IMPACT OF PSYCHOLOGICAL VARIABLES ON HEALTH STATUS OVER TIME

IN ADOLESCENTS WITH INFLAMMATORY BOWEL DISEASE

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DEDICATION

For the man who, during these last four years, loved to sit down and soak up every bit of information about my courses. The one who watched YouTube videos about the human brain because he found my profession fascinating, and continuously asked me what "book chapter" I was on.

*Papi*, this is the last chapter of this 4-year-long book.

# IMPACT OF PSYCHOLOGICAL VARIABLES ON HEALTH STATUS OVER TIME IN ADOLESCENTS WITH INFLAMMATORY BOWEL DISEASE

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# IMPACT OF PSYCHOLOGICAL VARIABLES ON HEALTH STATUS OVER TIME IN ADOLESCENTS WITH INFLAMMATORY BOWEL DISEASE

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The relationship between psychological factors and health outcomes over time in adolescents with Inflammatory Bowel Disease (IBD) is complex. The pediatric IBD literature with respect to these relationships is limited, yet the broader IBD and health psychology literatures offer clues as to the negative impact of alexithymia, depressive symptoms, and stress on health status and health care utilization. Studies have revealed higher rates of alexithymia in adult IBD populations, which in turn has been associated with worse emotional functioning and lower quality of life (QOL). Depression has been associated with worse disease status in children with IBD, but this relationship requires additional exploration, as it remains equivocal. In the adult IBD literature, stress has been associated with disease relapse and avoidant coping. Our study sought to understand the relationship between these psychological factors, health status as

determined by disease severity, and health care utilization (i.e., outpatient GI visits, ED visits, nights hospitalized, and time to medical care) over the course of 3 months and 12 months after baseline.

Our study revealed correlations between disease severity and age, race, and ethnicity. However, no associations emerged between disease severity and our psychological factors of interest. Conversely, significant associations emerged between our health care utilization variables and psychological factors. For instance, stress was predictive of nights hospitalized over the course of 3 months post-baseline while both alexithymia and depressive symptoms emerged as significantly predictive of number of nights hospitalized over the course of 12 months. Additionally, increasing depressive symptoms were associated with shorter time to hospitalization post-baseline. These results highlight the complex and important relationship between psychological factors and markers of health outcome, and the importance of continuing research efforts to elucidate the mechanisms underlying these relationships. Ultimately, clearer understanding of these dynamics has important implications for pediatric IBD patients and the providers who treat them.

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# GLOSSARY OF TERMS

| | |
|---|---|
| Adrenocorticotropic hormone (ACTH) | A hormone produced by the pituitary gland. It signals the adrenal glands to produce cortisol and other steroid hormones. |
| Corticotropin-releasing-factor (CRF) | Hormone produced by the hypothalamus. It signals the anterior pituitary gland to release ACTH. |
| Immunomodulators | Medicines with an effect on the immune system. Immunomodulators may prompt immunostimulation or immunosuppression. Some of the drugs that fall under this category include: azathioprine, mercaptopurine, and methotrexate. |
| Substance P (SP) | A neuropeptide that is released from the terminals of specific sensory nerves. It is found in the brain and spinal cord, and is associated with inflammation and pain. |

*Note*. Definitions adapted from *The Free Dictionary online*. Retrieved from http://encyclopedia.thefreedictionary.com/

# CHAPTER ONE
# Introduction

Approximately 1.4 million people in the United States live with inflammatory bowel disease (IBD), and about 10% of all IBD cases occur in childhood (Centers for Disease Control and Prevention [CDC], 2012). Although the etiology of the disease remains unknown, it is believed to be multifactorial in nature, derived from and impacted by genetic, organic, and environmental factors. The relationship between psychological factors and disease status in pediatric IBD is also complex and has not been studied comprehensively or systematically. The primary goal of the current study is to expand the pediatric IBD literature by examining the extent to which three psychological variables (i.e., stress, depressive symptoms, and alexithymia) impact the health status of adolescents with IBD over time. In this study, health status will be measured by physician-rated disease severity and utilization of non-routine health services.

The three psychological variables examined in this study have been analyzed in the adult IBD literature to different degrees; however, comparable research has not been conducted with pediatric IBD populations. In the literature, stress has been examined in relation to objective health status in adults with IBD (Bitton et al., 2008; Bitton et al., 2003; Levenstein et al., 2000); however, similar studies have not been completed with pediatric populations. While an increasing body of research is exploring the relationship between depressive symptoms and disease activity in the adult literature (Mardini, Kip, & Wilson, 2004; Mittermaier et al., 2004; Persoons et al., 2005), only a handful of studies have been devoted to examining similar associations among children with IBD (Burke, Neigut, Kocoshis, Chandra, & Sauer, 1994; Mackner & Crandall, 2005; Szigethy et al., 2004; Wood et al., 1987). Finally, alexithymia, which

is a construct characterized by a lack of words for feelings, has been implicated in the understanding of adolescent IBD due to the complex relationship between mood, disease flare-up, and somatic complaints in this chronic illness population (Porcelli, Leoci, Guerra, Taylor, & Bagby, 1996). In adult medical populations, alexithymia has been associated with worse disease outcomes, lower quality of life, and decreased psychological functioning (Iglesias-Rey, 2012; Moreno-Jiménez et al., 2007). Although research on alexithymia in pediatric chronic illness populations is limited, alexithymia has been associated with glycemic control in type 1 diabetes mellitus in children (Housiaux, Luminet, Van Broeck, & Dorchy, 2010).

With regard to outcome measures, extant research has frequently focused on disease status as an outcome variable in health care research. Other important indicators are non-routine health services, such as hospitalization, which are particularly salient in these times of rising health care costs. For instance, in pediatric populations with type 1 diabetes, psychosocial variables explain time to hospitalization (Stewart, Rao, Emslie, Klein, & White, 2005) and health care utilization (Clayton, et al., 2013) after controlling for disease management. Indicators of health status in the current study will include not only disease severity but also utilization of non-routine health services, specifically emergency department use, time to hospitalization following baseline, and days hospitalized.

The present study will add a longitudinal component to a recently completed study at Children's Medical Center Dallas (Crowley, 2012) with several interesting findings: a high prevalence of alexithymia in adolescents with IBD (21%) relative to the general population (7.3%, Honkalampi et al., 2009); a significant correlation between alexithymia and each

psychological variable measured (i.e., impact of major life events, stress of daily hassles, recent stress, and depressive symptoms); and a significant association between disease severity and impact of major life events. One limitation and possible explanation for the lack of significant findings related to health status variables was the cross-sectional nature of the project, which failed to capture the relationship over time between psychological variables and objective health status in adolescent IBD. The current study seeks to add to the current literature by providing a more comprehensive, multivariate representation of the relationship between psychological variables and health status over time in adolescent IBD by examining data longitudinally and including health care utilization indicators of health status. Ultimately, this information may help inform future clinical interventions, thereby improving quality of care and quality of life for pediatric IBD patients.

