

THE IMPACT OF HEALTH BELIEFS AND FAMILY ASTHMA MANAGEMENT ON
BIOLOGICAL OUTCOMES IN YOUTH WITH ASTHMA

by

HOPE ALAYNE WALKER

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ABSTRACT

Childhood asthma is a chronic inflammatory disease, with symptoms likely affected by physical, environmental and social factors. With regard to social factors, previous research has linked asthma management and beliefs to morbidity outcomes in children with asthma. In two studies, it was tested whether beliefs about and management of one's illness would predict biological outcomes cross-sectionally (in Study 1), and longitudinally over 18 months (in Study 2) in a sample of children with asthma. Associations of asthma management-related beliefs and behaviors with immune markers and clinical outcomes were examined in a sample of 66 children with asthma (ages 9-18) in Study 1, and longitudinal associations of asthma management-related beliefs and behaviors with changes in asthma-relevant biological markers in a subsample of 40 children with asthma in Study 2. Children and parents were interviewed about asthma management beliefs and behaviors. In Study 1, immune measures included stimulated production of cytokines implicated in asthmatic airway inflammation, eosinophil counts, and IgE levels. Clinical outcomes included pulmonary function, symptoms, beta agonist use, and physician contacts. In Study 2, asthma outcomes included lung function (FEV₁%), eosinophil counts, and daily cortisol measured at two time points, 18 months apart. In Study 1, children's reports of greater conceptual understanding of asthma, parents' reports of quicker responses to asthma symptoms, and children's and parents' reports of more balanced integration of asthma into daily life were all associated with reduced inflammatory profiles. Inflammatory profiles were found to be a statistically significant pathway linking asthma beliefs and behaviors to clinical outcomes. In Study 2, children with a less sophisticated disease belief (the "no symptoms, no asthma" belief) displayed eosinophil counts that increased over time, controlling for baseline levels. Poorer family asthma management was associated with increasing eosinophil

counts over time. Poorer child asthma management was associated with cortisol output that declined over time. Families who reported poorer collaboration with their physician had children who displayed worsening lung function over time. These findings suggest that interventions aimed at teaching families better asthma management approaches and more accurate disease beliefs may have the potential to alter biological profiles in children with asthma.

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CO-AUTHORSHIP STATEMENT

Hope A. Walker has made significant contributions to several parts of these studies, in particular the project management, interview training, study designs, data collection, data analysis, and manuscript preparation. Dr. Edith Chen has made significant contributions to several parts of these studies, including interview training, study designs, data analysis, and manuscript preparation.

CHAPTER ONE

Introduction

Researchers have long been interested in the role of psychological beliefs in physical illnesses (Kirscht, Haefner, Kegeles, & Rosenstock, 1966). Health-related beliefs may include cognitions and attitudes about what illness is, how one should respond to symptoms, and how efficacious such responses would be. In turn, beliefs are thought to underlie the behaviors that individuals engage in, and subsequently, their health outcomes (Rosenstock, Strecher, & Becker, 1988; Bandura, 1986). Very little empirical data exist, however, testing whether there are biological correlates of beliefs that could explain how beliefs might affect clinical outcomes. As such, we endeavored to test in a preliminary investigation, biological pathways between psychological beliefs and behaviors and clinical outcomes in a sample of children with asthma.

Asthma is the most common chronic illness in youth, and is a leading cause of school absenteeism and a major cause of hospitalizations in Canada (Asthma Society of Canada, 2005) and the United States (Akinbami, 2006; DeFrances, Cullen, & Kozak, 2007), with an associated annual cost of \$3.2 billion to treat youth under the age of 18 (Weiss, Sullivan, & Lytle, 2000). Reasons for asthma exacerbation are numerous, and include physical, environmental and psychological factors. With respect to psychosocial contributors to asthma exacerbations and symptoms, one important area of research has found that asthma-related beliefs are linked to both behavioral and clinical outcomes. Several studies of adults with asthma have found that certain beliefs are associated with behavioral outcomes such as treatment adherence. In particular, poorer adherence to medication regimens has been associated with beliefs that medications are inefficacious or only necessary when symptomatic, and the belief that asthma only exists when one is symptomatic (Byer & Myers, 2000; Horne & Weinman, 2002; Halm,

Mora, & Leventhal, 2006). Maladaptive disease beliefs such as these are of particular relevance to study, when health status is potentially threatened due to non-adherence. As such, it is important to attempt to identify effects of disease beliefs on health outcomes, in an attempt to discern maladaptive disease beliefs and rectify them. Further, poorer adherence to medication regimens has been associated with concerns about the adverse effects of medications (Jessop & Rutter, 2003). Ideally, with proper educational information from physicians, concern about adverse effects of medications may be dissuaded, again in an effort to promote adherence to preventive medications. Conversely, attributing one's asthma to external causes has been shown to be associated with greater adherence (Byer & Myers, 2000), which suggests that certain beliefs are prone to promote adherence, in contrast to those which hinder it. Beliefs are consequently an important construct to study among individuals with asthma, due to the potential resultant impact on biology.

In children with asthma, belief about one's ability to perform behaviors beneficial to asthma (self-efficacy) has been associated with clinical outcomes such as asthma morbidity. Both greater child self-efficacy as well as greater parent self-efficacy have been shown to be associated with better child health status and fewer symptoms among children with asthma (Bursch, Schwankovsky, Gilbert, & Zeiger, 1999). In addition, positive beliefs among parents about how helpful asthma management behaviors would be were associated with fewer days of wheezing and better health status in children with asthma (Wade, Holden, Lynn, Mitchell, & Ewart, 2000). Parent self-efficacy has also been linked to a host of morbidity outcomes in their children with asthma, including: functional status, hospital admissions in the past year, emergency room visits in the past year, days of school missed in the past 2 months and in the past year, parents having to change plans, the child waking up because of asthma, taking asthma

medications, and a parent losing sleep (Grus et al., 2001). Across these studies, evidence supports the notion that both parental and child beliefs about asthma and their abilities to manage it, have an impact on relevant clinical and morbidity outcomes.

With respect to asthma-related beliefs, previous research has found that beliefs are related to both management behaviors, as well as clinical outcomes (Walker, Chim, & Chen, 2009). Much of the work in this area with families of children with asthma has documented beliefs about behavioral outcomes such as treatment adherence. For example, parental fear and overconcern about medications have been linked to poor adherence in children, in a study where only 22% of parents reported being completely adherent with their child's asthma medications (Conn, Halterman, Fisher, Yoos, Chin, & Szilagyi, 2005). Further, in another study it was shown that poorer medication adherence among children was associated with parental concern about medication side effects (Chan & DeBruyne, 2000). Recent findings from Conn and colleagues (2007) suggest that the balance between parents' positive and negative beliefs about medication use (that is, the balance between necessity and concern beliefs regarding their child's asthma medications) impacts medication adherence in children, such that a higher rating of necessity rather than concern, predicted better adherence. Beliefs about the chronicity of asthma have also been examined, and in a sample of inner-city adults, Halm and colleagues (2006) identified an acute disease belief termed the "no symptoms, no asthma" belief, held by those who believed they had asthma only when symptomatic, rather than believing that asthma is a chronic illness that is always present. This belief was found to be associated with lower adherence to inhaled corticosteroids (ICS) when asymptomatic. Since asthma is a chronic illness, if individuals consider it to be an acute recurring condition, rather than a chronic illness which

requires regular controller medications to treat, there are likely treatment implications as manifested by poorer adherence, which has been demonstrated by Halm and colleagues.

Better asthma management in terms of a better integration of asthma into the family's daily life, a more collaborative relationship with physicians, and more timely responses to symptoms all have been associated with decreased asthma morbidity in children (McQuaid, Walders, Kopel, Fritz, & Klinnert, 2005). Also, there is some evidence to suggest that knowledge is associated with behaviors in childhood asthma. Having better knowledge is a likely first step in correct management of the illness (Sin, Kang, & Weaver, 2005). Greater knowledge about asthma was associated with better management behaviors among African-American adolescents, such as seeking help from others or resting, when symptomatic (Sin et al., 2005). However, other studies have not found significant effects of knowledge (McQuaid et al., 2005; Wade et al., 2000). These inconsistencies may be due to differences in the way asthma knowledge was tested, or perhaps due to differences in age or demographics. As such this is a relationship which merits further investigation in order to determine whether knowledge impacts asthma management and behaviors. Developmental changes in understanding childhood illness have also been examined (McQuaid, Howard, Kopel, Rosenblum, & Bibace, 2002), and in a sample of children ages 7-16 with persistent asthma, age was positively associated with factual knowledge regarding asthma, and the conceptual sophistication of reasoning about asthma.

Researchers have also focused on the role of asthma management and beliefs. This research has shown that within the family, better asthma management and certain asthma beliefs can have an impact on childhood asthma. However, the bulk of research in this area has focused on clinical outcomes such as healthcare utilization, while the specific biological mechanisms through which asthma management and beliefs come to impact asthma outcomes have been

largely neglected. Previous research has also linked both asthma management techniques as well as asthma-related beliefs, to morbidity outcomes in children with asthma. Asthma management refers broadly to both preventive and rescue strategies implemented by families to improve symptoms in children with asthma. Research on asthma management has focused on identifying associations between at-home behaviors, such as washing bed sheets regularly in hot water, with asthma morbidity. These behaviors have been shown to be related to decreased rates of hospitalizations and emergency room (ER) visits (Lieu, Quesenberry, Capra, Sorel, Martin, & Mendoza, 1997). Another research focus has been on the association between better medical management and morbidity. For example, having a written action plan has been found to be associated with fewer return ER visits, more well visits, and greater confidence in the ability to prevent asthma episodes (Sockrider et al, 2006), as well as with decreased rates of hospitalizations and emergency room (ER) visits (Lieu et al, 1997). Further, increasing medication use at the onset of a cold or flu was also related to decreased rates of hospitalizations and emergency room (ER) visits (Lieu et al, 1997). Overall, these studies indicate that having prescribed management techniques and behaviors have a positive impact on asthma outcomes.

Some research has focused on specific components of family asthma management and their associations with morbidity. In particular, using the well-validated Family Asthma Management System Scale interview (FAMSS), decreased asthma morbidity in children has been shown to be associated with such family asthma management dimensions as better integration of asthma into the family's daily life, a more collaborative relationship with physicians, and more timely responses to symptoms (McQuaid et al., 2005). However, there are some authors who have argued that the associations between asthma management and school absenteeism, asthma attacks, hospitalizations, hospital days, or ER visits are not reliable

(Bernard-Bonnin, Stachenko, Bonin, Charette, & Rousseau, 1995). Again, this dissonance requires further investigation, and a more systematic conceptualization of family asthma management. With the relatively recent availability of the FAMSS, this type of in-depth analysis is possible.

Other asthma management research has focused on interventions and patient education to improve at-home management. Shegog and colleagues created the Stop Asthma Clinical System (SACS, 2006), an intervention targeting physician behavior, with resultant effects on patient asthma management and clinical outcomes. The intervention was shown to be effective at improving patient self-management via improved physician behavior during clinic visits, resulting in the creation of an action plan, assessment of asthma severity and control, and identification of environmental trigger management problems. Another intervention approach, the asthma self-management and education program Health Buddy, enlisted children to assess and monitor their asthma symptoms and transmit this information to health care providers through a website (Guendelman, Meade, Benson, Chen, & Samuels, 2002). This intervention has been shown to be associated with reporting fewer limitations in activity levels, as well as better peak flow readings, and fewer urgent calls to the hospital. Further, a recent meta-analysis found that providing pediatric asthma education reduced the mean number of hospitalizations and ER visits, and the odds of an ER visit for asthma, but not the mean number of urgent physician visits or the odds of hospitalization (Coffman, Cabana, Halpin, & Yelin, 2008).

