting in typical asthma

symptoms such as airway constriction and inflammation. 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.

Stimulated cytokine production

At each visit participants underwent a blood draw during which peripheral blood was drawn into Cell-Preparation Tubes (CPTs; Becton-Dickinson, Franklin Lakes, NJ) containing Sodium Heparin. Stimulated production of IL-4, IL-5, and IL-13 were measured in vitro. Within two hours of the blood draw all tubes were spun using density-gradient centrifugation. Peripheral mononuclear blood cells (PBMCs) 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 x 10^6 cells/ml. Cells were immediately incubated for 48 hours with phorbol 12-myristate 13-acetate (PMA; 25ng/ml f.c.) and ionomycin (1μg/ml f.c.) at 37°C, 5% CO_2 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 (ELISAs, R&D System, Minneapolis, MN). All assay CVs 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 NAEPP/EPR2 Guidelines based on the higher of symptom frequency and medication use, paralleling the approach of previous researchers (Bacharier et al., 2004).

Procedure

Written assent and consent was obtained from participating youth and their parents, respectively. Participating youth visited the lab 4 times over 1.5 years, on average once every six months, together with a parent. At each visit, youth underwent a peripheral blood draw. At the same time, parents completed computer questionnaires (at baseline) and reported on their children's asthma symptoms over the past two weeks as part of a semi-structured interview conducted by a trained research assistant (at every visit). 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. See Appendix A for copies of the relevant certificates.

Statistical Analyses

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

We first tested the main effect of family routines on stimulated cytokine production. Our dependent variable was stimulated cytokine production, calculated as slope over the 4 assessment time points, thereby representing overall increasing or decreas-

ing trends in stimulated production of IL-4, IL-5, and IL-13 across the 18 month study period. Our main predictor, family routines, was assumed to be a fairly stable variable that differed across families and hence was modeled as a between-person factor (level 2). Youth's asthma severity was entered as a level 2 (between-person) covariate,

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 vary together. To do this, we predicted stimulated cytokine production from youth's asthma symptoms, which, given that they could vary 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, a factor that varies over time. These analyses resulted in person-specific slopes reflecting differential cytokine production at times during which youth are reported to have fewer or more syptoms.

Lastly we assessed potential mechanisms for the relationship between routines and inflammatory trajectories by entering variables that could potentially explain this effect into the model described above. Adherence to medication was entered as a level 1 factor as medication adherence behaviors could change from visit to visit and hence represented a within-person factor. We entered parent depression, parent perceived stress, and general family functioning as level 2 factors because all three variables are assumed to be fairly stable, were only assessed once and represent between-person factors. Hence in this set of analyses, trajectories of stimulated cytokine production

were predicted from asthma severity, the mechanism variable of interest, and family routines.

All relationships were estimated using full maximum likelihood and robust standard errors. Cytokine data were standardized to account for any potential non-systematic 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 below controlling for age and gender. However, neither variable affected our results and thus these additional analyses will not be detailed below. Seventy-six percent of participants had level 1 data available for three or more visits.

RESULTS

Parents reported an average score on the FRI of M = 40.25 (SD = 5.24) on a scale from 14 to 52. Average scores on questionnaires reporting on parental characteristics were M = 10.14 (SD = 8.23) on the CES-D, M = 15.50 (SD = 6.94) on the PSS, and M = 24.43 (SD = 4.40) on the general functioning scale of the FAD. Mean scores on the latter three questionnaires were similar to those found in other studies using these questionnaires in the general population (Byles et al., 1988; Cohen et al., 1983; Radloff, 1977). Parents reported their children to have experienced daytime, nighttime, or exertional asthma symptoms on an average of 3.78 to 4.25 days over the 2 weeks prior to their visiting the lab. See Table 2.1 for an overview of our participants' characteristics.