# CHAPTER TWO
# Review of the Literature

## INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is characterized by a chronic, dysregulated inflammation of the intestinal mucosa (Hanauer, 2006; Matricon, Barnich, & Ardid, 2010). In healthy individuals, the intestines' mucosal immune system activates with the presence of potentially invasive elements and down-regulates once the threat is eliminated. However, in individuals with IBD, the mucosal immune system mistakenly detects benign substances (e.g., food, good bacteria) in the intestines as pathogenic, therefore remaining chronically activated and perpetuating the inflammation of the intestine. The two diagnoses associated with IBD are ulcerative colitis (UC) and Crohn's disease (CD). Despite some similarities in disease presentation, UC and CD are different in disease process and treatment. UC is restricted to the colon, rectum, and cecum while CD may affect any part of the gastrointestinal tract, an area that extends from the mouth to the anus (Hanauer, 2006; Szigethy, McLafferty, & Goyal, 2011). Common symptoms of both types of IBD include abdominal pain, fatigue, diarrhea, aching joints, fever, nausea/vomiting, and decreased appetite, with symptoms occurring at different rates in each disease type (S. Singh et al., 2011). In pediatric populations with CD, patients may also experience malnutrition, short stature, fatigue, delayed puberty, and fistulizing disease (Szigethy et al., 2011). In the United States, the incidence of IBD development is between 5–29 out of 100,000 individuals per year (Matricon et al., 2010). It is reported that approximately 1.4 million

people in the United States live with IBD (Centers for Disease Control and Prevention [CDC], 2012), while the lifetime prevalence in the Western world is approximately 0.1% (B. Singh, Powrie, & Mortensen, 2001). IBD accounts for 700,000 medical visits, 100,000 hospitalizations, and 119,000 disability cases per year in the United States (Center for Disease Control and Prevention [CDC], 2012), resulting in over $1.7 billion in estimated health care costs annually (CDC, 2012).

## RISK FACTORS FOR IBD

### *Genetic Factors*

It is likely that IBD results from a combination of genetic, immunologic, and environmental factors (Hanauer, 2006). However, a family history of the disease continues to be the most significant risk factor for developing IBD, particularly in Crohn's disease (Satsangi, Jewell, Rosenberg, & Bell, 1994). Some studies have found that 5 to 10 percent of patients with the disease have a first-degree relative with IBD, with the risk increasing 30- to 40-fold for siblings of individuals with CD and 10- to 20-fold for siblings of those with UC (Binder & Orholm, 1996; Peeters et al., 1996). Twin studies have also contributed significantly to this literature, with findings suggesting that concordance rate for IBD is greater in monozygotic (identical) twins than in dizygotic (fraternal) twins (Binder & Orholm, 1998; Tysk, Lindberg, Jarnerot, & Floderus-Myrhed, 1988). Historically, racial differences have also been detected in

IBD. Individuals of Caucasian heritage are more susceptible to developing the disease and those odds are even greater for individuals of Ashkenazic Jewish descent (Loftus & Sandborn, 2003; Nguyen et al., 2006; Roth, Petersen, McElree, Feldman, & Rotter, 1989). Genome-wide association (GWA) studies have made a significant contribution to understanding the disease at the molecular level. To date, more than 30 possible susceptibility loci have been identified for CD (Cuffari, 2010). These include the DLG5 gene on chromosome 10, toll-like receptors (TLRs), and variations in the gene encoding the interleukin-23 receptor (Cario & Podolsky, 2000; Duerr et al., 2006; Friedrichs et al., 2006; Szigethy et al., 2011). In the last few decades, chromosome 16 has been linked to a relative risk of inheriting CD (Hugot et al., 1996) and, in many cases, to a relative early onset of the disease (Brant et al., 2000). The gene *NOD-2* (nucleotide oligomerization domain 2) on chromosome 16 has also been linked to individuals with CD (Hampe et al., 2002; Lesage et al., 2002). Carriers of one NOD2 mutation have a 2 to 4-fold risk of developing CD, and the chances increase 20 to 40 times with 2 mutations (Szigethy et al., 2011). However, genetic risk factors do not fully predict who will develop IBD (or if it will develop at all), suggesting that environmental variables also play a role.

*Environmental Factors*

Although IBD undeniably has significant genetic and biological underpinnings, sociocultural trends in IBD populations in the last few decades suggest an environmental component to the manifestation of the disease. For instance, rates of IBD are higher among

white-collar workers (Krishnan & Korzenik, 2002; Sonnenberg, 1990). Additionally, IBD is more common in developed countries and is becoming more prevalent in countries experiencing industrialization, such as India and China (Andres & Friedman, 1999; Desai & Gupte, 2005; Zheng et al., 2005). Historically, Caucasian and Ashkenazic Jews have shown higher incidences of IBD. In recent years the number of African Americans and second-generation South Asians living in industrialized countries who are diagnosed with the disease has been on the rise (Bernstein & Shanahan, 2008; Carr & Mayberry, 1999; Loftus & Sandborn, 2003). These rather quick changes cannot be explained by biological factors alone, supporting the role of environmental factors in disease etiology. Environmental explanations for the rise of IBD associated with industrialization include the following: (1) the sanitation theory, suggesting that increased hygiene and decreased exposure to enteric pathogens during childhood leads to disease susceptibility (Gent, Hellier, Grace, Swarbrick, & Coggon, 1994); (2) residence in more densely populated areas (Green, Elliott, Beaudoin, & Bernstein, 2006); and (3) smoking—with active smoking decreasing the likelihood of developing UC but increasing the risk of developing CD (Calkins, 1989). Additional environmental factors implicated include (4) the use of oral contraceptive pills (Cornish et al., 2008), (5) diet (Wild, Drozdowski, Tartaglia, Clandinin, & Thomson, 2007), (6) exposure to antibiotics (Hildebrand, Malmborg, Askling, Ekbom, & Montgomery, 2008), and (7) nonsteroidal anti-inflammatory drugs (Felder et al., 2000). As these examples suggest, the extent and variation of potential environmental factors implicated in IBD etiology speaks to the complexity of the disease and its root causes.

## TREATMENT OF IBD

IBD is a chronic disease with no cure, and treatment regimens vary depending on the type of IBD. In the case of CD, treatment depends on variables such as location, type of disease (inflammatory, structuring, or perforating), and whether fistulas or abscesses are present (Szigethy et al., 2011). Steroids are the first-line therapy for remission of the disease. When CD is restricted to the terminal ileum (the final section of the small intestine) and cecum areas, oral budesonide may be preferred to steroids due to its lesser side effects. Mesalamine, a drug used for the treatment of ulcerative colitis, may also be used, but may not be as effective as steroids in leading to disease remission (Szigethy et al., 2011). During the maintenance phase, immunomodulators such as mercaptopurine and methotrexate may be employed. Other medications may include adalimumab, certolizumab, and natalizumab (Szigethy et al., 2011). For children, nutritional therapy may also be recommended (Borrelli et al., 2006; Smith, 2008; Zachos, Tondeur, & Griffiths, 2007). For more serious cases of the disease, surgery may be necessary, although this is not a permanent solution (Rutgeerts, Vermeire, & Van Assche, 2009; Schwartz & Cohen, 2008).

For patients with UC, oral and rectal mesalamines are often used for therapy (Rutgeerts et al., 2009). When patients do not respond to this treatment or exhibit a more severe form of the disease, use of oral or intravenous steroids as well as immunomodulators or infliximab may be recommended. When these methods do not work, surgery (colonectomy) may become an option,

although placement of an ostomy is necessary in these cases (Devlin & Panaccione, 2009; Rutgeerts et al., 2009; Schwartz & Cohen, 2008). Most cases of pediatric IBD, however, may be managed with corticosteroids to induce remission and/or immunomodulatory agents for maintenance of remission (Kim & Ferry, 2002). These treatments do not come without risks and side effects, particularly in the case of children, given that interference with growth, osteoporosis, hirsutism, acne, and mood difficulties may result. For instance, steroid treatment has also been demonstrated to cause difficulties in memory, executive functioning, and mood among this population (Mrakotsky et al., 2005; Szigethy et al., 2004).