All of the above studies have focused on either the links between beliefs or asthma management and clinical or behavioral outcomes in asthma. However, many of them have been cross-sectional, thus preventing direct testing of whether beliefs and management come to impact asthma outcomes, or whether the reverse may be true. It may be that having worse

asthma is more difficult to manage, and has an impact on illness beliefs. Much research has also focused on either children or parents, and has not incorporated both family members in assessing asthma management practices. Finally, very little research has explored the possible biological mechanisms through which asthma management beliefs and behaviors may be linked to clinical outcomes, or how these beliefs and management practices might alter biological processes to explain associations with clinical outcomes. Elucidating biological mechanisms is important for developing plausible models of how it is that psychological factors such as beliefs can have clinical manifestations in terms of disease outcomes. With respect to possible biological mechanisms, asthma is known to be an inflammatory disease. During an asthma exacerbation, antigens activate T cells which release chemical messengers known as cytokines (IL-4 and IL-13) that activate B cells and signal these cells to produce immunoglobulin E (IgE), which in turn stimulates mast cells to release histamine (Janeway, Travers, Walport, & Shlomchik, 2001, p.472). Additionally, other cytokines (IL-5) activate eosinophils, which also produce histamine and leukotrienes. The production of histamines and leukotrienes leads to the symptom profile associated with asthma (airway constriction and mucus production). Thus assessing the production of these cytokines, known as Th2 cytokines (IL-4, IL-5, IL-13), as well as circulating levels of IgE and eosinophils provides an indication of the extent of an inflammatory profile relevant to asthma. Further, the anti-inflammatory hormone cortisol is implicated in the dampening or cessation of this response, such that cortisol binds to immune cells to signal termination of the production of certain cytokines. Thus assessing the production of cortisol, as well as circulating levels of asthma-relevant cytokines and eosinophils provides an indication of inflammatory processes relevant to asthma. Also relevant to studying the effects of beliefs and

management on biological measures is a more direct measure of pulmonary function, via spirometry. Such a measure provides an indication of the clinical profile of asthma.

Despite the fact that asthma is quite well characterized biologically, very little research exists which explores associations between psychological characteristics of the illness experience (e.g. health beliefs; illness management) with relevant biological outcomes. Though largely neglected, this is an important area which requires future investigation due to the potential for intervention. If for example, we are able to discern which beliefs or management strategies are closely tied to biology, it may be that we are able to intervene and improve health outcomes among children with asthma. This is especially crucial given the increasing prevalence of the illness among children in North America - 13% in Canada (Garner & Kohen, 2008) and 9.1% in the United States (Akinbami, Moorman, Garbe, & Sondik, 2009). Alternative treatment strategies may be adopted in concert with those already prescribed, and by enlisting parents, adherence may be strengthened. Traditionally, physicians and health psychologists have not typically worked together in an effort to improve the physical health of children with asthma, and as such this is a necessary first step towards improved treatment outcomes, by first identifying psychological contributors to relevant biological processes implicated in asthma. Once we identify which elements of family asthma management are most closely tied to biology, we can attempt to ameliorate these particular components of asthma management (e.g. physician collaboration; asthma knowledge). Further, if we determine whether holding certain disease beliefs are related to poor biological outcomes, we can aim to correct such false beliefs.

In consideration of this gap in the existing literature, we sought to identify relationships among these psychological variables relevant to the illness process (health beliefs and family asthma management) with a number of different biological measures related to asthma. It was

our intention to uncover whether these psychological processes were related in a meaningful way to asthma biology, among youth with asthma.

The Current Studies

In a first attempt to discern whether asthma management beliefs and behaviors have biological correlates in children with asthma, Study 1 sought to explore this cross-sectionally among a sample of children physician-diagnosed with asthma. Since this was a preliminary investigation, we measured asthma-related beliefs among children and their parents, along with immune and clinical measures relevant to asthma biology in children, with two research questions in mind: 1) whether beliefs and self-reported behaviors were associated with immune markers implicated in asthma; and 2) whether these immune markers statistically mediated the relationship between asthma management beliefs/behaviors and clinical asthma outcomes. With these questions in mind, we hypothesized 1) that asthma management dimensions including greater knowledge, better response strategies, and better integration of asthma into daily life would be associated with reduced inflammatory profiles in children with asthma, and 2) that these inflammatory profiles would serve as one pathway between asthma management and clinical outcomes.

Evidence for this relationship emerged, such that children from those families with better ratings of asthma management beliefs and behaviors, in terms of greater conceptual understanding of asthma among children, belief in quicker responsiveness to symptoms among parents, and better integration of asthma into daily life, were all associated with decreased inflammatory profiles in children. However, this study had a number of limitations – refer to Chapter 4 for an extensive discussion – primarily being that it was cross-sectional, and that the

assessment of beliefs and behaviors was brief. We wanted to test these relationships again, using a more intensive interview of family asthma management, which included both parents and children on each dimension, and we wanted to test whether biological measures were changing over time among youth with asthma, depending on their family's asthma management. As a direct result of the promising findings of Study 1, we endeavored to address some of these limitations with Study 2. This second investigation sought to elucidate some of the biological mechanisms through which family beliefs about and management of one's illness, are related to asthma biological outcomes longitudinally in a sample of children with asthma.

More specifically, in Study 2 we examined whether family asthma management and beliefs could predict longitudinal changes over time in biological measures in a sample of children with asthma, using a more extensive and well-established family asthma management interview (the FAMSS, McQuaid et al., 2005). In this study, we also incorporated the disease belief characterized by Halm and colleagues (2006) called the "no symptoms, no asthma" disease belief whereby children considered their asthma to be either acute episodic, or chronic. We were interested in knowing whether children with this less sophisticated disease belief (to think of asthma as being a series of acute episodes rather than it being a chronic illness which requires regular treatment) had poorer health outcomes on a number of asthma-relevant biological indicators. We hypothesized that children from families with poorer asthma management strategies, as well as those children who held the "no symptoms, no asthma" acute disease belief, would show increases in inflammatory profiles, decreases in cortisol output, and poorer pulmonary function over an 18 month period. This study, to the best of our knowledge, was the first attempt at examining these relationships longitudinally, and holds promise for future intervention potential.

Overall, this pair of studies was a unique attempt at documenting associations between beliefs and family asthma management with biological processes implicated in asthma, and offered a focus on youth. Results from Studies 1 and 2 have been written up for publication in scientific journals and are contained within Chapters 2 and 3, respectively. Study 1 has been published exactly as it reads in Chapter 2, and Study 2 will be submitted for publication as it reads presently in Chapter 3. As such, each of these chapters are self-contained and the reader may detect some redundancy in the following chapters. An overarching discussion may be found in the concluding chapter.

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CHAPTER TWO¹

Study 1: The Role of Asthma Management Beliefs and Behaviors in Childhood

Asthma Immune and Clinical Outcomes

INTRODUCTION

Researchers have long been interested in the role of psychological beliefs in physical illnesses (Kirscht, Haefner, Kegeles, & Rosenstock, 1966). Health-related beliefs may include cognitions and attitudes about what illness is, how one should respond to symptoms, and how efficacious such responses would be. In turn, beliefs are thought to underlie the behaviors that individuals engage in, and subsequently, their health outcomes (Rosenstock, Strecher, & Becker, 1988; Bandura, 1986). Very little empirical data exist, however, testing whether there are biological correlates of beliefs that could explain how beliefs might affect clinical outcomes. The present study tested biological pathways between psychological beliefs and behaviors and clinical outcomes in a sample of children with asthma.

Previous research has found that asthma-related beliefs are linked to both behavioral and clinical outcomes. Several studies of adults with asthma have found that certain beliefs are associated with behavioral outcomes such as treatment adherence. For example, poorer adherence to medication regimens has been associated with beliefs that medications are inefficacious or only necessary when symptomatic, concerns about adverse effects of medications, and the belief that asthma only exists when one is symptomatic (Byer & Myers, 2000; Jessop & Rutter, 2003; Horne & Weinman, 2002; Halm, Mora, & Leventhal, 2006).

In children with asthma, belief about one's ability to perform behaviors beneficial to asthma (self-efficacy) has been associated with clinical outcomes such as asthma morbidity.

¹ A version of this chapter has been published. Walker, H.A., Chim, L., & Chen, E. (2009). The role of asthma management beliefs and behaviors in childhood asthma immune and clinical outcomes. *Journal of Pediatric Psychology, 34*, 379-388.

Both greater child self-efficacy as well as greater parent self-efficacy were associated with better child health status and fewer symptoms among children with asthma (Bursch, Schwankovsky, Gilbert, & Zeiger, 1999). In addition, positive beliefs among parents about how helpful asthma management behaviors would be were associated with fewer days of wheezing and better health status in children with asthma (Wade, Holden, Lynn, Mitchell, & Ewart, 2000). Better asthma management in terms of a better integration of asthma into the family's daily life, a more collaborative relationship with physicians, and more timely responses to symptoms all have been associated with decreased asthma morbidity in children (McQuaid, Walders, Kopel, Fritz, & Klinnert, 2005). Finally, there is some evidence to suggest that knowledge is associated with behaviors in childhood asthma. For example, greater knowledge about asthma was associated with better management behaviors in African-American adolescents (Sin, Kang, & Weaver, 2005), although other studies have not found significant effects of knowledge (McQuaid et al., 2005; Wade et al., 2000). Developmental changes in understanding childhood illness have also been examined (McQuaid, Howard, Kopel, Rosenblum, & Bibace, 2002), and in a sample of children ages 7-16 with persistent asthma, age was positively associated with factual knowledge regarding asthma, and the conceptual sophistication of reasoning about asthma.

All of the above studies have focused on the links between beliefs and clinical and behavioral outcomes in asthma. Very little research has explored the possible biological mechanisms through which asthma management beliefs and behaviors may be linked to clinical outcomes. Elucidating biological mechanisms is important for developing plausible models of how it is that psychological factors such as beliefs can have clinical manifestations in terms of disease outcomes. With respect to possible biological mechanisms, asthma is known to be an inflammatory disease. During an asthma exacerbation, antigens activate T cells which release

chemical messengers known as cytokines (IL-4 and IL-13) that activate B cells and signal these cells to produce immunoglobulin E (IgE), which in turn stimulates mast cells to release histamine (Janeway, Travers, Walport, & Shlomchik, 2001, p.472). Additionally, other cytokines (IL-5) activate eosinophils, which also produce histamine and leukotrienes. The production of histamines and leukotrienes leads to the symptom profile associated with asthma (airway constriction and mucus production). Thus assessing the production of these cytokines, known as Th2 cytokines (IL-4, IL-5, IL-13), as well as circulating levels of IgE and eosinophils provides an indication of the extent of an inflammatory profile relevant to asthma.

Thus the current study sought to explore whether asthma management beliefs and behaviors have biological correlates in children with asthma. Specifically, we examined: 1) whether beliefs and self-reported behaviors were associated with immune markers implicated in asthma; and 2) whether these immune markers statistically mediated the relationship between asthma management beliefs/behaviors and clinical asthma outcomes. We hypothesized 1) that asthma management dimensions including greater knowledge, better response strategies, and better integration of asthma into daily life would be associated with reduced inflammatory profiles in children with asthma, and 2) that these inflammatory profiles would serve as one pathway between asthma management and clinical outcomes.

METHODS

Participants

Sixty-six children with asthma living in Vancouver, B.C., Canada between the ages of 9 and 18 comprised this sample. Average age was 12.8 ($SD = 2.8$), 66% were male, 66% were Caucasian (19% Asian descent, 1% African descent, 1% Latin American descent, 4% Native descent, and 9% self-identified as Other ethnicity), 83% of parents participating were mothers,

average years of maternal education was 15.9 ($SD = 3.0$), and average family income fell into the \$50,000 – 74,999 category. Families were recruited via asthma and allergy clinics, newspaper ads, school newsletters, and community flyers. Eligibility criteria included physician diagnosis of asthma, no other chronic illnesses, proficiency in English, and not on any prescription medications other than asthma medications. Study visits were postponed if children were sick on the day of their scheduled appointment. Ethical approval was granted by the Ethics Board of the University of British Columbia.

Measures

The Health Beliefs Interview

Children and parents were interviewed separately about asthma management beliefs and behaviors, using the Health Beliefs Interview. This open-ended interview developed for this study assessed children's and parents' beliefs about asthma and its management, as well as the behaviors that they engaged in associated with asthma exacerbations. Although the Health Beliefs Interview was a shorter interview, and was administered separately to children and parents, a number of the questions paralleled those of the Family Asthma Management System Scale (FAMSS), a more extensive asthma management interview that has excellent reliability and validity (McQuaid et al, 2005; Klinnert, McQuaid, & Gavin, 1997). We drew on the conceptualization of the FAMSS when we developed our coding scheme for the Health Beliefs Interview. The subscales included in this interview were child conceptual understanding, child and parent response to asthma symptoms, and child and parent balanced integration.