Family Routines Predicting Trajectories of Stimulated Cytokine Production

Levels of family routines significantly predicted changes in youth's stimulated IL-13 production over time when controlling for asthma severity (B = -.0196, 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. Family routines did not predict changes in IL-4 or IL-5.

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 Adherence Behaviors as a Pathway?

We next tested whether youth's medication adherence behaviors could explain the associations between family routines and stimulated cytokine production trajectories by controlling for medication use. After controlling for medication and asthma severity, family routines did not significantly predict changes in youth's stimulated IL-13 production over time ($B = -.0010$, $SE = .0145$, $p > .50$), suggesting that one possible behavioral pathway through which family routines come to impact childhood asthma is through medication adherence. In contrast, child asthma symptoms were still associated with stimulated production of IL-13 over time when controlling for both severity and medication ($B = .0880$, $SE = .0394$, $p < .05$), suggesting that the relationship between stimulated IL-13 production and asthma symptoms over time persists, even independently of medication adherence.

Parental Psychosocial and General Family Characteristics as Pathways?

We next investigated whether levels of family routines were associated with stimulated cytokine production trajectories via psychosocial parental or more general family characteristics. Pearson correlations revealed that while parental depression was not correlated with family routines ($r = -.20$, $p > .10$), parental perceived stress and scores on the GFS were significantly and marginally correlated with family routines ($r = -.29$, $p < .05$ and $r = -.25$, $p < .10$, respectively).

However, after controlling for parental depression and asthma severity, family routines remained a significant predictor of trajectories of stimulated production of IL-13 ($B = -.0206$, $SE = .0064$, $p < .01$). Similarly, after controlling for parental stress and asthma severity, family routines remained a significant predictor of IL-13 trajectories ($B = -.0223$, $SE = .0068$, $p < .01$). Finally, when family functioning was entered in addition to asthma severity, family routines remained a significant predictor of IL-13 trajectories ($B = -.0180$, $SE = .0148$, $p < .05$). This indicates that the relationship between family routines and youth's stimulated cytokine production is different from the effect of commonly implicated psychosocial parent characteristics and general family functioning. See Table 2.2 for a more detailed overview of our main results.

Table 2.1.

Participant Characteristics.

	n (%)	M (± SD)
N = 59		
Male	46 (78%)	
Female	13 (22%)	
Age		12.68 (± 2.55)
Asthma Severity (%)		
Mild intermittent	12 (20.3%)	
Mild persistent	20 (33.9%)	
Moderate persistent	21 (35.6%)	
Severe persistent	6 (10.2%)	
Parent questionnaires		
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)

Table 2.2.

Family Routines Predicting Trajectories of Stimulated IL-13 Production.

	B	SE	p
IL-13			
Severity	-.0007	.0373	.98
Family Routines	-.0196	.0067	.005
Severity	-.3507	.1925	.07
Inhaled Corticosteroids	-.0482	.0300	.11
Beta Antagonists	.0552	.0345	.11
Family Routines	-.0010	.0145	.94
Severity	-.0002	.0363	.99
Parental Depression	-.0040	.0048	.41
Family Routines	-.0206	.0064	.002
Severity	-.0011	.0362	.98
Parental Stress	-.0057	.0063	.37
Family Routines	-.0223	.0068	.002
Severity	-.0003	.0382	.99
General Family Functioning	.0046	.0148	.76

Family Routines	-.0180	.0086	.04

Note: Each of the five 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 four 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.

BIBLIOGRAPHY

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 & Critical Care Medicine, 170*(4), 426-432.

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*(1), 97-104.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24*(4), 385-396.

Epstein, N. B., Baldwin, L. M., & Bishop, D. S. (1983). The McMaster Family Assessment Device. *Journal of Marital & Family Therapy, 9*(2), 171-180.

Jensen, E. W., James, S. A., Boyce, W. T., & Hartnett, S. A. (1983). The Family Routines Inventory: Development and validation. *Social Science & Medicine, 17*(4), 201-211.