## CHILDREN AND ADOLESCENTS WITH IBD

About 20-30% of IBD cases are diagnosed in childhood (Griffiths, 2004; Hanauer, 2006). Incidence of UC in Western countries is about 1-2 per 100,000 children (Bentsen, Moum, & Ekbom, 2002; Kugathasan et al., 2003; Lindberg, Lindquist, Holmquist, & Hildebrand, 2000) while the incidence of pediatric CD is about 1.3-5 per 100,000 children (Hildebrand et al., 2003; Lindberg et al., 2000). Research suggests that IBD diagnosed in childhood tends to be more aggressive and have a stronger genetic component than IBD diagnosed in adulthood (Oliva-Hemker & Fiocchi, 2002). For instance, family history of the disease is present in 30% of children diagnosed before the age of 20 compared to 18% at 20-29 years of age and 13% after

age 40 (Sauer & Kugathasan, 2009; Van Limbergen et al., 2008; Vernier-Massouille et al., 2008).

Recent research has also uncovered noticeable differences in the expression of the disease in pediatric versus adult populations. While the rates of CD and UC tend to be almost equal in adult populations, the ratio of pediatric CD to pediatric UC is closer to 2.8:1 (Van Limbergen et al., 2008). In addition, the same study noted sex differences among children diagnosed with CD, with greater incidence of the disease among pre-pubertal males than among females at a ratio of 1.5:1 (Van Limbergen et al., 2008). The reasons for these changes remain unclear and are most likely complex and multifactorial in nature. Regardless of how it manifests itself, IBD is one of the most impactful chronic diseases among children and adolescents (Baldassano & Piccoli, 1999).

*Measuring Disease Severity in IBD*

The pediatric IBD literature highlights 3 primary measures used to capture and describe disease severity in patients with IBD: the Pediatric Ulcerative Colitis Activity Index (PUCAI), the Pediatric Crohn's Disease Index (PCDAI), and the Physician Global Assessment (PGA). The PUCAI is calculated by looking at indices of abdominal pain, rectal bleeding, stool consistency, activity level, among other markers of severity in patients with ulcerative colitis. Scores range from 0 to 85. The PCDAI is used with patients with Crohn's disease. It is calculated similarly,

but in addition to relying on clinical observations and patient report, it also uses laboratory findings to calculate a final value of disease severity. The total scores range from 0 to 100. These two measures are continuous and include cutoff scores that allow clinicians to determine whether a patient is in remission or experiencing mild, moderate, or severe disease. The PGA is a similar measure but is completely categorical in nature and can be used with both IBD subgroups in both children and adults. On the PGA, patients are classified as experiencing remission, mild, moderate, or severe disease. Many of the pediatric IBD studies have focused on operationalizing disease outcomes as either remission or active disease, or studying relapse. Some of this focus may be driven by the convenience of the categorizations already established, as well as the difficulties presented by the varying metrics of the PUCAI and PCDAI measures. Findings in the literature have been mixed, with some recent studies using the PGA as an outcome variable in a pediatric IBD population not finding significant associations with health related quality of life or depressive symptoms (Ryan et al., 2014). Conversely, other studies have found important associations between psychological variables and PCDAI (Mackner et al., 2005; Szigethy et al., 2004).

*Impact of IBD*

With a peak age of onset in late childhood and adolescence, a diagnosis of IBD may be particularly challenging for a child who is likely immersed in a process of identity exploration and mood/behavioral changes due to a natural maturation course. In addition to the diagnosis

itself, accompanying symptoms of IBD can be uncomfortable or, in more serious cases, functionally impairing. Presenting symptoms may include weight loss, anorexia, fever, arthritis, rectal bleeding, anemia, and growth failure, while the most common symptoms reported by children with IBD include abdominal pain and lack of energy (King, R., 2003).

*Pediatric IBD and Health-Related Quality of Life*

Also impacted by pediatric IBD is health-related quality of life (HRQoL), which refers to the subjective experiences of psychological, social, and physical abilities related to a chronic illness. Research suggests that in pediatric IBD populations, HRQoL is more impaired than in control groups, but not more so than in other pediatric chronic illness populations (Greenley et al., 2010). Some of the specific variables affecting HRQoL in this population include increased disease activity (van der Zaag-Loonen, Grootenhuis, Last, & Derkx, 2004), fatigue (Marcus et al., 2009), and in some cases, type of treatment (Cunningham, Drotar, Palermo, McGowan, & Arendt, 2007). Poorer outcomes on HRQoL measures have also been associated with older age (Otley et al., 2006), less adaptive coping skills (van der Zaag-Loonen et al., 2004), and family variables such as problem solving and communication (Herzer, Denson, Baldassano, & Hommel, 2011).

*Pediatric IBD and Family Functioning*

Family factors such as low support, conflict, and limited emotional expression have been associated with the health-related quality of life and emotional functioning of children with chronic illnesses (Grey, Boland, Yu, Sullivan-Bolyai, & Tamborlane, 1998; Walker & Greene, 1989; Whittemore et al., 2002). However, to date, the literature remains equivocal as to overarching trends regarding family functioning in pediatric IBD populations (Mackner et al., 2013). More specifically, family dysfunction has been associated with illness-related problems in adolescents with IBD such as greater pain, increased fatigue, and increased bowel movements (Tojek, Lumley, Corlis, Ondersma, & Tolia, 2002). However, other research has noted no significant difference between family functioning in clinical and nonclinical samples (Mackner & Crandall, 2006). When family dysfunction has been reported, it is in tandem with poor communication and problematic family involvement, among other relational difficulties (Herzer et al., 2011).

As highlighted in this brief overview, progression of IBD in childhood can be more aggressive than in adults. It can also be comorbid with psychiatric disorders and other psychosocial difficulties, including lower health-related quality of life. However, not enough attention has been devoted to exploring some of the recurrent psychological variables in the IBD literature (i.e., stress, depressive symptoms, and alexithymia) and their relationship to health status over time in this particular pediatric population.

## STRESS

*Definitions*

In the last few decades, an increasing body of literature has correlated stress and illness (Taylor, 2009). However, despite the increasing interest in this area of study, there is not a single, universally accepted definition of stress. Three primary models of stress have evolved in the literature which are based on the constructs that their respective measures purport to address: response-based, environmental (i.e., stimulus-based), and transactional (i.e., person-environment) models. Each model not only reflects a different approach to stress, but also a progression in the conceptualization of stress from a purely bio-physiological mechanism to a fluid and dynamic interaction between biological, physiological, environmental, emotional, and cognitive factors.

Hans Selye proposed one of the older working definitions of stress. He described stress as a physiological response to a threat in the environment or any disruption in the organism's homeostasis (Monroe, 2008). The physiological response described by Selye involved a fixed activation of the sympathetic nervous system, or what is commonly known as the "fight-or-flight response" (Keefer, Keshavarzian, & Mutlu, 2008). Although his conceptualization of stress is no longer accepted in its entirety due to its failure to account for known variations in the stress response (Taylor, 2009), it continues to represent a cornerstone of this literature (Taylor, 2009). In tandem with this biophysiological approach to stress, a cursory overview of possible mechanisms through which stress may impact IBD will be reviewed later in this chapter, as it is

relevant to a more comprehensive understanding of psychological variables and disease progression specific to IBD.