Conceptual Understanding of Illness (Child). Children's understanding of asthma was probed by asking them to explain what asthma was, and any potential causes, triggers, and biological mechanisms involved in asthma. Responses were scored on a 1-6 scale with higher

numbers reflecting a greater conceptual understanding of asthma. The categories of this scale included: 'Phenomenism,' representing a score of 1, reflecting the least amount of knowledge; 'Contagion,' a score of 2; 'Contamination,' a score of 3; 'Internalization,' a score of 4; 'Physiological,' a score of 5; and 'Psychophysiological,' the highest score of 6, reflecting the greatest conceptual understanding of asthma. Guidelines for rating conceptual understanding were drawn from the Developmental Levels of Illness Concepts scale (McQuaid et al., 2002). At the lower end of the scale, children described asthma without clear differentiation between cause and effect – for example, confusing triggers with symptoms of asthma by believing that asthma is caused by chest tightness. At the upper end of the scale, children were able to describe the illness in a psychophysiological sense, attributing multiple causes and their resultant effects on the illness – for example, attributing allergic and psychological triggers and describing changes to the airways and immune system, leading to the symptoms experienced.

Family Response to Asthma (Child and Parent). Children and parents were asked about their beliefs regarding how they would respond to asthma symptoms. Children's responses were coded in terms of how quickly they believed they would respond to symptoms with inhaler use. The majority of children (75%) reported they believed they would take their inhaler 'right away,' hence this variable was coded into two categories: those who believed they would respond immediately, and those who believed they would wait some time before taking medications.

Parents' responses to asthma exacerbations their child experienced was coded in terms of how long they would wait, after their child's symptoms began, before seeking medical attention. The majority of parents (74%) reported that they would contact their physician that day if symptoms persisted. Hence this variable was coded into two categories: contacting their

physician that day (coded as prompt responses) versus waiting at a day or longer (responses ranging from one day to one week, coded as longer responses). Some families (11%) reported that they had never contacted their physician because of an uncontrolled asthma exacerbation, and thus these families had no response coded on this dimension.

Balanced Integration (Child and Parent). Balanced integration referred to the extent to which families were able to integrate illness management into their everyday lives. Children were asked about their beliefs about how much asthma interfered with or changed their daily activities. Those who endorsed the importance of maintaining usual levels of activity as much as possible when feeling symptomatic were coded as having a better balanced integration of their illness into everyday life. Twenty-five percent gave responses indicating that they would keep up with their usual activities, or could not think of any they would stop. The remaining 75% of participants reported a limited set of activities that they would continue (that is, only continuing with certain activities, rather than all activities), or reported that they would stop all activities when their asthma worsened. Because only 6% reported that they would stop all activities, we grouped these children together with those that limited activity levels. Hence there were two categories for this variable: children who would keep up with most things versus those who would stop some or everything they were doing when symptomatic.

Parents were asked to discuss the demands they experienced in their daily lives that competed with taking care of their child's asthma. Their beliefs were assessed using the following probes: whether work demands, other child or family responsibilities, or any additional responsibilities conflicted with taking care of their child's asthma. The number of competing demands was coded, and scores ranged from 0 to 3, with a lower score indicating fewer competing demands, and hence a better balanced integration.

For each of the subscales of the Health Beliefs Interview, participants were asked to provide responses based on their beliefs and how they would respond currently. Thirty percent of interviews were independently re-coded by a second interviewer and intraclass correlations were computed. Across all subscales, the average coefficient was .72 (range .60-.80).

Biological Pathways

Immune Measures

Cytokine Production. White blood cells' cytokine secretion in response to mitogen stimulation was measured as an in vitro model of allergen exposure, as has been done in previous studies on stress and cytokines in asthma (Kang et al., 1997; Marshall et al., 1998). This technique involved isolating mononuclear cells from blood samples and exposing the cells to an equivalent dose of a mitogen, known as phorbol myristate acetate combined with ionomycin (PMA/INO). Mitogens are substances that trigger T cells to produce cytokines. Cytokines are chemical messengers of the immune system that coordinate inflammatory responses. Because the types of cytokines implicated in asthma are largely released in response to a stimulus, we measured the production of cytokines after experimental exposure to PMA/INO, as opposed to basal levels of cytokines (which are often undetectable). Greater cytokine production indicates the tendency for immune cells to mount a heightened inflammatory response, which in the context of an inflammatory condition such as asthma, would be considered detrimental.

The protocol for this technique has been detailed elsewhere (Chen et al., 2006), but briefly, involved drawing 16 cc of blood and exposing a fixed number of peripheral blood mononuclear cells (3 million cells/ml) to 25 ng/ml PMA and 1 ug/ml INO for 48 hours. After incubation, supernatants were removed and assayed to determine levels of IL-4, IL-5, and IL-13 using enzyme-linked immunosorbent assays (ELISA) (R&D System, Minneapolis, MN).

Basal Immune Markers. Three cc of peripheral blood was drawn into an ethylenediaminetetraacetic acid (EDTA) tube and a complete blood count with differential (Bayer ADVIA 70 hematology system, Holiston, Massachusetts) was performed to enumerate eosinophil count. Ten cc of peripheral blood was drawn into a Serum Separator Tube (SST), and total IgE values were obtained from serum (Pharmacia UniCAP 100).

Clinical Outcomes

Pulmonary Function

Pulmonary function was assessed using spirometry (Vmax/Spectra, SensorMedics, Yorba Linda, California). Measurements included Forced Expiratory Volume in 1 second (FEV₁), the amount of air forced from the lung starting from full lung capacity. Percentiles were calculated by comparing this value to reference values based on child age, ethnicity, gender, height, and weight. Lower FEV₁ percentiles indicated poorer pulmonary function. Participants in our study had FEV₁ percentiles that indicate largely well-managed asthma (Table 1).

The Health Symptoms Questionnaire

Children were asked to report their asthma symptoms during the last 2 weeks. They were asked about the number of days they experienced symptoms (coughing, wheezing, shortness of breath or chest tightness) throughout the day ($M = 2.8$), while being active ($M = 0.8$), and at nighttime ($M = 2.8$), (1997 National Asthma Education and Prevention Program (Emond, Camargo, & Nowak, 1998)). A total asthma symptom score was created by averaging responses to these three questions, and the reliability of this measure was 0.79 (Cronbach's alpha).

Medical Variables

Children were asked the number of times they had to use a beta agonist inhaler because of asthma symptoms during the last 2 weeks (beta agonist use). Children were also asked the

number of times they or their parents had to contact their physician in the last 6 months because of asthma exacerbations, not during a regular appointment (physician contacts).

Procedure

Families who participated in this study were first screened for eligibility, and then scheduled for an appointment at our laboratory. Consent and assent forms were signed at the laboratory. A local topical anaesthetic cream (EMLA) was applied to the antecubital area of the child's arm an hour before the blood draw. Interviews were administered and audiotaped. Interviewers were trained by the study's primary investigator, and were either undergraduate-level research assistants, graduate students, or the project coordinator. Medications were brought in by the parents, and prescription information was recorded. Height and weight were taken on a standard medical-grade balance beam scale. The child's lung function was assessed via spirometry. Children were coached in appropriate blowing techniques, and 6-8 trials were done for each child to obtain a laboratory best FEV₁, according to American Thoracic Society guidelines (Miller et al., 2005). Measures were taken at least 4 hours after the last use of a beta agonist. Following spirometry, a sample of the child's blood was drawn. Participants were paid an honorarium of \$25 each for their time.

Data Analysis

Data analyses proceeded in three steps: 1) testing relationships between asthma management beliefs/behaviors and immune markers; 2) testing relationships between immune markers and clinical outcomes; and 3) testing whether immune markers statistically mediated the relationship between asthma management beliefs/behaviors and clinical outcomes. Our primary interest was in testing whether specific types of asthma management variables would be associated with immune or clinical variables. Because we did not expect associations to vary

depending on which immune marker or clinical variable was used, we created composite immune and clinical indicators. Because each immune marker and each clinical variable had different means and ranges, we first standardized these variables so that each immune marker and each clinical variable would have a mean of 0 and a standard deviation of 1 so that they would each contribute equally to the composite score. We then averaged all immune variables (IL-4, IL-5, IL-13, eosinophil count, and IgE) to generate the average, composite immune score and similarly, we created the composite clinical score by standardizing and then averaging the clinical variables (FEV₁% to indicate lung function, asthma symptoms, use of a rescue inhaler, and physician contacts). However, because the measure of lung function is in an opposite direction to the other clinical variables – that is, higher scores are better for lung function, whereas higher scores are worse for symptoms – scores on the lung function measure were reverse coded (multiplied by -1) so that the directionality would be the same as the other clinical variables (i.e., better lung function percentiles would now be represented as lower, more negative, scores). Hence, we tested associations between asthma management variables and composite immune and composite clinical variables. All analyses controlled for child age, maternal years of education, and number of days of inhaled corticosteroid use in the two weeks prior to the visit. Child age and maternal education were controlled because of the associations reported below. Child self-reported inhaled corticosteroid use was controlled as an indicator of adherence to medications. Medication adherence could serve as an alternative explanation for why beliefs and biological variables may be correlated. Controlling for asthma severity did not modify the pattern of results reported, and thus it was not controlled for.

Partial correlations were used for variables that were continuous, and one-way analyses of covariance (ANCOVAs) were used for variables that were dichotomized. If participants were

missing data for a specific variable, they were excluded from analyses using that variable. Effect size estimates are presented for primary analyses in terms of d , with values of .2 considered small, .5 considered medium, and .8 considered large (Cohen, 1988).

RESULTS

Descriptive Information

The distribution of scores for the children's understanding of illness question was as follows: 11% of respondents scored a 1 on the 6-point scale, reflecting the least amount of knowledge in the "Phenomenism" category; 21% of children scored a 2, corresponding to the "Contagion" category; 31% of children scored a 3, corresponding to the "Contamination" category; 24% of children scored a 4, corresponding to the "Internalization" category; and 13% of children scored a 5, corresponding to the "Physiological" level of understanding. None of our participants received the maximum possible score on this scale, of 6 points, corresponding to the "Psychophysiological" level of understanding.

Responses to the Health Beliefs Interview did not differ by child gender or race, but they did differ by age. Child age was positively correlated with children's conceptual understanding of asthma, $r(65) = .25, p < .05$. Children with better balance ratings were on average older than those children with worse balance ratings, $t(64) = 2.37, p < .05$. Children whose parents waited longer to contact their physician once asthma symptoms started were also older on average, than those children whose parents contacted their physician sooner, $t(54) = 3.30, p < .01$. Mother's years of education was positively correlated with children's conceptual understanding of asthma, $r(65) = .35, p < .01$. Greater years of education also correlated with fewer parent competing demands, $r(60) = -.28, p < .05$. Given these associations, we controlled for child age and maternal education in all analyses.

Health Beliefs and Immune measures

Conceptual Understanding of Asthma

Ratings of children's conceptual understanding of asthma were negatively correlated with the composite immune variable, controlling for age, maternal education, and inhaled corticosteroid use, $r(63) = -.25, p < .05, d = .51$. This correlation indicated that a greater conceptual understanding of asthma in children was associated with reduced inflammatory profiles (i.e., lower stimulated production of cytokines, lower basal levels of eosinophils and IgE).

Family Response to Asthma

A one-way ANCOVA controlling for child age, maternal education, and child self-reported inhaled corticosteroid use was conducted to examine the relationship between child response to asthma symptoms and the composite immune variable. The results revealed no statistically significant main effect of ratings of child response to asthma on the immune composite, $F(1,55) = 3.12, p < .08, d = .48$.

There was a main effect of ratings of parents' response to asthma with the immune composite, $F(1,54) = 4.15, p < .05, d = .55$. Parents who reported calling their doctor by the end of the day after symptom onset had children with significantly reduced immune composite scores ($M = -.17, SD = .51$) compared to parents who reported waiting longer to contact their physician ($M = .19, SD = .90$), (see Fig. 1).

Balanced Integration

A one-way ANCOVA controlling for child age, maternal education, and child self-reported inhaled corticosteroid use was conducted to examine the effect of balanced integration (child) on the composite immune variable. There was a significant effect of ratings of child

balanced integration on the composite immune variable, $F(1,64) = 9.27, p < .01, d = .76$.

Children who reported keeping up with usual activities had lower scores on the immune composite ($M = -.28, SD = .43$) compared to children who reported that they stopped some or most things when their asthma worsened ($M = .17, SD = .76$), (see Fig. 2).

Partial correlations were conducted to assess the relationship between ratings of parents' balanced integration (as measured by the number of competing demands in their daily lives) and the composite immune variable. Ratings of parents' balanced integration were positively correlated with children's immune composite score, $r(58) = .26, p < .05, d = .54$. This pattern indicates that an increased number of competing demands in parents' daily lives was associated with an increased inflammatory profile in children.