Moos, R. H., Insel, P., & Humphrey, B. (1974). *Family Environment Scale: Preliminary Manual*. Palo Alto, CA: Consulting Psychologists Press.

Radloff, L. S. (1977). The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*(3), 385-401.

CHAPTER THREE[3]

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 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. Furthermore, these differences in stimulated IL-13 production have clinical relevance as within-person changes in IL-13 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 can lead to 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.

[3] A version of this chapter will be submitted for publication. Schreier, H. M. C. and Chen, E. Longitudinal Relationships Between Family Routines and Biological Profiles in Youth With Asthma.

In addition, our study examined several possible psychological and behavioral pathways through which family routines could have come to impact youth's stimulated IL-13 production over time. One possibility was that family routines would affect asthma through effects on medication adherence. Research suggests that medication adherence 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 medication use the 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 successfully adhere to their prescribed medication regimen. Fiese, Wamboldt, and Anbar (2005) reported that specific medication routines were related to clinical asthma outcomes in youth. Specifically, building routines around medication taking and reminding youth to take their medication were related to a greater number of asthma-related physician visits (perhaps indicating that these families are more frequently getting medications refilled), greater adherence to daily medication, fewer missed controller puffs and a smaller number of rescue inhaler puffs at a time. Thus, family functioning in the form of asthma-related routines impacts the amount of medication actually taken on a regular basis and needed in case of asthma exacerbations.

One reason that family routines may facilitate adherence to asthma medication 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. For example, families that stress the importance of having breakfast together every morning may simply regulate their child's medication adherence by integrating it into preexisting breakfast routines. This may be as straightforward as keeping the child's medication on the breakfast table, visible for everyone. However, in families where every member of the family independently prepares to leave the house in the morning, supervising a child's regular medication adherence may be markedly more difficult. In other words, 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.

In contrast, we found that parent psychological characteristics, such as parental depression or stress, and overall family functioning could not explain 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. While 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 parent psychosocial characteristics. Hence our results imply that family routines contribute to youth's asthma morbidity in ways separate from parent psychological states and overall family functioning.

There are a number of strengths to this study. Firstly, 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 time points, we were also able to take advantage of a more powerful statistical technique, hierarchical linear modeling, in order to model trajectories of change over time in biological variables.

Limitations of the current study include 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.

Future studies should also conduct more rigorous investigations of whether family routines impact immunological asthma outcomes through adherence to medication, for example by electronically monitoring youth's medication adherence over a period of time to get a more detailed and unbiased account of medication use. Focusing on improving medication adherence by integrating it into family routines instead of simply educating people about the importance of medication adherence without providing concrete recommendations for daily implementation may improve youth's adherence to their daily controller medication.

In addition, future research should explore whether there are certain types of families for which family routines are more important than others. Family routines may be particularly beneficial to youth living in families where caregivers are able to spend only limited time with their children, for example because of work demands. By nonetheless providing youth with structure through ensuring that certain family activities are part of a stable family routine that remains in place despite other demands on the family members, parents may be able to install added feelings of security in their children and thus exert protective effects on them. 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. Lastly, future research should explore the possibility that family routines impact youth's inflammatory markers through other pathways, such as nighttime waking as a result of poor bedtime routines.

Finally, it is worth noting 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. Unlike IL-13, IL-5 increases eosinophils production in the airways. Increased numbers of eosinophils in turn damage the lining of airways and are thought to be at least partly responsible for the longer-term inflammatory process of asthma. Because IL-5 operates through a different pathway from IL-13 it is not entirely surprising that family routines would impact one but not the other.

However, IL-4 and IL-13 are assumed to impact airway inflammation through the same pathway and 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 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.

In sum, our study demonstrated that family routines impact clinical asthma outcomes through biological pathways, in this case through stimulated IL-13 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 while there exists a relationship between family routines and stimulated IL-13 production, this relationship is not explained by other psychosocial characteristics including parental depression and perceived stress as well as general family functioning, 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 result in improved profiles, both biologically and clinically, in youth with asthma.