A second way in which stress has been conceptualized in the literature is using an environmental, or stimulus-based, approach. This perspective works under the assumption that certain environmental circumstances are more loaded with stress-inducing qualities than others, allowing for a blueprint of hierarchical life stressors or events (Monroe, 2008). T.H. Holmes and R. H. Rahe created the first inventory of stressful life events in 1967, and similar measures and inventories soon followed. This stimulus-based model of stress is typically assessed using measures that rely on discrete lists of life events or stressors that can be more easily operationalized (e.g., Life Events Checklist, hassles scales). Despite noteworthy shortcomings reviewed in the stress literature (Monroe, 2008; Taylor, 2009), these measures have been associated with physical health. For instance, some studies have reported a relationship between participants' stressful life events scores and illness rates over a period of 6-8 months (Rahe, Mahan, & Arthur, 1970). The adult literature has also reported a relationship between daily stress or minor life events, negative mood (Bolger, DeLongis, Kessler, & Schilling, 1989), and medical utilization in certain populations (Brantley et al., 2005). Among adolescents, stressful life events have been associated with depressive symptoms (Low et al., 2012) and anxiety (Meng, Tao, Wan, Hu, & Wang, 2011), which may be partially mediated by coping (Meng, Tao, Wan, Hu, & Wang, 2011).

Current literature has brought awareness to the fact that stress responses may also vary significantly based on factors other than the objective stressor. The evolving literature in the past 2-3 decades has set the stage for the study of appraisal, coping, and other cognitive and emotional triggers for physiological stress responses. In 1984, in what is now considered a landmark theory in the psychological study of stress and health, researchers Lazarus and Folkman proposed a person-environment transaction model to explain stress. This model honed in on the dynamic between person-environment in the advent of a potential stressor, and advanced the idea that the experience of stress is highly contingent on the individual's appraisal of the event in question (the stressor).

According to Lazarus and Folkman's cognitive-transactional model of stress, the experience of stress begins with a potential stressor (external event) that leads a person to engage in a primary appraisal of the situation (e.g., "is the event positive, negative, neutral?"). This step is closely followed by a secondary appraisal process (e.g., "do I have enough resources and coping abilities to deal with this stressor?"), and ultimately leads the person to make a decision about whether the external event should be regarded as a stressor. If deemed a stressor, then the stress response is activated along with its corresponding physiological, cognitive, behavioral, and emotional components (Lazarus & Folkman, 1984; Taylor, S., 2008).

As Keefer and colleagues (2008) point out, Lazarus and Folkman's model functions within a person-environment transaction that is bidirectional and context-dependent. Whereas previous models had emphasized a stimulus-based or response-based approach to stress,

conceptualization of stress after introduction of this person-environment transaction model involved the recognition of stress as dependent on "a real or perceived imbalance between environmental demands required for survival and an individual's capacity to adapt to these requirements" (p. 194). Examples of measures that elicit perceived stress include the Perceived Stress Questionnaire frequently used with IBD populations, as well as the Adolescent Minor Stress Inventory (AMSI).

Ultimately, as Monroe (2008) highlights in his review of stress, stimulus-based and transactional models of stress may tap into different underlying mechanisms of stress and could potentially be linked to various diseases or disorders, as they may be mediated by different biological mechanisms (Cohen, Tyrrell, & Smith, 1993; Monroe, 2008). Using several measures that assess various stress constructs may shed light on the relationship between this psychological variable and disease status.

*Chronic Stress*

Chronic stress in particular has garnered significant attention in recent years, as it is believed to be particularly damaging to an organism. While the short-term activation of the stress response can be evolutionarily appropriate and adaptive in situations that are perceived as taxing, long-term activation of the stress response can lead to harmful emotional and physiological outcomes. Many examples in the literature support a connection between chronic stress and health problems in both adults and children.

In the adult literature, chronic stress has been linked to cardiac problems as well as cognitive difficulties. As outlined by Taylor (2009), long-term release of norepinephrine and epinephrine can suppress immune function; lead to increased blood pressure; increase heart rate, and cause changes in the normal patterns of heart rhythms. These changes, in turn, may result in heart problems and mortality. Extensive cortisol secretion due to stress has also been connected to neuron damage in the hippocampus (Taylor, 2009). Ultimately, this damage can lead to cognitive atrophy.

Research suggests that children and other at-risk populations (e.g., the poor and elderly) may be particularly susceptible to the deleterious effects of chronic stressors, as they are likely to experience less control over their environment (Taylor, 2009; p. 156). For instance, children from families that experience conflict, abuse, or decreased nurture tend to demonstrate increased reactivity to stressors as well as an increased cortisol response (Repetti, Taylor, & Seeman, 2002). In turn, as noted previously, chronic elevations in cortisol secretion can lead to hippocampus damage, and such damage may lead to problems with memory, concentration, and verbal abilities (Starkman, Giordani, Berent, Schork, & Schteingart, 2001). In children, exposure to chronic stress may also result in chronic dysregulation of the nervous system, which may last into adulthood. This latter hypothesis stems partly from studies conducted with laboratory rats in which early experiences were demonstrated to impact HPA axis function at the genomic level, provoking permanent changes in reactions to stressors (Meaney & Szyf, 2005).

*Stress and Personality Factors*

Research suggests that personality variables impact the way in which individuals perceive or cope with any type of stress (chronic or otherwise), thereby moderating the effect or impact of the stressful situation. If stress is conceptualized partly as a person-environment transaction in which the individual's perception of the potential stressor is paramount, then it is easy to imagine why personality factors may play a critical role in the stress response. The literature suggests that the perception of stress is linked to certain personality styles laden with negative affectivity, as well as overall ways of appraising events that exacerbate distress (Taylor, 2009).

The construct of neuroticism has been examined frequently in relation to the stress response. In a study examining neuroticism (or negative affectivity) among college students, participants were asked to complete questionnaires at the end of every day for a total of 14 days and their answers were analyzed based on levels of neuroticism (Gunthert, Cohen, & Armeli, 1999). Researchers found that students scoring higher on neuroticism endorsed more interpersonal stressors, more negative appraisals of the situations, and responded with more distress than students who were low on the construct (Gunthert, Cohen, & Armeli, 1999). Other studies on neuroticism and the stress response have also noted similar findings—individuals who received high scores on neuroticism also tend to experience and perceive increased stress ("threat appraisals"), while they remain low on positive affect and high on negative affect (Schneider, Rench, Lyons, & Riffle, 2012). Studies have also shown that individuals high on negative

affectivity also tend to use health services more frequently during times of stress (Cohen & Williamson, 1991), as they are likely less able to modulate their stress in a positive and productive manner.

*Stress and Illness*

Stress has been associated with various health outcomes as measured by subjective markers of health (e.g., reported pain levels, fatigue) and objective markers of disease severity. In a study looking at the relationship between perceived stress and self-reported health status, perceived stress was significantly correlated with lower health status as measured by physical and social functioning, mental health, vitality, bodily pain, and general health (Young et al., 2004). When examining objective markers of disease severity, perceived stress has also proven to have a significant impact on health status. In examining the experience of an adult acute myocardial infarction (AMI) population, moderate/high perceived stress was related to poor health status one year after baseline, including worse disease-specific health status (Arnold, Smolderen, Buchanan, Li, & Spertus, 2012). The relationship between stress and health status persisted even after accounting for mood variables such as depressive symptoms (Arnold, Smolderen, Buchanan, Li, & Spertus, 2012). These studies highlight the impact of perceived stress on health status, whether the latter is appraised subjectively or objectively.

*Stress and Adult IBD*

In the 1980s and 1990s, more studies began to examine the relationship between disease activity and stress in adults with IBD, but the methodology varied significantly in terms of the selection of assessment time points, diagnoses, and measures utilized. In a meta-analysis of the research conducted on ulcerative colitis before the 1990s, North and colleagues (1994) concluded that the methodology employed in previous decades was often faulty or too variable to draw many meaningful conclusions (North et al., 1994; Riley et al., 1990). Even throughout the 1990s some of the results were inconsistent or not always generalizable, particularly for studies that used very small sample sizes or a mixed sample of patients with ulcerative colitis and Crohn's disease.