Immune Variables and Clinical Asthma Outcomes

Overall, immune variables were significantly associated with asthma clinical variables. Controlling for child age, maternal education, and child self-reported inhaled corticosteroid use, higher scores on the immune composite variable were associated with higher scores on the clinical composite variable, $r(64) = .49, p < .001, d = 1.12$. This result is consistent with previous research which indicates that greater inflammatory profiles are associated with greater asthma morbidity (Busse & Lemanske, 2001).

Immune Markers as a Pathway Between Asthma Management Beliefs/Behaviors and Clinical Outcomes

Finally, we conducted formal tests of statistical mediation to analyze whether immune markers served as a pathway between asthma management beliefs/behaviors and clinical asthma outcomes. Specifically, we analyzed the significance of the following pathway: asthma management → immune variables → clinical asthma outcomes. We applied the Sobel test with

the distributional properties recommended by MacKinnon, Lockwood, Hoffman, West, and Sheets (2002). This statistical test uses a product of coefficients test to determine whether the indirect pathway from an IV (asthma management) through a mediator (immune variables) to the DV (clinical asthma outcomes) is statistically significant. A coefficient of $z > |.97|$ indicates a statistically significant pathway. While other approaches (e.g., Baron & Kenny, 1986) stipulate a set of conditions that must be met for mediation, one limitation of these approaches is that they do not provide a joint test of all the conditions required for mediation, nor do they provide a statistical test of the indirect mediational effect. Hence the product of coefficients tests is recommended for tests of statistical mediation.

We tested the role of immune markers for each asthma management variable (see Fig. 3). The composite immune variable formed a significant pathway between ratings of children's conceptual understanding of asthma and the composite clinical variable ($z = -2.77, p < .05$). Similarly, the composite immune variable formed a significant pathway between ratings of children's response to asthma and the composite clinical variable ($z = 1.66, p < .05$), as well as between ratings of parents' response to asthma and the composite clinical variable ($z = 1.57, p < .05$). Finally, the composite immune variable was a significant pathway between ratings of children's level of balanced integration and the composite clinical variable ($z = 1.79, p < .05$), as well as between ratings of parents' level of balanced integration and the composite clinical variable ($z = 1.66, p < .05$). These findings suggest that immune markers serve as one link between management-related beliefs and behaviors and clinical outcomes of asthma.

DISCUSSION

This study is one of the first to document associations between family asthma management and biological processes implicated in asthma, and offers a unique focus on youth.

We found that better ratings of asthma management beliefs and behaviors, in terms of greater conceptual understanding of asthma among children, belief in quicker responsiveness to symptoms among parents, and better integration of asthma into daily life, were all associated with decreased inflammatory profiles in children, as indicated by reduced production of asthma-relevant cytokines, eosinophil counts, and IgE levels. Effect sizes were moderate, suggesting that management-related beliefs and behaviors may be important to understand, for predicting biological profiles in children with asthma. These findings extend previous research on relationships between asthma beliefs or behaviors and clinical outcomes by documenting associations with biological markers. For example, the direction of our findings are consistent with previous research demonstrating that beliefs such as self-efficacy and beliefs in the benefit of asthma management were associated with both behaviors such as better treatment adherence as well as morbidity outcomes such as fewer symptoms (Bursch et al., 1999; Wade et al., 2000).

In addition, decreased inflammatory profiles were associated with better clinical outcomes in youth with asthma, as indicated by a better clinical composite comprised of FEV₁%, symptoms, rescue inhaler use, and physician contacts. The effect size for these associations was large. These results indicate that inflammatory mechanisms associated with Th2 cytokine production and its downstream effects contribute to the clinical manifestation of asthma.

Third, we found that inflammatory profiles constituted a statistically significant pathway from asthma management to clinical outcomes. This was true for ratings of multiple types of management dimensions, including children's conceptual understanding of asthma, child and parent response to symptoms, and child and parent balanced integration. Although these data are cross-sectional, the patterns are consistent with an explanation that immunologic mechanisms

serve as one factor explaining how the beliefs and behaviors associated with asthma management come to be linked to clinical outcomes.

Overall, these findings document that asthma management beliefs and behaviors are associated with inflammatory profiles that in turn have clinical implications. These findings are preliminary, however, given the small sample size, cross-sectional design, and limited assessment of beliefs and behaviors. In order to further substantiate these findings, future studies need to incorporate longitudinal designs with repeated assessments to determine whether changes in beliefs or management behaviors actually precede changes in immune markers. In addition, future studies need to conduct more in-depth interviews of asthma management, or incorporate multi-method assessments of management behaviors, and test their associations with immune markers.

As briefly noted above, we cannot draw conclusions about the directionality of our findings. It is possible that greater asthma morbidity or heightened inflammatory profiles may shape families' beliefs and behaviors associated with asthma. In addition, the time frame for each of the study constructs did not overlap perfectly. For example, pulmonary function and immune measures were taken at the time of the laboratory visit, whereas physician contacts were assessed over the past six months. Future longitudinal studies would allow the time frame for each of these constructs to be more consistent.

Another limitation was the brief assessment of beliefs. Because this was a preliminary study, we conducted a brief interview, and have limited information on psychometrics. Inter-rater reliability for some subscales of the HBI was not high. In theory, this would add noise to a measure, making it less likely to find associations; however, the present study detected a number of associations despite this limitation. Further, parental understanding of illness could also affect

asthma management, and was not assessed in the present study. Future research that is able to incorporate more comprehensive, well-validated interviews including both parents and children, such as the Family Asthma Management System Scale (McQuaid et al., 2005), into studies of biological processes would provide an important contribution to this literature.

Finally, study measures were limited by relying largely on child and parent self-report. Hence social desirability may have shaped some responses. However, to the extent that social desirability masked true responses, one would expect this to weaken associations with outcome variables; the fact that responses were associated with inflammatory profiles suggests that social desirability may not have been a strong confounding factor in this study. As well, shared-method variance could account for some of the findings, although this would not apply to analyses of immune markers. Future studies that are able to provide additional sources of information and objective measures of adherence (e.g., health care records and electronic medication monitoring devices) would be important to conduct in order to alleviate concerns about shared-method variance and the inaccuracies of self report measures.

Future research with larger sample sizes should also explore how age affects these relationships. For example, perhaps parent behaviors aimed at managing their child's asthma will be effective in younger children, but less useful in older children as they become more independent and spend more time away from home. Future research should also examine other factors that might predict asthma management beliefs and behaviors, such as socioeconomic background, cultural beliefs, and experiences with the health care system, in order to better understand the origins of asthma management beliefs and behaviors. Finally, future studies could include a more comprehensive set of pulmonary function tests, including small airway measures of lung function.

In sum, the present study found that ratings of asthma management dimensions, including children's conceptual understanding of asthma, parents' responses to asthma symptoms, and families' ability to integrate asthma into their daily lives all were associated with asthma inflammatory profiles, such that those who reported better asthma management beliefs and behaviors exhibited reduced asthma inflammatory profiles. Furthermore, inflammatory profiles constituted a statistically significant pathway between asthma management and clinical outcomes. This study suggests that interventions that seek to ameliorate asthma morbidity may want to include a focus on asthma management-related beliefs and behaviors since these factors may influence childhood asthma not only at the clinical level but also at the biological level.

Table 2.1

Descriptive information of sample

	%	M	SD	Range
Medications				
Beta agonist		4.2	5.6	0 - 14
Inhaled corticosteroid		4.5	6.0	0 - 14
Asthma severity				
Mild intermittent	15.4			
Mild persistent	38.5			
Moderate	32.1			
Severe	14.1			
Biological outcome measures				
IL-4 (pg/ml)		19.5	27.2	0 - 131
IL-5 (pg/ml)		114.8	83.5	17 - 452
IL-13 (pg/ml)		534.2	349.0	62 - 1782
Eosinophil count (10^9 cells/L)		0.4	0.3	0 - 1.5
IgE		519.8	1175.8	2 - 9104
Clinical outcome measures				
FEV1 percent		97.4	15.6	53 - 137
Asthma symptoms score		2.3	2.8	0 - 14
Beta agonist use		2.0	3.9	0 - 14
Physician contacts		0.7	1.9	0 - 15

Medications = number of days participants used inhaled corticosteroids and beta agonists in the two weeks prior to their visit. Asthma symptoms score = number of days experiencing symptoms during the day, while being active, and at night during the past two weeks. Beta agonist use = number of the days the child had to use beta agonists in the previous two weeks because of asthma exacerbations (the earlier measure of beta agonists included regular use, such as preventatively before exercise or physical activities). Physician Contacts = number of times they or their parents had to contact their physician in the last 6 months because of asthma exacerbations. Normative values in healthy volunteers for IgE is 22 kU/L, expressed as a geometric mean (Pharmacia Diagnostics). The geometric mean for our sample was 144 kU/L. Normal range for eosinophil counts is .05-.35 x 10^9 cells/L (Nelson Textbook of Pediatrics).

Figure 2.1. Mean immune composite score by parental response to their child’s asthma exacerbations ($p < .05$). Parents were asked how long they would wait, after their child’s symptoms began, before seeking medical attention (e.g., phoning their doctor). Responses were coded as prompt (calling that day) versus longer responses (waiting from one day to one week). Mean immune composite score was created by standardizing each immune variable and calculating the average; lower numbers reflect better immune composite scores.

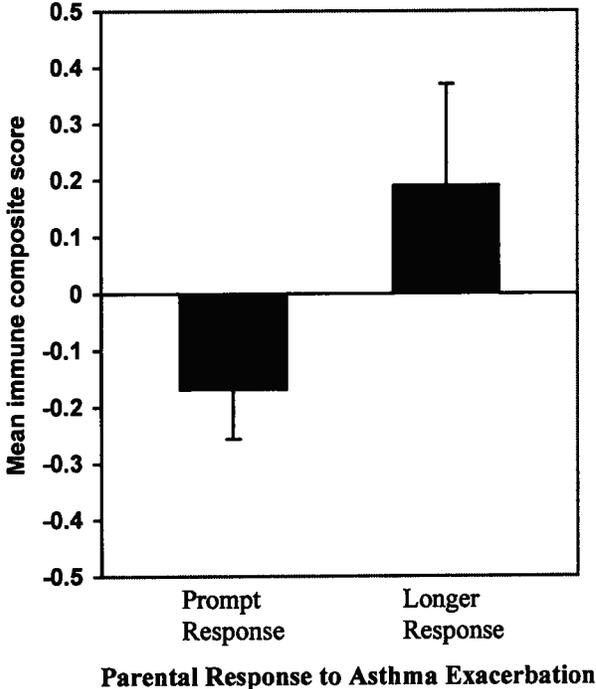


Figure 2.2. Mean immune composite score by child balanced integration ($p < .01$). Children were asked about how much asthma interfered with or changed their daily activities. Responses were coded as those who would maintain most activities versus those who would stop some or all activities when symptomatic. Mean immune composite score was created by standardizing each immune variable and calculating the average; lower numbers reflect better immune composite scores.