BIBLIOGRAPHY

Bender, B., Milgrom, H., Rand, C., & Ackerson, L. (1998). Psychological factors associated with medication nonadherence in asthmatic children. *Journal of Asthma, 35*(4), 347-353.

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*(2), 171-176.

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*(4), 185-193.

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*(6), 1274-1280.

Appendix A

The University of British Columbia
Office of Research Services
Behavioural Research Ethics Board
Suite 102, 6190 Agronomy Road, Vancouver, B.C. V6T 1Z3

CERTIFICATE OF APPROVAL- MINIMAL RISK RENEWAL

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC BREB NUMBER:
Edith Chen	UBC/Arts/Psychology, Department of	H03-80540

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
UBC	Vancouver (excludes UBC Hospital)
Children's and Women's Health Centre of BC (incl. Sunny Hill)	Children's and Women's Health Centre of BC (incl. Sunny Hill)

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):

Alexander C. Ferguson
Greg Miller
Robert Strunk
Ronald Barr
Sheldon Cohen

SPONSORING AGENCIES:

Canadian Institutes of Health Research (CIHR) - "Socioeconomic Status, Stress, & Asthma Biological Markers" - "Effects of Socioeconomic Status and Stress on Children's Health"
National Institutes of Health - "Socioeconomic Status, Stress, & Asthma Biological Markers"
UBC Human Early Learning Partnership (HELP) - "Socioeconomic Status, Stress, & Asthma Biological Markers"
William T. Grant Foundation - "Socioeconomic Status, Stress, & Asthma Biological Markers"

PROJECT TITLE:
Socioeconomic Status, Stress, & Asthma Biological Markers

EXPIRY DATE OF THIS APPROVAL: May 22, 2009

APPROVAL DATE: May 22, 2008

The Annual Renewal for Study have been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.

Approval is issued on behalf of the Behavioural Research Ethics Board and signed electronically by one of the following:

Dr. M. Judith Lynam, Chair
Dr. Ken Craig, Chair
Dr. Jim Rupert, Associate Chair
Dr. Laurie Ford, Associate Chair
Dr. Daniel Salhani, Associate Chair
Dr. Anita Ho, Associate Chair

The University of British Columbia
Office of Research Services and Administration
Behavioural Research Ethics Board

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	NUMBER
Chen, E	Psychology	**B03-0540**

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

UBC Campus ,

CO-INVESTIGATORS:

Cohen, Sheldon, ; Miller, Gregory, Psychology; Strunk, Robert,

SPONSORING AGENCIES

National Institutes of Health

TITLE :

Socioeconomic Status, Stess, & Asthma Biological Markers

APPROVAL DATE	TERM (YEARS)	DOCUMENTS INCLUDED IN THIS APPROVAL:
SEP 25 2003	1	Sept. 23, 2003, Assent form / Consent form / Aug. 18, 2003, Advertisement / Questionnaires

CERTIFICATION:

The protocol describing the above-named project has been reviewed by the Committee and the experimental procedures were found to be acceptable on ethical grounds for research involving human subjects.

Approval of the Behavioural Research Ethics Board by one of the following:
Dr. James Frankish, Chair,
Dr. Cay Holbrook, Associate Chair,
Dr. Susan Rowley, Associate Chair

This Certificate of Approval is valid for the above term provided there is no change in the experimental procedures

The University of British Columbia
Office of Research Services and Administration
Behavioural Research Ethics Board

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	NUMBER
Chen, E.	Psychology	**B03-0540**

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

Children's & Women's Health Centre , UBC Campus,

CO-INVESTIGATORS:

Barr, Ronald, Paediatrics; Cohen, Sheldon, ; Ferguson, Alexander, Paediatrics; Miller, Greg, Psychology; Strunk, Robert,

SPONSORING AGENCIES

Human Early Learning Partnership (HELP)

TITLE :

Socioeconomic Status, Stress, & Asthma Biological Markers

APPROVAL DATE	TERM (YEARS)	AMENDMENT:	AMENDMENT APPROVED:
03-09-25 (yr/mo/day)	1	Jan. 8, 2004, Consent form / Questionnaire / Reimbursement / New source of fund / New co-inve. / Study location	

CERTIFICATION:

The protocol describing the above-named project has been reviewed by the Committee and the experimental procedures were found to be acceptable on ethical grounds for research involving human subjects.