Among the few studies from the 1980s and 1990s that demonstrated sound methodology, findings were mixed. In an outpatient cohort of 60 adult individuals in UC remission, researchers found a significant relationship between life events and earlier time to relapse (Bitton et al., 2003). A subsequent study by Bitton and colleagues (1992) examining an outpatient cohort of 101 adult individuals with Crohn's disease also determined that stress and poor coping were significantly related to earlier time to relapse (Bitton et al., 2003). In a cross-sectional study conducted by Levenstein and colleagues (1994) examining life experiences and stress in a sample of 79 adults with ulcerative colitis, researchers found no relationship between life events and disease activity, but noted asymptomatic patients with endoscopical mucosal abnormalities had endorsed greater stress than participants with no abnormalities. In this same study, patients

who reported symptoms of their disease were also more likely to endorse major life events in the past 6 months.

Since the year 2000, several prospective studies have examined in more depth the relationship between stress and disease status in adults with IBD. Some of these studies have used mixed samples while others have focused on either ulcerative colitis or Crohn's disease. In the longest prospective study conducted to date, 62 patients with inactive ulcerative colitis were followed for 4 to 5 years (Levenstein et al., 2000). Findings revealed that life events alone did not account for risk of disease relapse; however, higher stress at baseline significantly increased the risk of disease exacerbation in this study sample. In fact, longstanding stress tended to triple the risk of experiencing illness exacerbation in the 8 months that followed (Levenstein et al., 2000). In a similar study measuring life events and IBD relapse using the Spanish version of the Social Readjustment Rating Scale (SRRS), researchers also failed to find an association between rates of relapse and stressful events despite having a significant sample size of 163 adult IBD patients (Vidal et al., 2006). With a smaller sample of 60 adult patients with ulcerative colitis, Bitton and colleagues (2003) reported an association between recent stressful events and earlier time to relapse. Interestingly, the study also found that risk of relapse increased with an increasing number of stressful life events. A subsequent study by Bitton and colleagues (2008) examining a sample of Crohn's disease patients failed to find an independent relationship between stress and disease relapse, but reported that the interaction between perceived stress and avoidance coping predicted time to relapse (Bitton et al., 2008).

*Stress and Pediatric IBD*

While the adult IBD literature has made progress in its exploration of the relationship between stress and health status over time, similar studies have not been conducted with pediatric IBD populations. Instead, psychosocial research with pediatric IBD populations has focused primarily on examining the comorbidity of disease with psychiatric disorders, as well as their relationship with psychosocial functioning and quality of life. When psychological variables have been explored in relation to health status, the focus has been on subjective indicators of health. For instance, a recent study conducted in Sweden explored the relationship between perceived stress and mental and subjective health complaints among adolescents (Wiklund, Malmgren-Olsson, Ohman, Bergstrom, & Fjellman-Wiklund, 2012). Results revealed that perceived stress was related to reported subjective health complaints such as headache, tiredness, sleeping difficulties, and musculoskeletal pain; perceived stress was also associated with sadness and anxiety (Wiklund, Malmgren-Olsson, Ohman, Bergstrom, & Fjellman-Wiklund, 2012). Objective measures of health status were not included in this study. Another study conducted in the Netherlands has examined the relationship between physiological and perceived physiological stress reactivity in children and adolescents from the general population (Evans et al., 2013). In this study, findings revealed that perceived physiological stress reactivity predicted cortisol reactivity among adolescents but not in younger children (Evans et al., 2013). However, similar studies examining the congruence between perceived and physiological stress have not been conducted among children and adolescents with IBD.

# DEPRESSION

*Definition*

A diagnosis of major depressive disorder is warranted when an individual exhibits certain mood and behavior patterns that are persistent for at least 2 weeks, and when this behavior marks a change from baseline and leads to functional impairment. These symptoms may include negative change in mood as well as disruptions in sleep, appetite, loss of pleasure in previously enjoyed activities, increased crying, decreased sexual drive in adults, and/or an inability to concentrate. In the United States, the lifetime prevalence of depression is estimated to be about 12% in men and 20% among women (Kessler et al., 2003). Among children, prevalence of depression is estimated to be between 1-2%, while the number increases to 3-8% among adolescents (Lewinsohn, Rohde, & Seeley, 1998). Beginning in adolescence, females tend to exhibit a 1.5-3.0-fold higher incidence of the disorder in comparison with males (DSM-V). In comparison to adults with depression, children and adolescents may express their low mood by exhibiting increased irritability, sadness, decreased frustration tolerance, as well as somatic concerns (Birmaher et al., 2007). Given the increased prevalence in adolescence, this developmental period marks a particularly important time to screen for symptoms of depression. Despite its prevalence, much about the course and mechanism of action in depression remains unclear. Research shows that the disease's course—as well as individuals' response to various treatments—is variable.

*Depression and Psychological Variables*

Chronic depression tends to be associated with more severe psychiatric problems, including personality disorders, anxiety, and substance disorders (DSM-V; p. 165). Risk factors include the presence of chronic medical conditions as well as certain personality characteristics such as neuroticism. The relationship between personality characteristics, stress, and mood variables is likely graded and additive, as higher indices of personality traits such as neuroticism have been associated with increased likelihood of developing depressive episodes in response to stressful life events (DSM-V; p. 166). More specifically, major depression tends to be comorbid with anorexia nervosa, bulimia nervosa, panic disorder, obsessive-compulsive disorder and borderline personality disorder (DSM-V; p. 168). Additionally, lower rates of recovery from depression have been associated with the duration of current depressive episodes, presence of psychotic features, significant anxiety, personality disorders, and severity of presenting symptoms (DSM-V; p. 165).

*Depression and Illness*

Research shows that depression impacts the expression and course of several adult chronic illnesses. For instance, depression has been linked to survival rates in breast cancer patients (Watson, Haviland, Greer, Davidson, & Bliss, 1999). Depression has also been linked to difficulties related to rheumatoid arthritis (McFarlane & Brooks, 1988), inadequate glycemic

control maintenance in patients with diabetes (Lustman, Griffith, Freedland, & Clouse, 1997), cardiac disorders and increased mortality rates (Frasure-Smith, Lesperance, & Talajic, 1995).

The literature linking depression and illness is extensive within the adult oncology literature. Rates of depression have been demonstrated to vary significantly based on cancer site. For instance, the rate of depression has been reported to be as high as 50% in patients with carcinoma of the pancreas (Joffe, Rubinow, Denicoff, Maher, & Sindelar, 1986), while much lower rates have been observed in patients with advanced abdominal neoplasm (Holland et al., 1986). Although highly controversial in the literature, some studies have found a modest but significantly higher risk of mortality among breast cancer patients based on timing of depression and cancer stage (Hjerl et al., 2003).

*Depression and Adult IBD*

A few studies in the adult IBD literature have examined the relationship between depression and various indicators of health status in this population, including disease activity, treatment outcome, and time to relapse. In a 2-year prospective study examining the relationship between psychological distress and disease activity in outpatients with Crohn's disease, findings revealed an association between depression and disease activity (Mardini, Kip, & Wilson, 2004). Also associated with disease activity were life changes, anxiety, and other indicators of psychological distress, but these effects were not independent from the effect of depressive symptoms (Mardini, Kip, & Wilson, 2004). Another study of Crohn's disease also reported a

significant association between major depressive disorder and (1) lower remission rates and (2) significantly decreased time to retreatment among adult patients receiving infliximab treatment (Persoons et al., 2005). Other prospective research has opted for combining the diagnoses of ulcerative colitis and Crohn's disease in their investigations. In a study examining a sample of 60 patients in remission after a disease flare, researchers found a significant relationship between depression scores at baseline and time to relapse (Mittermaier et al., 2004). Specifically, for patients endorsing depression, time to relapse was 97 days while time to relapse was 362 days for the non-depressed patients. Researchers also noted that depressive mood at baseline also correlated significantly with development of disease flares as well as the total number of flares during study follow-up. Despite this increasing body of literature on the impact of depressive symptoms on health status among adult IBD patients, few studies to date have conducted similar studies among pediatric IBD populations.