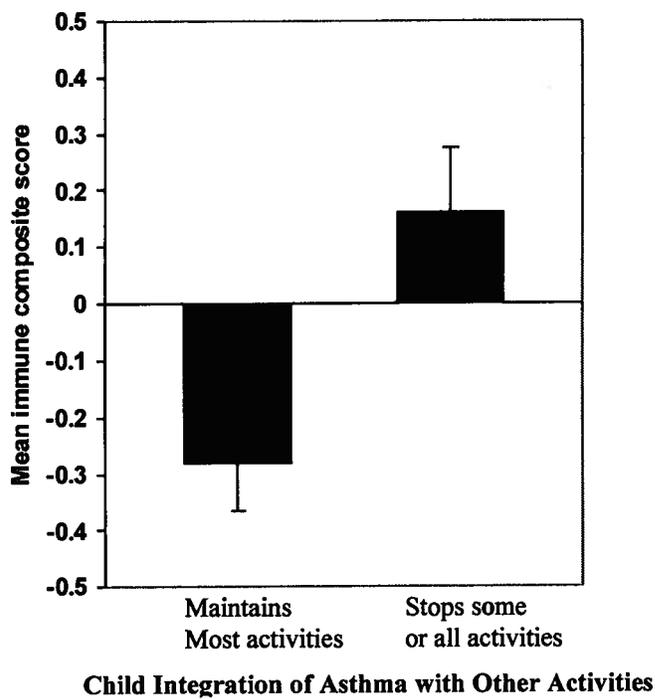
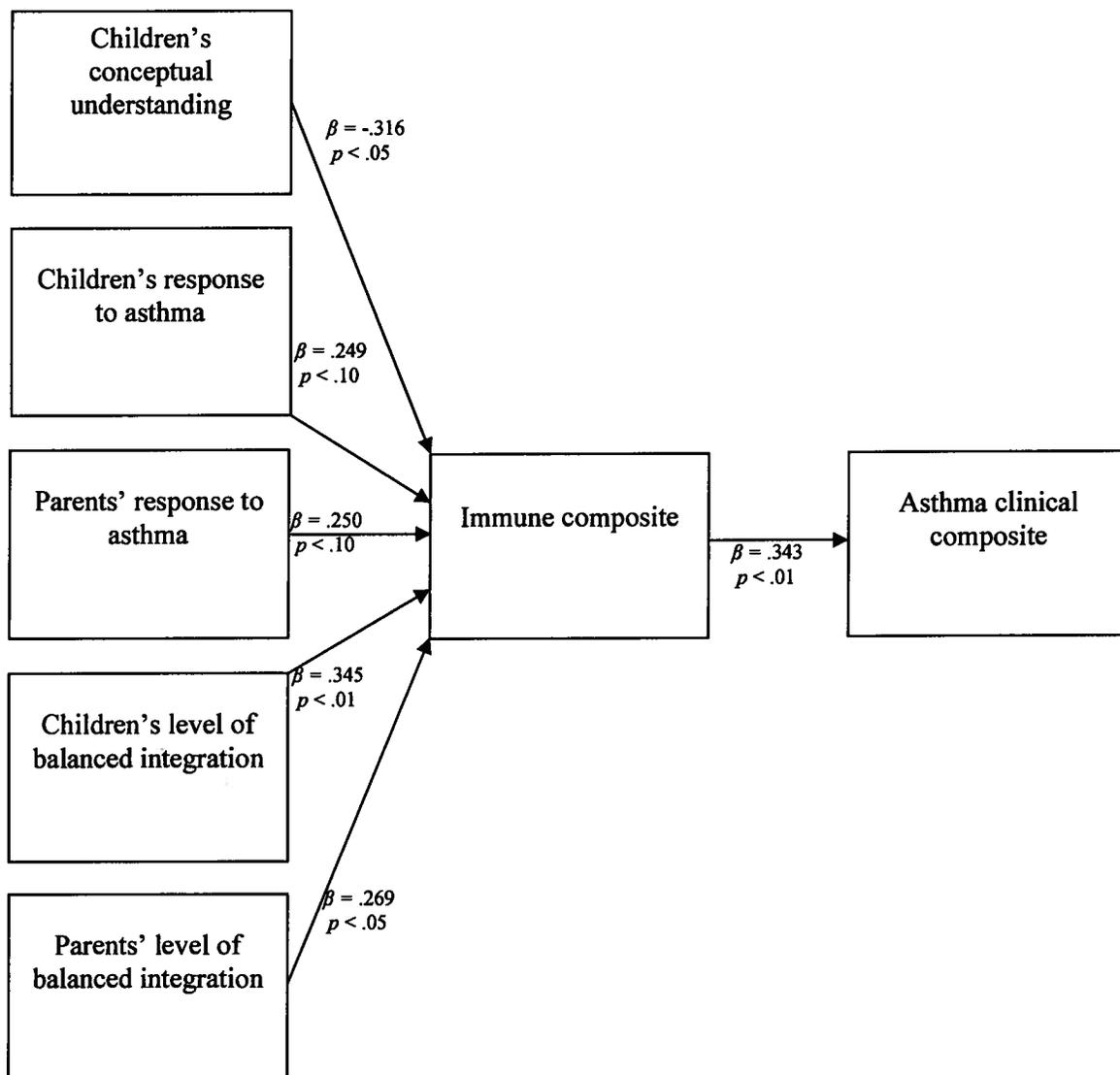


Figure 2.3. Diagram showing the statistically significant indirect pathways from asthma management variables through the immune composite to the clinical asthma composite. All z statistics for mediation were significant at $p < .05$. Higher numbers for children's conceptual understanding indicates a more sophisticated understanding of asthma. Higher numbers for children's and parents' response to asthma indicates slower response times in dealing with asthma exacerbations. Higher numbers for parents' and children's balanced integration indicate poorer integration of asthma into family's daily lives. The immune composite is scored such that higher numbers reflect greater asthma-relevant inflammation. The clinical composite is scored such that higher numbers reflect greater asthma morbidity.



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CHAPTER THREE²

Study 2: The Impact of Family Asthma Management on Biology: A Longitudinal Investigation of Youth with Asthma

INTRODUCTION

Asthma is the most common chronic illness in youth, and is a leading cause of school absenteeism and a major cause of hospitalizations in Canada (Asthma Society of Canada, 2005) and the United States (Akinbami, 2006; DeFrances, Cullen, & Kozak, 2007), with an associated annual cost of \$3.2 billion to treat youth under the age of 18 (Weiss, Sullivan, & Lytle, 2000). Reasons for asthma exacerbation are numerous, and include physical, environmental and psychological factors. With respect to psychosocial contributors to asthma exacerbations and symptoms, one important area of research has focused on the role of asthma management and beliefs. This research has shown that within the family, better asthma management and certain asthma beliefs can have an impact on childhood asthma. However, the bulk of research in this area has focused on clinical outcomes such as healthcare utilization, while the specific biological mechanisms through which asthma management and beliefs come to impact asthma outcomes have been largely neglected. Thus, the current study sought to elucidate some of the biological mechanisms through which family beliefs about and management of one's illness, are related to asthma biological outcomes over time in a sample of children with asthma.

Previous research has linked both asthma management techniques as well as asthma-related beliefs, to morbidity outcomes in children with asthma. Asthma management refers broadly to both preventive and rescue strategies implemented by families to improve symptoms in children with asthma. Research on asthma management has focused on identifying

² A version of this chapter will be submitted for publication. Walker, H.A. and Chen, E. The Impact of Family Asthma Management on Biology: A Longitudinal Investigation of Youth with Asthma.

associations between at-home behaviors, such as washing bed sheets regularly in hot water, with asthma morbidity. These behaviors have been shown to be related to decreased rates of hospitalizations and emergency room (ER) visits (Lieu, Quesenberry, Capra, Sorel, Martin, & Mendoza, 1997). Another research focus has been on the association between better medical management and morbidity. For example, having a written action plan has been found to be associated with fewer return ER visits, more well visits, and greater confidence in the ability to prevent asthma episodes (Sockrider et al, 2006), as well as with decreased rates of hospitalizations and emergency room (ER) visits (Lieu et al, 1997). Further, increasing medication use at the onset of a cold or flu, was also related to decreased rates of hospitalizations and emergency room (ER) visits (Lieu et al, 1997).

Some research has focused on specific dimensions of family asthma management and their associations with morbidity. In particular, using the well-validated Family Asthma Management System Scale interview (FAMSS), decreased asthma morbidity in children has been shown to be associated with such family asthma management dimensions as better integration of asthma into the family's daily life, a more collaborative relationship with physicians, and more timely responses to symptoms (McQuaid, Walders, Kopel, Fritz, & Klinnert, 2005). However, there are some authors who have argued that the associations between asthma management and school absenteeism, asthma attacks, hospitalizations, hospital days, or ER visits are not reliable (Bernard-Bonnin, Stachenko, Bonin, Charette, & Rousseau, 1995).

Other asthma management research has focused on interventions and patient education to improve at-home management. Shegog and colleagues created the Stop Asthma Clinical System (SACS, 2006), an intervention targeting physician behavior, with resultant effects on patient

asthma management and clinical outcomes. The intervention was shown to be effective at improving patient self-management via improved physician behavior during clinic visits, resulting in the creation of an action plan, assessment of asthma severity and control, and identification of environmental trigger management problems. Another intervention approach, the asthma self-management and education program Health Buddy, enlisted children to assess and monitor their asthma symptoms and transmit this information to health care providers through a website (Guendelman, Meade, Benson, Chen, & Samuels, 2002). This intervention has been shown to be associated with reporting fewer limitations in activity levels, as well as better peak flow readings, and fewer urgent calls to the hospital. Further, a recent meta-analysis found that providing pediatric asthma education reduced the mean number of hospitalizations and ER visits, and the odds of an ER visit for asthma, but not the mean number of urgent physician visits or the odds of hospitalization (Coffman, Cabana, Halpin, & Yelin, 2008).

With respect to asthma-related beliefs, previous research has found that beliefs are related to both management behaviors, as well as clinical outcomes (Walker, Chim, & Chen, 2009). Much of the work in this area with families of children with asthma has documented beliefs about behavioral outcomes such as treatment adherence. For example, parental fear and overconcern about medications have been linked to poor adherence in children (Conn, Halterman, Fisher, Yoos, Chin, & Szilagyi, 2005; Chan & DeBruyne, 2000), and recent findings from Conn and colleagues (2007) suggest that the balance between parents' positive and negative beliefs about medication use (that is, the balance between necessity and concern beliefs regarding their child's asthma medications) impacts medication adherence in children, such that a higher rating of necessity rather than concern, predicted better adherence. Beliefs about the chronicity of asthma have also been examined, and in a sample of inner-city adults, Halm and

colleagues (2006) identified an acute disease belief termed the “no symptoms, no asthma” belief, held by those who believed they had asthma only when symptomatic, rather than believing that asthma is a chronic illness that is always present. This belief was found to be associated with lower adherence to inhaled corticosteroids (ICS) when asymptomatic. Finally, other studies have provided support for the notion that child and parent self-efficacy beliefs as well as parental beliefs about the helpfulness of asthma management behaviors, have been linked to clinical outcomes, such as fewer symptoms among children with asthma, fewer days of wheezing, better health status, as well as fewer days of school missed (Bursch, Schwankovsky, Gilbert, & Zeiger, 1999; Wade, Holden, Lynn, Mitchell, & Ewart, 2000; Grus et al., 2001).

All of the above studies have focused on the links between asthma management and beliefs with clinical outcomes in asthma. However, many of them have been cross-sectional, thus preventing direct testing of whether beliefs and management come to impact asthma outcomes, or whether the reverse may be true. It may be that having worse asthma is more difficult to manage, and has an impact on illness beliefs. Much research has also focused on either children or parents, and has not incorporated both family members in assessing asthma management practices. Finally, very little research has explored how these beliefs and management practices might alter biological processes to explain associations with clinical outcomes. Elucidating biological mechanisms is important for developing plausible models of how it is that psychological factors such as beliefs can have clinical manifestations in terms of disease outcomes. With respect to biological mechanisms, asthma is known to be an inflammatory disease. During asthma exacerbations, antigens activate T cells which release chemical messengers known as cytokines that activate eosinophils. Activated eosinophils in turn produce histamine and leukotrienes, leading to the symptom profile associated with asthma

(airway constriction and mucus production). Further, the anti-inflammatory hormone cortisol is implicated in the dampening or cessation of this response, such that cortisol binds to immune cells to signal termination of the production of certain cytokines. Thus assessing the production of cortisol, as well as circulating levels of eosinophils provides an indication of inflammatory processes relevant to asthma. Also relevant to studying the effects of beliefs and management on biological measures is a more direct measure of pulmonary function.

In a preliminary study by our team, inflammatory profiles were linked to asthma beliefs and management behaviors in a cross-sectional sample of children with asthma, using a brief interview (Walker et al, 2009). In the present study, we tested these associations more stringently by 1) examining whether family asthma management and beliefs could predict longitudinal changes over time in biological measures in a sample of children with asthma, and 2) using a more extensive and well-established family asthma management interview (Family Asthma Management System Scale; FAMSS, McQuaid et al., 2005). We hypothesized that children from families with poorer asthma management strategies, as well as those children who held the “no symptoms, no asthma” acute disease belief, would show increases in inflammatory profiles, decreases in cortisol output, and poorer pulmonary function over an 18 month period.

METHODS

Participants

This sample consisted of 40 children with asthma between the ages of 9 and 18 years living in Vancouver, B.C., Canada. Each child participated with one parent. Families were recruited via asthma and allergy clinics, newspaper ads, school newsletters, and community flyers. Eligibility criteria included child age, physician diagnosis of asthma, no other chronic illnesses, proficiency in English, and not on any prescription medications other than asthma

medications. Study visits were postponed if children were sick on the day of their scheduled appointment. Ethical approval was granted by the Behavioral Research Ethics Board of the University of British Columbia.

Measures

The Family Asthma Management System Scale

Children and parents were interviewed together about asthma management beliefs and behaviors, using the Family Asthma Management System Scale (FAMSS; McQuaid et al., 2005). This semi-structured interview assessed children's and parents' asthma management behaviors over the past 6 months. The FAMSS consists of 8 subscales described below which assess different domains of family asthma management.