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INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

Children's & Women's Health Centre , UBC Campus,

CO-INVESTIGATORS:

Barr, Ronald, Paediatrics; Cohen, Sheldon, ; Ferguson, Alexander, Paediatrics; Miller, Greg, Psychology; Strunk, Robert,

SPONSORING AGENCIES

Canadian Institutes of Health Research

TITLE :

Effects of Socioeconomic Status and Stress on Children's Health

APPROVAL DATE	TERM (YEARS)	AMENDMENT:	AMENDMENT APPROVED:
04-08-31 (yr/mo/day)	1	Oct. 26, 2004, Procedures / Oct. 25, 2004 Consent form / Assent form / Questionnaires	NOV 12 2004

CERTIFICATION:

The protocol describing the above-named project has been reviewed by the Committee and the experimental procedures were found to be acceptable on ethical grounds for research involving human subjects.

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Dr. Susan Rowley, Associate Chair
Dr. Anita Hubley, Associate Chair

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INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

Children's & Women's Health Centre , UBC Campus,

CO-INVESTIGATORS:

Barr, Ronald, Paediatrics; Cohen, Sheldon, ; Ferguson, Alexander, Paediatrics; Miller, Greg, Psychology; Strunk, Robert,

SPONSORING AGENCIES

Canadian Institutes of Health Research

TITLE :

Socioeconomic Status, Stress, & Asthma Biological Markers

APPROVAL DATE	TERM (YEARS)	AMENDMENT:	AMENDMENT APPROVED:
03-09-25 (yr/mo/day)	1	March 23, 2004, Questionnaire	APR - 5 2004

CERTIFICATION:

The protocol describing the above-named project has been reviewed by the Committee and the experimental procedures were found to be acceptable on ethical grounds for research involving human subjects.

Approval of the Behavioural Research Ethics Board by one of the following:
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CO-INVESTIGATORS:

Barr, Ronald, Paediatrics; Cohen, Sheldon, ; Ferguson, Alexander, Paediatrics; Miller, Greg, Psychology; Strunk, Robert,

SPONSORING AGENCIES

Canadian Institutes of Health Research

TITLE :

Socioeconomic Status, Stress, & Asthma Biological Markers

APPROVAL DATE	TERM (YEARS)	AMENDMENT:	AMENDMENT APPROVED:
03-09-25 (yr/mo/day)	1	Feb. 26, 2004, Questionnaire	MAR 1 [illegible] 2004

CERTIFICATION:

The protocol describing the above-named project has been reviewed by the Committee and the experimental procedures were found to be acceptable on ethical grounds for research involving human subjects.

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CO-INVESTIGATORS:

Barr, Ronald, Paediatrics; Cohen, Sheldon, ; Ferguson, Alexander, Paediatrics; Miller, Greg, Psychology; Strunk, Robert,

SPONSORING AGENCIES

Grant (William T.) Foundation (US)

TITLE:

Socioeconomic Status, Stress, & Asthma Biological Markers

APPROVAL DATE	TERM (YEARS)	AMENDMENT:	AMENDMENT APPROVED:
03-09-25 (yr/mo/day)	1	Jan. 8, 2004, Consent form / Questionnaire / Reimbursement / New source of fund / New co-inve. / Study location	JAN 2 2 2004

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Dr. Susan Rowley, Associate Chair

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