*Depression and Pediatric IBD*

Children and adolescents with IBD are at greater risk for psychiatric difficulties when compared with other clinical and nonclinical populations. A meta-analysis of psychological adjustment among adolescents with IBD revealed higher rates of depressive symptoms in this population compared to adolescents with other chronic conditions (Greenley et al., 2010). Higher prevalence rates of depression have been reported among children with IBD than among children with cystic fibrosis (Burke et al.,1989). The rate of depressive symptoms in pediatric IBD

populations has been reported to be as high as 25 percent (Szigethy et al., 2004), and a diagnosis of depression may also place children with IBD at risk for other disorders such as anxiety (Mackner, Crandall, & Szigethy, 2006; Szigethy et al., 2006).

Despite an increasing understanding about the comorbidity between pediatric IBD and depression, research exploring the impact of this psychological construct on health status is very limited. Additionally, findings can be divergent, with some researchers finding a strong association between pediatric IBD and depression (Ondersma, Lumley, Corlis, Tojek, & Tolia, 1997; Szigethy et al., 2004) and other studies not supporting this relationship (Burke, Neigut, Kocoshis, Chandra, & Sauer, 1994; Mackner & Crandall, 2005; Wood et al., 1987). One cross-sectional study examining depressive symptoms and disease activity in youths with IBD revealed an association between depression and disease severity, with moderate to severe disease symptoms correlating with greater depressive symptoms (Szigethy et al., 2004). Disease severity was determined based on the Pediatric Crohn's Disease Activity Index (PCDAI) and the Clinical Score of Kozarek (CSK) for Crohn's disease and ulcerative colitis, respectively; depressive symptoms were assessed using the Children's Depression Inventory (CDI). In this study, CDI scores did not correlate with illness course (i.e., acute, chronic intermittent, chronic) even though the scores correlated with disease severity in patients who were symptomatic.

Other studies have not found a relationship between depressive symptoms and disease activity. In a study examining psychosocial functioning and IBD in children between 11 and 17 years of age, researchers did not find a significant relationship between disease factors and

emotional difficulties (Mackner & Crandall, 2005). Disease activity was measured using the PCDAI while emotional difficulties were measured using the Youth Self-Report, Children's Depression Inventory (CDI), the Revised Children's Manifest Anxiety Scale, and the Piers-Harris Children's Self-Concept Scale. In an older study examining 36 children and adolescents with IBD, Burke and colleagues (1993) found that depressed children were more likely to have less severe illness, mothers with depression, families impacted by greater conflict, and more life events (Burke, Neigut, Kocoshis, Chandra, & Sauer, 1994). The psychiatric evaluation consisted of the Kiddie-SADS-E, the Family Relationship Index Scale (FRI), the A-SADS-L (Adult Schedule for Affective Disorders and Schizophrenia, Lifetime Version), as well as the FILE (Family Inventory of Life Events). IBD disease severity was rated using the Lloyd-Still and Green Scale. Finally, a study by Wood and colleagues (1987) also reported a non-significant relationship between illness and psychological dysfunction, but found an association between internalizing psychological styles and disease activity (Wood et al., 1987).

## ALEXITHYMIA

*Definition*

Alexithymia emerged over 30 years ago as a construct to describe patients who demonstrated chronic deficits in recognizing and expressing their emotions, had a limited capacity for fantasy life, and whose thinking was characterized as concrete and excessively concerned with external stimuli (Sifneos, 1973; Sifneos, Apfel-Savitz, & Frankel, 1977). In its

more literal sense, alexithymia means "absence of words for emotions" (from Greek: *a* = lack, *lexis* = word, *thymos* = mood or emotion). While Sifneos (1973) coined the term "alexithymia," his work draws significantly from the theories and research of other pioneers in the field. For example, work by Ruesch (1948) and MacLean (1949) proposed that unregulated emotional states could result from an individual's inability to represent emotions via the symbolic system of language, perhaps eventually affecting the body and health. The concept of alexithymia also draws from what the French psychosomaticists (Marty & de M'Uzan, 1963) called *pensée opératoire*—a term used to describe individuals who exhibited concrete thought processes and a propensity to focus on external stimuli. In another article published in 1976, Nemiah, Sifneos, and colleagues further crystallized the concept (Nemiah, Freyberger, & Sifneos, 1976). As we understand it today, alexithymia is composed of the following traits: (1) difficulty identifying and distinguishing between feelings and the bodily sensations of emotional arousal; (2) difficulty describing feelings to other people; (3) constricted imaginal processes, as evidenced by a paucity of fantasies; and (4) a stimulus-bound, externally oriented cognitive style (Taylor et al., 1997).

*Epidemiology*

Many of the epidemiological studies on alexithymia have been conducted with adult populations, and findings indicate that alexithymia is associated with older age, low economic status, limited educational achievement, and an adult male to female sex ratio that approximates 2:1 (Honkalampi, Hintikka, Tanskanen, Lehtonen, & Viinamaki, 2000; Salminen et al., 1999).

Studies completed among the Finnish general adult population have revealed prevalence rates of alexithymia ranging from 9-17% among men and 5-10% among women, with even higher prevalence rates among the elderly (Kokkonen et al., 2001; Mattila et al., 2006; Salminen et al., 1999). To date, similar studies have not been conducted in the United States.

*Adolescent Alexithymia*

The research exploring the epidemiology and mechanisms of alexithymia remains scarce among adolescents in general. However, the prevalence rates have been estimated to be somewhere in the range between 6 – 18%. A Finnish study revealed a prevalence rate of 14.6% among males and 17.3% among females in a group of twelve through seventeen-year-olds (Sokkinen et al., 2007). Another study by Joukamaa et al. (2007) reported an incidence of 6.9 percent in males and 9.5 percent in females between the ages of fifteen and sixteen years old. However, these results differ from the adult population findings in that no significant sex gap was found. The study by Joukamaa et al. (2007) also revealed a relationship between alexithymia scores and difficult childhood circumstances, such as low maternal educational achievement and family stressors.

The present study will add a longitudinal component to a recently completed study (Crowley, 2012) with several interesting findings related to alexithymia in adolescents with IBD. In the study conducted by Crowley (2012), findings revealed a high prevalence of alexithymia in adolescents with IBD (21%) relative to the general population (7.3%, Honkalampi et al., 2000); a

significant correlation between alexithymia and each psychological variable measured (i.e., depressive symptoms, perceived stress of major life events, perceived stress of daily hassles, and perceived recent stress); and a significant association between disease severity and perceived stress of major life events. One limitation and possible explanation for the lack of significant findings related to health status variables was the cross-sectional nature of the project, which failed to capture the relationship over time between psychological variables and objective health status in adolescent IBD. The current study seeks to add to the current literature by providing a more comprehensive, multivariate representation of the relationship between psychological variables and health status over time in adolescent IBD by examining data longitudinally and including health care utilization indicators of health status.