Asthma Knowledge. Families were asked to explain their understanding of asthma (e.g.: "what do you know about asthma"; "if I didn't know anything about asthma, what could you tell me about it?") Interviewers assessed knowledge about anatomy, symptoms, and medications.

Knowledge and Assessment of Symptoms. Children and parents were asked to report the course of symptomatology during the child's typical asthma exacerbation. Ratings were based on knowledge of triggers, early warning signs, seasonality and course of symptoms.

Appropriateness of Family's Response to Symptoms and Exacerbations. Families were asked to describe their course of management strategies in response to asthma exacerbation. Response elements included timeliness of taking medications, and decisions regarding seeking medical treatment.

Appropriateness of Child's Response to Symptoms and Exacerbations. This domain paralleled the family's response, but children were asked to describe their course of management strategies if they were not with their parents during an asthma exacerbation.

Environmental Control. Exposure to environmental triggers of asthma was assessed, as well as any preventive strategies to reduce their child's exposure to triggers. Examples of triggers included smoke and pet exposure. Examples of controls included removing carpet, dusting frequently, installing air filters or purifiers, and washing linens regularly in hot water.

Adherence with Asthma Medications. Families were asked how often their child took asthma medications, how often their child had medications with them when away from home, about systems for taking medications, and about difficulties with adherence. Adherence to both rescue inhalers and daily preventive medications was assessed.

Collaborative Relationship with Provider. Families were asked about their relationship with their physician, including how often they saw him or her, how well they communicated, and how up to date their treatment plan was. Relevant variables included continuity of care, appropriate use of physician resources, the family's understanding of their physician's instructions, and suitability of the child's medication regime.

Balanced Integration of Asthma into Family Life. Families reported the extent to which asthma interfered with their regular activities or routines, and their balance of attention between asthma vs. other aspects of daily life. Basic categories were distress about asthma, maintaining appropriate activity levels and responsiveness to environmental triggers.

The FAMSS has been demonstrated to have excellent reliability and validity (McQuaid et al., 2005; Klinnert, McQuaid, & Gavin, 1997). Ratings were made based on a combination of informant reporting and behavioral observations (McQuaid et al., 2005). In each subscale, children were asked first to respond and parents were then asked to contribute additional information. Each subscale was given a score from 1 to 9 by a rater, with higher ratings indicative of better management. The majority of tapes were coded independently by 2 raters

(43%) or by the entire research team (44%). Intraclass correlations were computed and across all subscales, and the average coefficient was .84 (range .69-.91).

No Symptoms, No Asthma: The Acute Episodic Disease Belief

Children were asked, “do you think you have asthma all of the time, or only when you are having symptoms?” Response choices were: all of the time, most of the time, some of the time, or only when symptomatic (Halm, Mora, & Leventhal, 2006). This question was developed within the Leventhal Common Sense Self-Regulation Model framework (Leventhal, Brissette, & Leventhal, 2003) to examine patients’ underlying beliefs about asthma and its treatment (Halm et al., 2006). The least sophisticated understanding of asthma, termed the “no symptoms, no asthma” belief is considered a suboptimal belief that does not acknowledge the chronicity of asthma (Halm et al., 2006). Among children in our sample, 54.7% thought they had asthma only when they had symptoms, 27.9% thought they had asthma some of the time, 2.3% thought they had asthma most of the time, and 15.1% of respondents reported they had asthma all of the time. In accordance with Halm and colleagues (2006), this variable was dichotomized into two groups: those children who thought they had asthma only when they had symptoms comprised one group (the “no symptoms, no asthma” group) with all other respondents grouped together, and considered to have a more sophisticated conceptualization of the chronicity of asthma.

Biological and Clinical Measures

Basal Immune Markers

Three cc of peripheral blood was drawn into an ethylenediaminetetraacetic acid (EDTA) tube and a complete blood count with differential (Bayer ADVIA 70 hematology system, Holiston, Massachusetts) was performed to enumerate eosinophil count. Eosinophils are

implicated in the allergic response associated with asthma.

Endocrine Measures

Salivary cortisol was collected for two days after each laboratory visit using Salivettes (Sarstedt, Nuembrecht, Germany) at 1, 4, 9 and 11 hours after awakening in accordance with MacArthur Research Network of Socioeconomic Status and Health (2000) guidelines. This protocol is described in detail elsewhere (Wolf, Nicholls & Chen, 2008), but briefly, involved instructing children to chew gently on a sterile Salivette cotton swab for one minute.

Compliance was monitored using MEMS caps (MEMS 6 TrackCap Monitors, Aardex Ltd., Switzerland), which recorded the date and time when a bottle housing all Salivettes was opened. We defined compliance as being within one hour in either direction of the predetermined collection time, and when this definition was applied, 88% of participants met our criteria. Samples were mailed back to the laboratory when completed, and Salivettes were centrifuged at 800g for 5 minutes to extract saliva. Samples were frozen at -30 degrees until data collection was complete, and were then shipped to Dresden, Germany for analysis. Free cortisol levels in saliva were measured in duplicate using a commercially available chemiluminescence assay (IBL, Hamburg, Germany). Inter- and intra-assay variation was below 10%. Because of substantial skew, cortisol data were log transformed (Tabachnick and Fidell, 2001). Daily cortisol profiles were calculated using area-under-the-curve (AUC; trapezoid formula (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) for each of the two days and then averaged.

Pulmonary Function

Pulmonary function was assessed using spirometry (Vmax/Spectra, SensorMedics, Yorba Linda, California). Children were coached in-lab in appropriate blowing techniques, and 6-8 trials were done for each child to obtain a laboratory best FEV₁, according to American Thoracic

Society guidelines (Miller et al., 2005). Measures were taken at least 4 hours after the last use of a beta agonist. Measurements included Forced Expiratory Volume in 1 second (FEV₁), the maximal amount of air forcibly exhaled in the first second starting from full lung capacity. Percentiles were calculated by comparing this value to reference values based on child age, ethnicity, gender, height and weight. Lower FEV₁ percentiles indicated poorer pulmonary function.

Medical Variables

Children were asked the number of times they had to use a beta agonist inhaler because of asthma symptoms during the last 2 weeks (beta agonist use), as well as the number of times they took inhaled corticosteroids (ICS) during the last 2 weeks (ICS use). Asthma severity was determined from the NAEP/EP2 guidelines based on the higher of symptom frequency and medication use, paralleling the approach of previous researchers (Bacharier, Strunk, Mauger, White, Lemanske, & Sorkness, 2004).

Procedure

Families came to the laboratory for two visits: at baseline, and then 18 months later (when biological measures were re-assessed). Families who participated in this study were first screened for eligibility, and then scheduled for an appointment at our laboratory. Consent and assent forms were signed at the laboratory. A local topical anaesthetic cream (EMLA) was applied to the antecubital area of the child's arm an hour before the blood draw. The FAMSS Interview was administered and audiotaped. Medications were brought in by the parents, and prescription information was recorded. Height and weight were taken on a standard medical-grade balance beam scale. At each visit, the child's lung function was assessed via spirometry, and then a sample of the child's blood was drawn. Participants were paid an honorarium of \$25

each for their time. Following both laboratory visits, children collected saliva samples (from which we measured salivary cortisol) at home 4 times per day, for 2 days.

Data Analysis

For all of the child biological and clinical measures, change scores were first computed to assess the difference in these variables over the time children were involved in the study. Scores were computed by subtracting earlier values from later values (e.g. Time 1 values subtracted from Time 2 values). All analyses controlled for baseline biological variables (eosinophils, FEV₁%, and cortisol values) and child age. For cortisol analyses, ICS use in the two weeks prior to the visit was also added as a control variable. If participants were missing data for a specific variable, they were excluded from analyses using that variable. To test whether asthma disease beliefs were related to asthma management, we conducted one-way ANOVAs to examine differences in the “no symptoms, no asthma” groups on the FAMSS. Next, we tested whether disease beliefs were related to biological outcomes by conducting one-way ANCOVAs to examine the effect of the “no symptoms, no asthma” disease belief on change in lung function, eosinophils and cortisol over time (controlling for baseline values and child age). Finally, we tested whether family asthma management was related to biological outcomes by conducting partial correlations in which the FAMSS dimensions were correlated with change in lung function, eosinophils and cortisol over time, again controlling for baseline values and child age.

RESULTS

Preliminary Analyses

Preliminary analyses revealed associations between age and eosinophil counts ($r = -.297$, $p < .05$), as well as between age and AUC (r 's $> .319$, $p < .05$); given these associations we controlled for age in all analyses. Other potential confounders (socioeconomic status, gender,

ethnicity, asthma severity, inhaled corticosteroid (ICS) use, and beta agonist use) were unrelated to biological outcomes (FEV₁, eosinophil counts, and AUC) so they were not included as covariates. Table 3.1 contains demographic information for the sample.

FAMSS Dimensions and the “No Symptoms, No Asthma” Disease Belief

One-way ANCOVAs controlling for child age, were conducted to examine the effect of the “no symptoms, no asthma” disease belief on the eight FAMSS dimensions. Results are outlined in Table 3.2, along with mean ratings on each of the dimensions for both groups. The overall pattern that emerged was that those children who held the “no symptoms, no asthma” conceptualization had poorer scores on 4 of the 8 FAMSS dimensions than children with a more sophisticated belief about asthma. More specifically, those children who held the “no symptoms, no asthma” acute disease belief had poorer responses to exacerbation both when alone, and with their parents, compared to all other respondents. Further, those children who held this belief had a less sophisticated understanding of asthma, and were not as good at describing their typical course and overall pattern of symptoms.

Asthma Beliefs and Management and Biological Outcomes

Basal Immune Markers. A significant effect emerged of having the “no symptoms, no asthma” disease belief on eosinophil counts over time ($F(1, 39) = 4.41, p < .05$). After controlling for baseline levels and child age, children with the “no symptoms, no asthma” disease belief had eosinophil counts that increased over time ($M = 0.14$) significantly more than children with a more sophisticated understanding ($M = -.06$) (see Figure 3.1). In addition, Family Response to Symptoms was negatively correlated with eosinophil counts ($r = -.34, p < .10$), such that children from families with more proactive and prompt responses, had eosinophil counts which decreased over the 18 month follow-up period.

Pulmonary Function. After controlling for baseline values and child age, having a collaborative relationship with one's provider was positively correlated with change scores in FEV₁% over time ($r = .36, p < .05$), such that those children from families who had a better working relationship with their health care provider had lung function that improved over time.

Endocrine Measures. Knowledge and Assessment of Symptoms was positively correlated with change in AUC over time ($r = .48, p < .05$), such that children whose families were better able to identify the child's typical symptom profile, had levels of daily cortisol output which increased over time (even after controlling for baseline levels, child age, and inhaled corticosteroid use). Further, Children's Response to Symptoms were positively correlated with change in AUC over time ($r = .46, p < .05$), such that children with a more proactive and prompt response, had levels of daily cortisol output which increased over time.

DISCUSSION

This study is one of the first to document longitudinal associations between family asthma management and biological processes implicated in asthma, and offers a unique focus on youth. We found that children who held a less sophisticated disease belief regarding the chronic nature of asthma (the "no symptoms, no asthma" disease belief) had poorer asthma management, in terms of less asthma knowledge, less sophisticated description of asthma symptoms and course, and poorer responses to symptoms, both when alone and with family. Evidence of this relationship lends further support to the notion that beliefs are related to asthma management behaviors (e.g., Harris & Shearer, 2001). In the present investigation we also found that more sophisticated asthma beliefs and management also predicted beneficial changes over an 18-month study period in asthma-related biological profiles in children, as indicated by reduced eosinophil counts, improving lung function, and increased daily cortisol output.

In the present investigation, we found that those children who had an understanding of asthma being a chronic illness, as well as children from families who had more proactive responses to symptoms, had reduced eosinophil counts over time. This suggests that both child beliefs, as well as family response strategies, may be able to influence inflammatory profiles relevant to asthma over time. Mobilizing the entire family may be effective for administering medications appropriately and regularly monitoring asthma during times when symptoms worsen. In turn, to the extent that asthma exacerbations are managed early on, this may reduce inflammatory markers such as eosinophils over the long term. Further, previous research has found that family response to symptoms is an important mediator in the relationship between child symptom perception and asthma morbidity (McQuaid, Koinis Mitchell, Walders, Nassau, Kopel, Klein, et al., 2007).

In addition, children's knowledge and assessment of symptoms, as well as response to symptoms when alone, were also found to be associated with increasing levels of daily cortisol output over time. Within immune cells, cortisol binds to glucocorticoid receptors, signaling gene transcription, resulting in a net anti-inflammatory effect (Janeway, 2001, p. 555). Immune cell apoptosis is initiated for a number of cells such as eosinophils, and the production of inflammatory mediators such as cytokines is reduced. By exerting these anti-inflammatory effects, it may be that higher cortisol levels are beneficial for reducing the chronic airway inflammation associated with asthma. Further, it has been demonstrated that nocturnal asthma symptoms are worst among children with lower cortisol levels (e.g. Szeffler, Ando, CiCutto, Surs, Hill, Martin et al., 1991), in support of the anti-inflammatory maintenance role of cortisol in asthma.

Finally, results also indicated that children from families with a stronger collaborative relationship with their physician, had lung function which was improving over time. By having better communication with the family physician, families may be more likely to be educated about asthma, to have a well-formulated action plan, and to be aware of the benefits of peak flow monitoring, possibly resulting in improved lung function over time. Consistent with this notion, a review of the effects of educational interventions for self-management among children found that such programs were associated with modest to moderate improvements in lung function, and that those based on peak flow monitoring (rather than just monitoring of symptoms) showed the greatest reductions in asthma morbidity (Guevara, Wolf, Grum & Clark, 2003). Written action plans have also been associated with reduced acute care visits among children with asthma, reduced school absenteeism, and better symptoms scores, suggesting further utility of a strong collaborative relationship with physicians (Zemek, Bhogal & Ducharme, 2008).

Of the eight family asthma management dimensions, four were not found to have any associations with biological variables: Asthma Knowledge, Balanced Integration of Asthma into Family Life, Adherence to Asthma Medications, and Environmental Control. In the FAMSS interview, asthma knowledge refers to overall knowledge of the illness, rather than specific knowledge about the child's asthma. It may be that general knowledge about a disease does not always translate into behaviors and actions for a specific child, thus resulting in no effect on an individual child's biological profile. The fact that balanced integration was not found to be related to asthma biological markers could be because balanced integration may be more relevant to other aspects of asthma, such as quality of life. This notion is consistent with previous research documenting that an asthma self-management intervention was accompanied by both better balance of asthma within daily life (as indicated by fewer days of limited activity) as well

as improved asthma-specific quality of life (Thoonen et al., 2003). The fact that adherence to medications was not associated with asthma biological markers may have been due to the time frame of the interview. The FAMSS interview assesses general adherence tendencies over the previous 6 months. As such, it is possible that the adherence measure was not proximal enough to the laboratory visit to detect associations with biological markers. Finally, environmental control (exposure to environmental triggers such as pet dander and smoking) also was not associated with biological markers. It may be that social desirability prevented some families from accurately reporting environmental exposures, and that objective indicators of exposures (e.g., cotinine levels as an indicator of smoke exposure) would provide more precise measures in future studies. It may also be that this rating scale would benefit from being adapted to the local environment.

The study's main findings indicate that having better responses on certain dimensions of family asthma management have implications for biological processes relevant to asthma in youth. This is especially important since family asthma management is amenable to improvement with education and willingness on behalf of the family. By educating families about tangible, practical management techniques such as having and implementing an action plan, knowing the early signs and symptoms of an exacerbation, and stressing the importance of regular and effective communication with physicians, there is potential for these strategies to have a direct impact on biology. Thus far, family asthma management interventions have been effective at promoting such strategies as the use of an action plan and improving collaboration with physicians, with resultant impact on clinical variables (fewer return ER visits and more well visits, fewer limitations in activity levels, better peak flow readings, and fewer urgent calls to the hospital; Sockrider et al., 2006, Shegog et al., 2006, Guendelman et al., 2002), yet these studies

have not identified possible biological mechanisms. Identifying biological mechanisms underlying the relationship between management variables and clinical outcomes is a necessary next step to further our understanding of this process. In addition, elucidating these mechanisms may have treatment implications – for example, alterations in cortisol levels may suggest the need for different dosing of inhaled corticosteroids. The next step in this process would be to replicate these findings with a larger sample size, and design such an intervention to target these specific domains of family asthma management.

The primary limitation to the present investigation is the small sample size, which was due to the patient population and lengthy follow-up periods; consequently, it may be that some of our null findings were due to the low statistical power to detect associations between some management dimensions or potential confounds, with biological outcomes. Future studies that are able to include larger sample sizes would be helpful for testing the reliability of our results as well as to confirm our null findings. Also, there was a wide age range in this study, and although child age was controlled in all analyses, future research with larger samples should incorporate a developmental focus to discern the age at which family asthma management becomes more the responsibility of youth rather than parents, and whether this has implications for biology. A primary strength of the study is its longitudinal design, being that we were able to monitor changes in biological variables over time, helping us discern directionality between asthma management strategies and biology. Our study also used a well-validated and comprehensive interview taking into consideration both parent and child contributions to the family asthma management effort. We were able to discern which asthma domains were more specifically linked to biology, and we quantified asthma biology over time from a number of complimentary measures, including an immune measure (eosinophil count), a lung function measure (FEV₁),

and an anti-inflammatory hormonal measure (cortisol). Furthermore, this study builds on our earlier work which found links between children's conceptual understanding of asthma, parents' reports of quicker responses to asthma symptoms, and children's and parents' reports of more balanced integration of asthma into daily life, with asthma-relevant biological outcomes, using a less intensive asthma management interview (Walker et al., 2009).

Overall, this study is a unique longitudinal attempt to identify links between biology and different domains of family asthma management in a sample of youth with asthma. Results indicate that an acute episodic disease belief among children is related to several behavioral and knowledge-based components of family asthma management, and that poorer ratings on several categories of family asthma management predict worse biological profiles in children with asthma over time. What this implies, is that beliefs and behaviors may have a resultant impact on biology in youth with asthma; consequently, this area is rife with potential for developing new interventions in an effort to improve symptoms and disease course in this patient population. Given the substantial prevalence of asthma in Canada (13% of all children; Garner & Kohen, 2008) and the United States (9.1% Akinbami, Moorman, Garbe, & Sondik, 2009) identifying contributors to worse biological outcomes is essential, especially within the context of such potentially modifiable factors as family asthma management, with ample opportunity for intervention.

Table 3.1

Descriptive information of sample

	%	M	SD	Range
Age		12.4	2.8	9 – 18
Child gender - male	75			
Parent participating - mother	80			
Level of maternal education (yrs)		15.7	2.9	11 - 25
Categorical family income		\$50,000 – 74,999		\$5,000 - \$200,000+
Child ethnicity				
Caucasian	59			
Asian descent	29			
African descent	4			
Latin American descent	4			
Native descent	4			
Asthma severity				
Mild intermittent	18			
Mild persistent	43			
Moderate	26			
Severe	14			
Time 1 FEV ₁ %		96.4	16.3	56 – 133
Time 2 FEV ₁ %		91.5	16.9	52 – 126
Time 1 eosinophil count (10 ⁹ cells/L)		0.33	0.22	0 - .90
Time 2 eosinophil count (10 ⁹ cells/L)		0.35	0.30	0 – 1.6
Time 1 AUC average		11.1	4.9	3.7 – 21.3
Time 2 AUC average		18.3	21.5	4.8 – 99.0

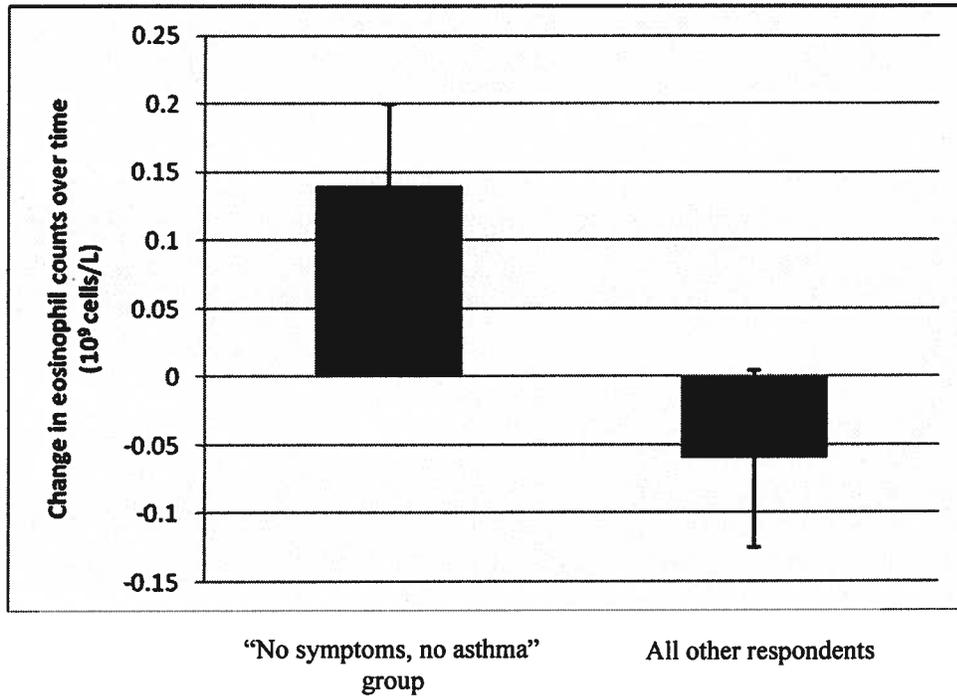
Asthma severity was coded as per the NAEPP/EPR2 guidelines based on the higher of symptom frequency and medication use, paralleling the approach of previous researchers (Bacharier et al, 2004). Forced Expiratory Volume in 1 second percentage (FEV₁%), the maximal amount of air forcibly exhaled in the first second starting from full lung capacity compared to a reference value. Normal range for eosinophil counts is .05-.35 x 10⁹ cells/L (Nelson Textbook of Pediatrics).

Table 3.2

FAMSS dimensions and the “no symptoms, no asthma” disease belief

	“No symptoms, no asthma” group		All other respondents		<i>F</i> (df)	<i>p</i>
	M	SE	M	SE		
Asthma knowledge	6.1	.37	7.1	.40	3.13 (1, 43)	.10
Knowledge and assessment of symptoms	6.1	.29	6.9	.29	3.76 (1, 38)	.10
Appropriateness of child’s response to symptoms and exacerbations	4.1	.31	5.6	.31	11.49 (1, 37)	.01
Appropriateness of family’s response to symptoms and exacerbations	5.8	.29	6.8	.29	5.37 (1, 38)	.05
Environmental control	3.1	.49	2.1	.53	1.73 (1, 43)	ns
Adherence with asthma medications	5.1	.48	5.6	.48	0.60 (1, 38)	ns
Collaborative relationship with provider	5.3	.35	5.7	.38	0.47 (1, 43)	ns
Balanced integration of asthma into family life	5.7	.41	5.7	.41	0.01 (1, 38)	ns

Figure 3.1. Effect of disease belief on eosinophil counts. After controlling for baseline levels and child age, children with the “no symptoms, no asthma” disease belief had eosinophil counts that increased over time significantly more than children with a more sophisticated understanding.



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CHAPTER FOUR

Discussion

These studies were first attempts at documenting associations between beliefs and family asthma management with biological processes implicated in asthma, and offered a unique focus on youth. In Study 1, we found that that better ratings of asthma management beliefs and behaviors, in terms of greater conceptual understanding of asthma among children, belief in quicker responsiveness to symptoms among parents, and better integration of asthma into daily life, were all associated with decreased inflammatory profiles in children, as indicated by reduced production of asthma-relevant cytokines, eosinophil counts, and IgE levels. Effect sizes were moderate, suggesting that management-related beliefs and behaviors may be important to understand, for predicting biological profiles in children with asthma. These findings extend previous research on relationships between asthma beliefs or behaviors and clinical outcomes by documenting associations with biological markers. For example, the direction of our findings are consistent with previous research demonstrating that beliefs such as self-efficacy and beliefs in the benefit of asthma management were associated with both behaviors such as better treatment adherence as well as morbidity outcomes such as fewer symptoms (Bursch et al., 1999; Wade et al., 2000).

In addition, decreased inflammatory profiles were associated with better clinical outcomes in youth with asthma, as indicated by a better clinical composite comprised of FEV₁%, symptoms, rescue inhaler use, and physician contacts. The effect size for these associations was large. These results indicate that inflammatory mechanisms associated with Th2 cytokine production and its downstream effects contribute to the clinical manifestation of asthma.