*Associated Traits and Constructs*

Some studies have reported alexithymia as a state-dependent phenomenon (Honkalampi, Hintikka, Saarinen, Lehtonen, & Viinamaki, 2000; Honkalampi et al., 2001) due to findings that alexithymia scores often correlate with symptoms of depression and anxiety. However, mounting evidence supports the notion of alexithymia as a personality trait. For instance, a study by Salminen, Saarijarvi, Aairela, & Tamminen (1994) revealed that levels of distress among psychiatric patients significantly decreased over a year, but their alexithymia scores did not. In another study looking at college students, Martínez-Sánchez and colleagues (1998) observed that

levels of distress fluctuated over a 17-week time period based on situational stressors (e.g., exams), but that alexithymia levels remained stable.

Whether alexithymia is a trait with absolute or relative stability also continues to be the subject of debate. Absolute stability is related to how much a trait changes over time, while relative stability assesses whether relative differences among people stay consistent over time. One study of psychiatric outpatients by Luminet et al. (2001) provided support for the relative stability of alexithymia, but more research continues to be warranted.

The construct of alexithymia has been conceptualized in other relevant ways as well. For instance, in an article from 1977, Freyberger described two types of alexithymia—primary and secondary. Primary alexithymia corresponds to a personality trait while secondary alexithymia is a state reaction stemming from difficult circumstances. Sifneos (1988) attributed primary alexithymia to neurobiological deficits and secondary alexithymia to psychosocial factors, including trauma and developmental stagnation. This continues to be a useful way of thinking about alexithymia.

*Alexithymia and Psychological Variables*

Alexithymia has been linked to multiple psychiatric disorders, including depression (Honkalampi et al., 1999), panic disorder, substance abuse, bulimia, and anorexia nervosa (Speranza et al., 2007; Taylor et al., 1996). Other studies have shown an association between alexithymia and inhibition, lack of emotional expressiveness, and limited emotional control

(King et al., 1992; Verissimo et al., 1998). These findings suggest that individuals who are limited in their awareness and control of emotions will experience less success modulating distressing feelings when they arise. Alexithymia has also been associated with inadequate coping mechanisms for the modulation of stress, particularly in individuals who tend to be highly anxious (Martin & Pihl, 1986; Newton & Contrada, 1994). It is important to note, however, that individuals with alexithymia differ from highly anxious individuals in their pronounced difficulty identifying and communicating their symptoms of discomfort. Another study by Luminet, Bagby, Wagner, Taylor, & Parker (1999) demonstrated that alexithymia does not fit neatly into any one category in the five-factor personality model, but instead correlates with several traits across the various dimensions, including lack of assertiveness, increased proneness to depression, and decreased openness to feelings.

*Alexithymia and Illness*

Early on, the construct of alexithymia was primarily associated with classic psychosomatic diseases (Taylor, Bagby, & Parker, 1999). Although functional somatic symptoms continue to be associated with alexithymia (DeGucht & Heiser, 2003; Kanaan, Lepine, & Wessely, 2007), alexithymia has been linked to other illnesses as well. For instance, cognitive and affective deficits consistent with alexithymia were observed in patients with posttraumatic stress (Krystal, 1968), drug problems (Krystal & Raskin, 1970), and eating disorders (Bruch, 1973) around the same time that the term "alexithymia" was coined. More

recently, alexithymia has been associated with the development of a host of medical and psychiatric disorders. One of the strongest associations established between disease and alexithymia to date relates to essential hypertension. A study by Todarello, Taylor, Parker, & Fanelli (1995) found that over 50 percent of the hypertensive patients in their sample met criteria for alexithymia, while the rate was 33 percent among psychiatric patients and 16 percent among the community participants in the same study. In a more recent study by Grabe et al. (2010), researchers found a significant association between hypertension and atherosclerotic plaques and concluded that alexithymia represents an independent risk factor for these conditions. In discussing their results, the authors hypothesized that mood dysregulation among alexithymic patients may be responsible for the over-activation of the sympathetic nervous system and decreased vagal function that frequently lead to cardiovascular difficulties. These findings support the hypothesis by Lumley et al. (1996) that mood dysregulation caused by alexithymia may lead to physiological irregularities that have negative repercussions on physical health.

Among adults with chronic pain, scores of somatosensory amplification have been associated with levels of alexithymia. The relationship suggests a significantly lower tolerance to painful electric stimulation among individuals scoring high on alexithymia traits (Nakao, Barsky, Kumano, & Kuhoki, 2002; Nyklicek & Vingerhoets, 2000). Results from past research have consistently found higher rates of alexithymia in individuals with conditions such as fibromyalgia, rheumatoid arthritis, and chronic low back pain. When these pain diagnoses have been compared with each other on the construct of alexithymia, fibromyalgia has been shown to

have a greater association with alexithymia on several occasions. Steinweg, Dallas, & Rea (2011) noted that 44% of patients with fibromyalgia in their study met criteria for alexithymia, a rate significantly higher than what was observed in the comparison group of rheumatoid arthritis patients (21%). The fibromyalgia group in the sample also endorsed higher rates of depression, typically in the moderate to severe range. Authors hypothesized that higher indices of alexithymia could be linked to the higher prevalence of depression in the group, and that both conditions may be suggestive of an inability to express feelings and adequately cope with demands. However, when controlling for depression, the significant differences in rates of alexithymia between the groups became non-significant. Another study examining patients with fibromyalgia reported higher levels of alexithymia in these patients in comparison to patients with chronic low back pain (Tuzer et al., 2011). Fibromyalgia patients scoring high on alexithymia also endorsed higher levels of somatization, depression, and anxiety.

Studies have also noted a significant relationship between alexithymia and other medical conditions not involving pain symptoms. For instance, in pediatric studies with patients with type 1 diabetes, the alexithymia factor of "difficulty describing feelings" (DDF) has been associated with problems with glycemic control, explaining about 12% of the total variance in $HbA_{1c}$ levels (Housiaux et al., 2010). Authors in this particular study hypothesized that children's abilities to express their feelings is critical to fostering adequate communication and conveying their medical or treatment needs to their parents, who may ultimately be responsible for adjusting the child's diabetes treatment accordingly. Findings in this study are consistent with similar studies

conducted with adult diabetic populations (Luminet, de Timary, Buysschaert, & Luts, 2006), with the potential implication in adults being that difficulties describing feelings to others may lead not only to inadequate glycemic control but also to increased health care utilization.

*Alexithymia and IBD*

The few alexithymia studies to date in the adult IBD population reveal a relationship between increased rates of alexithymia and IBD. Earlier studies using projective test measures revealed that compared to psychoneurotic patients, IBD patients had more difficulty verbalizing emotions and also experienced greater emotion dysregulation (Taylor & Doody, 1982; Taylor, Doody, & Newman, 1981). In fact, the prevalence of alexithymia in IBD populations is higher than the rate observed in a normal adolescent population (Honkalampi et al., 2000; 7.3%) and appears to be independent from disease activity (Porcelli, Zaka, Leoci, Centone, & Taylor, 1995). A study by Verissimo and colleagues (1998) found no association between alexithymia and illness duration and disease activity in patients with IBD, but found more bowel and systemic symptoms in patients with higher alexithymia scores. Additionally, they found that patients scoring higher on the alexithymia scale experienced worse emotional functioning. However, the literature in this area remains disputable, as some studies have linked positive medical outcomes and higher levels of alexithymia. For instance, in three studies of adult patients undergoing surgery for ulcerative colitis by Weinryb, Gustavsson, & Barber (1997, 2003) and Weinryb, Gustavsson, Liljeqvist, Poppen, & Rossel (1997), the presence of

alexithymia was associated with better postoperative adjustment and higher quality of life. It is important to note, however, that the TAS-20 was not used in these assessments, making it difficult to compare these findings to others that have employed the widely used TAS-20 measure.