Third, we found that inflammatory profiles constituted a statistically significant pathway from asthma management to clinical outcomes. This was true for ratings of multiple types of management dimensions, including children's conceptual understanding of asthma, child and parent response to symptoms, and child and parent balanced integration. Although these data are cross-sectional, the patterns are consistent with an explanation that immunologic mechanisms serve as one factor explaining how the beliefs and behaviors associated with asthma management come to be linked to clinical outcomes.

Overall, these findings document that asthma management beliefs and behaviors are associated with inflammatory profiles that in turn have clinical implications. These findings were preliminary, however, given the small sample size, cross-sectional design, and limited assessment of beliefs and behaviors. In order to further substantiate these findings, future studies need to incorporate longitudinal designs with repeated assessments to determine whether changes in beliefs or management behaviors actually precede changes in immune markers. In addition, future studies need to conduct more in-depth interviews of asthma management, or incorporate multi-method assessments of management behaviors, and test their associations with immune markers.

In an attempt to address some of these limitations, we conducted Study 2, which was one of the first to document longitudinal associations between family asthma management and biological processes implicated in asthma, among a sample of youth with asthma. We found that children who held a less sophisticated disease belief regarding the chronic nature of asthma (the "no symptoms, no asthma" disease belief) had poorer asthma management, in terms of less asthma knowledge, less sophisticated description of asthma symptoms and course, and poorer responses to symptoms, both when alone and with family. Evidence of this relationship lends

further support to the notion that beliefs are related to asthma management behaviors (e.g., Harris & Shearer, 2001). In the second investigation we also found that more sophisticated asthma beliefs and management also predicted beneficial changes over an 18-month study period in asthma-related biological profiles in children, as indicated by reduced eosinophil counts, improving lung function, and increased daily cortisol output.

We also found that those children who had an understanding of asthma being a chronic illness, as well as children from families who had more proactive responses to symptoms, had reduced eosinophil counts over time. This suggests that both child beliefs, as well as family response strategies, may be able to influence inflammatory profiles relevant to asthma over time. Mobilizing the entire family may be effective for administering medications appropriately and regularly monitoring asthma during times when symptoms worsen. In turn, to the extent that asthma exacerbations are managed early on, this may reduce inflammatory markers such as eosinophils over the long term. Further, previous research has found that family response to symptoms is an important mediator in the relationship between child symptom perception and asthma morbidity (McQuaid, Koinis Mitchell, Walders, Nassau, Kopel, Klein, et al., 2007).

In addition, children's knowledge and assessment of symptoms, as well as response to symptoms when alone, were also found to be associated with increasing levels of daily cortisol output over time. Within immune cells, cortisol binds to glucocorticoid receptors, signaling gene transcription, resulting in a net anti-inflammatory effect (Janeway, 2001, p. 555). Immune cell apoptosis is initiated for a number of cells such as eosinophils, and the production of inflammatory mediators such as cytokines is reduced. By exerting these anti-inflammatory effects, it may be that higher cortisol levels are beneficial for reducing the chronic airway inflammation associated with asthma. Further, it has been demonstrated that nocturnal asthma

symptoms are worst among children with lower cortisol levels (e.g. Szeffler, Ando, CiCutto, Surs, Hill, Martin et al., 1991), in support of the anti-inflammatory maintenance role of cortisol in asthma.

Finally, results also indicated that children from families with a stronger collaborative relationship with their physician, had lung function which was improving over time. By having better communication with the family physician, families may be more likely to be educated about asthma, to have a well-formulated action plan, and to be aware of the benefits of peak flow monitoring, possibly resulting in improved lung function over time. Consistent with this notion, a review of the effects of educational interventions for self-management among children found that such programs were associated with modest to moderate improvements in lung function, and that those based on peak flow monitoring (rather than just monitoring of symptoms) showed the greatest reductions in asthma morbidity (Guevara, Wolf, Grum & Clark, 2003). Written action plans have also been associated with reduced acute care visits among children with asthma, reduced school absenteeism, and better symptoms scores, suggesting further utility of a strong collaborative relationship with physicians (Zemek, Bhogal & Ducharme, 2008).

Of the eight family asthma management dimensions, four were not found to have any associations with biological variables: Asthma Knowledge, Balanced Integration of Asthma into Family Life, Adherence to Asthma Medications, and Environmental Control. In the FAMSS interview, asthma knowledge refers to overall knowledge of the illness, rather than specific knowledge about the child's asthma. It may be that general knowledge about a disease does not always translate into behaviors and actions for a specific child, thus resulting in no effect on an individual child's biological profile. The fact that balanced integration was not found to be related to asthma biological markers could be because balanced integration may be more relevant

to other aspects of asthma, such as quality of life. This notion is consistent with previous research documenting that an asthma self-management intervention was accompanied by both better balance of asthma within daily life (as indicated by fewer days of limited activity) as well as improved asthma-specific quality of life (Thoonen et al., 2003). The fact that adherence to medications was not associated with asthma biological markers may have been due to the time frame of the interview. The FAMSS interview assesses general adherence tendencies over the previous 6 months. As such, it is possible that the adherence measure was not proximal enough to the laboratory visit to detect associations with biological markers. Finally, environmental control (exposure to environmental triggers such as pet dander and smoking) also was not associated with biological markers. It may be that social desirability prevented some families from accurately reporting environmental exposures, and that objective indicators of exposures (e.g., cotinine levels as an indicator of smoke exposure) would provide more precise measures in future studies. It may also be that this rating scale would benefit from being adapted to the local environment.

The second study's main findings indicate that having better responses on certain dimensions of family asthma management have implications for biological processes relevant to asthma in youth. This is especially important since family asthma management is amenable to improvement with education and willingness on behalf of the family. By educating families about tangible, practical management techniques such as having and implementing an action plan, knowing the early signs and symptoms of an exacerbation, and stressing the importance of regular and effective communication with physicians, there is potential for these strategies to have a direct impact on biology. Thus far, family asthma management interventions have been effective at promoting such strategies as the use of an action plan and improving collaboration

with physicians, with resultant impact on clinical variables (fewer return ER visits and more well visits, fewer limitations in activity levels, better peak flow readings, and fewer urgent calls to the hospital; Sockrider et al., 2006, Shegog et al., 2006, Guendelman et al., 2002), yet these studies have not identified possible biological mechanisms. Identifying biological mechanisms underlying the relationship between management variables and clinical outcomes is a necessary next step to further our understanding of this process. In addition, elucidating these mechanisms may have treatment implications – for example, alterations in cortisol levels may suggest the need for different dosing of inhaled corticosteroids. The next step in this process would be to replicate these findings with a larger sample size, and design such an intervention to target these specific domains of family asthma management.

Strengths and Limitations

The primary limitation to both studies were the small sample size, which was due to the patient population and lengthy follow-up periods for the longitudinal investigation; consequently, it may be that some of our null findings were due to the low statistical power to detect associations between some management dimensions or potential confounds, with biological outcomes. Future studies that are able include larger sample sizes would be helpful for testing the reliability of our results as well as to confirm our null findings. Also, there was a wide age range in this study, and although child age was controlled in all analyses, future research with larger samples should incorporate a developmental focus to discern the age at which family asthma management becomes more the responsibility of youth rather than parents, and whether this has implications for biology. Also, as briefly noted earlier, we cannot draw conclusions about the directionality of our findings. It is possible that greater asthma morbidity

or heightened inflammatory profiles may shape families' beliefs and behaviors associated with asthma. In addition, the time frame for Study 1 constructs did not overlap perfectly. For example, pulmonary function and immune measures were taken at the time of the laboratory visit, whereas physician contacts were assessed over the past six months. Future longitudinal studies would allow the time frame for each of these constructs to be more consistent, which was a goal we achieved with the design of Study 2 in an effort to improve this.

Another limitation of the first study was the brief assessment of beliefs. Because Study 1 was a preliminary study, we conducted a brief interview, and had limited information on psychometrics. Inter-rater reliability for some subscales of the HBI was not high. In theory, this would add noise to a measure, making it less likely to find associations; however, the present study detected a number of associations despite this limitation. Further, parental understanding of illness could also affect asthma management, and was not assessed in the present study. Future research that is able to incorporate more comprehensive, well-validated interviews including both parents and children, such as the Family Asthma Management System Scale (McQuaid, Walders, Kopel, Fritz, & Klinnert, 2005), into studies of biological processes would provide an important contribution to this literature. Again, we sought to address these limitations with the design of Study 2.

Finally, study measures in both studies were limited by relying largely on child and parent self-report. Hence social desirability may have shaped some responses. However, to the extent that social desirability masked true responses, one would expect this to weaken associations with outcome variables; the fact that responses were associated with inflammatory profiles suggests that social desirability may not have been a strong confounding factor in this study. As well, shared-method variance could account for some of the findings, although this

would not apply to analyses of biological markers. Future studies that are able to provide additional sources of information and objective measures of adherence (e.g., health care records and electronic medication monitoring devices) would be important to conduct in order to alleviate concerns about shared-method variance and the inaccuracies of self report measures.

Future research with larger sample sizes should also explore how age affects these relationships. For example, perhaps parent behaviors aimed at managing their child's asthma will be effective in younger children, but less useful in older children as they become more independent and spend more time away from home. Future research should also examine other factors that might predict asthma management beliefs and behaviors, such as socioeconomic background, cultural beliefs, and experiences with the health care system, in order to better understand the origins of asthma management beliefs and behaviors. Finally, future studies could include a more comprehensive set of pulmonary function tests, including small airway measures of lung function (fractional exhaled nitric oxide).

A primary strength of the second study was its longitudinal design, being that we were able to monitor changes in biological variables over time, helping us discern directionality between asthma management strategies and biology. This study also used a well-validated and comprehensive interview taking into consideration both parent and child contributions to the family asthma management effort. We were able to discern which asthma domains were more specifically linked to biology, and we quantified asthma biology over time from a number of complimentary measures, including an immune measure (eosinophil count), a lung function measure (FEV_1), and an anti-inflammatory hormonal measure (cortisol). Furthermore, this study builds on our earlier work of Study 1 which found links between children's conceptual understanding of asthma, parents' reports of quicker responses to asthma symptoms, and

children's and parents' reports of more balanced integration of asthma into daily life, with asthma-relevant biological outcomes, using a less intensive asthma management interview (Walker, Chim, & Chen, 2009).

In sum, Study 1 found that ratings of asthma management dimensions, including children's conceptual understanding of asthma, parents' responses to asthma symptoms, and families' ability to integrate asthma into their daily lives all were associated with asthma inflammatory profiles, such that those who reported better asthma management beliefs and behaviors exhibited reduced asthma inflammatory profiles. Furthermore, inflammatory profiles constituted a statistically significant pathway between asthma management and clinical outcomes. This study suggests that interventions that seek to ameliorate asthma morbidity may want to include a focus on asthma management-related beliefs and behaviors since these factors may influence childhood asthma not only at the clinical level but also at the biological level.

Study 2 was a unique longitudinal attempt to identify links between biology and different domains of family asthma management in a sample of youth with asthma. Results indicate that an acute episodic disease belief among children is related to several behavioral and knowledge-based components of family asthma management, and that poorer ratings on several categories of family asthma management predict worse biological profiles in children with asthma over time. What this implies, is that beliefs and behaviors may have a resultant impact on biology in youth with asthma; consequently, this area is rife with potential for developing new interventions in an effort to improve symptoms and disease course in this patient population. Given the substantial prevalence of asthma in Canada (13% of all children; Garner & Kohen, 2008) and the United States (9.1% Akinbami, Moorman, Garbe, & Sondik, 2009), identifying contributors to worse

biological outcomes is essential, especially within the context of such potentially modifiable factors as family asthma management, with ample opportunity for intervention.

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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: Edith Chen	DEPARTMENT: UBC/Arts/Psychology, Department of	UBC BREB NUMBER: H03-80540
INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:		
<small>Institution</small>	<small>Site</small>	
UBC Children's and Women's Health Centre of BC (incl. Sunny Hill) Other locations where the research will be conducted: N/A	Vancouver (excludes UBC Hospital) Child & Family Research Institute	
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: April 20, 2010		
APPROVAL DATE: April 20, 2009		
The Annual Renewal for Study have been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.		
<p>Approval is issued on behalf of the Behavioural Research Ethics Board</p> <hr style="width: 50%; margin: auto;"/> <p>Dr. M. Judith Lynam, Chair Dr. Ken Craig, Chair Dr. Jim Rupert, Associate Chair Dr. Laurie Ford, Associate Chair Dr. Anita Ho, Associate Chair</p>		