*Alexithymia and Pediatric IBD*

The current literature on pediatric IBD and alexithymia is very limited, but the literature that is available has focused on two main objectives: 1) determining the rates of alexithymia in this population in relation to the general population, and 2) on determining whether alexithymia can be characterized as a transient state or a personality trait among patients (Martinez-Sanchez, Ato-Garcia, Adam, Medina, & Espana,1998). However, to date, no studies have examined the relationship between alexithymia and IBD disease activity longitudinally. This relationship deserves additional attention, as alexithymia has proven to be an important factor in disease activity and treatment among other medical pediatric populations. For instance, a recent study by Housiaux and colleagues (2010) examining the relationship between alexithymia and glycemic control in children with type 1 diabetes revealed a significant relationship between this psychological variable and medical outcomes. More specifically, the alexithymia factor of Difficulty Describing Feelings (DDF) was determined to be an additional predictor of HbA1c levels variance over and above medical and demographic variables. This particular study was

conducted with a group of 60 children between the ages of 8 and 12 years old (Housiaux, Luminet, Van Broeck, & Dorchy, 2010). Similar studies are needed in pediatric IBD.

Given these significant findings between psychological variables and IBD, as well as the potential impact on health, it is worthwhile to explore the complexity of the relationship between these key players in pediatric populations. The ultimate goal is to make better-informed decisions about targeted interventions that may reduce the emotional burden and rising health costs among this population.

*Measuring Alexithymia*

The twenty-item Toronto Alexithymia Scale (Bagby, Parker, & Taylor, 1994) is the most widely used measure of alexithymia to date (Taylor, 2004). The reliability and factorial validity of the measure are considered adequate, including among various languages and cultures (Bagby et al., 1994; Bagby, Taylor, & Parker, 1994; Parker, Taylor, & Bagby, 2003; Taylor, Bagby, & Parker, 2003). The scale has also been validated in an adolescent population (Sokkinen, Kaltiala-Heino, Ranta, Haataja, & Joukamaa, 2007), although continued debate surrounds its use with younger populations. According to the literature, cut-off scores above 60 are considered to be indicative of alexithymia. However, this cut-off has not been validated in an adolescent population.

In a study conducted by Heaven and colleagues (2010), researchers found the abbreviated 12-item TAS-20 to be a valid and reliable measure to use with adolescents. The scale was

internally consistent (Cronbach's alpha = 0.87) and could be distinguished from other psychological variables such as depression (Heaven et al., 2010). The 12-item version excludes the Externally Oriented Thinking (EOT) subscale.

## MECHANISMS OF TRANSFERENCE: PSYCHOLOGICAL VARIABLES AND DISEASE ACTIVITY

### *Stress and IBD*

Psychological stress has long been considered an important environmental factor in IBD, leading to a mind-gut theory of the disease (Goyal & Hirano, 1996). It is now believed that gastrointestinal inflammation may be partially accounted for by changes in the hypothalamic-pituitary-adrenal (HPA) axis, in bacterial-mucosal interactions, and via mucosal mast cells and the corticotrophin-releasing factor (CRF) (Mawdsley & Rampton, 2005).

According to the HPA axis model of IBD (Mawdsley & Rampton, 2005), stress causes the release of the neurotransmitter CRF from the hypothalamus, which triggers the anterior pituitary gland to release adrenocorticotrophic hormones (ACTH), leads to the release of cortisol from the adrenal cortex, and ultimately suppresses the immune system. Stress can also provoke inflammation through mechanisms other than the HPA axis. For instance, stress may trigger various neural pathways from the hypothalamus to the pontomedullary nuclei, which in turn stimulate the sympathetic and parasympathetic systems within the autonomic nervous system. The afferent and efferent neurons within these systems communicate with the neurons of the

enteric nervous system, thereby changing or controlling gut processes such as motility and exacerbating many other symptoms of IBD (Mawdsley & Rampton, 2005). In turn, the enteric nervous system (ENS) may employ several specific mechanisms through which it can exacerbate IBD.

The ENS has the capacity to release neurotransmitters (e.g., CRF, substance P (SP)) that connect to inflammatory cytokines, which lead to inflammation and the worsening of IBD symptoms. Alternatively, release of neurotransmitters (e.g., CRF, SP) by the ENS may directly affect other processes that lead to increased colonic motility, increased water and ion secretion, and increased colonic mucus secretion. Mast cell mediators (e.g., histamine, IL-8) in the ENS can also increase bacterial transfer into mucosa, activating T-cells and leading to subsequent gut inflammation (Mawdsley & Rampton, 2005). As can be gleaned from these complex and varied processes, the brain– particularly the hypothalamus, amygdala, and hippocampus– can dictate the neuroendocrine stress response via the HPA axis and the autonomic nervous system (Mawdsley & Rampton, 2005).

*Alexithymia and IBD*

According to Taylor (2004), "among the various emotion-related constructs that have been associated with health and disease, alexithymia has the longest history." In an article published in 1996, Lumley, Stettner, & Wehmer reviewed the literature on alexithymia in medical patients to illuminate possible pathways between alexithymia and disease. The authors

hypothesized that the relationship would likely follow one or more of the following patterns: (1) alexithymia leads to organic disease through physiological or behavioral means; (2) alexithymia leads to illness behavior; (3) physical illness leads to alexithymia; and/or (4) alexithymia and physical illness stem from sociocultural or organic factors. Based on the literature, the authors concluded that alexithymia is associated with a tonic sympathetic hyperarousal and dysregulated state, as evidenced by findings of elevated blood pressure among some of the participants; somatosensory amplification, perhaps due to an immature ability to interpret and process both physiological arousal and/or affective stimuli; and unhealthy behaviors, such as substance abuse and eating disorders. In sum, although alexithymia has not been linked directly to the development of organic disease, it may represent a risk factor in that affect dysregulation in alexithymia may cause disruptions in the autonomic nervous system and the neuroendocrine system, and illness behaviors and poor health patterns associated with alexithymia may provoke or exacerbate negative health outcomes.

The construct of alexithymia has also been studied in relation to the stress response. To address this noted relationship, researchers in this field have postulated a stress-alexithymia model to describe mechanisms by which stress and alexithymic traits can lead to stress-related illness. This theory suggests that deficits in identification and expression of emotion by individuals high on alexithymic characteristics may prevent them from coping effectively with stressful situations. In turn, this inability to cope effectively leads to extended and elevated autonomic activity (Martin & Pihl, 1985). In a study examining the physiological and cognitive

responses to stress in individuals with alexithymia, individuals with alexithymia demonstrated an increase in tension in anticipation of a stressor, while the non-alexithymic group demonstrated increased tension following the stressor (Papciak, Feuerstein, & Spiegel, 1985). Other studies also support this finding. For instance, in a study that examined individuals' responses to various laboratory stressors, alexithymic individuals showed an increased electrodermal activity and greater reported arousal and displeasure than their nonalexithymic counterparts (Friedlander, Lumley, Farchione, & Doyal, 1997).

## LIMITATIONS OF THE CURRENT IBD LITERATURE

Although the literature has established a relationship between psychological variables and IBD, the research remains inconclusive with respect to a possible causality between psychological variables and disease progression in the pediatric literature. There are multiple reasons for the inconsistencies and difficulties found in the literature. First, it is difficult to determine causality based on cross-sectional studies, and for reasons of feasibility and convenience, most studies to date tend to be cross-sectional in nature. However, even when the studies have been prospective in nature, the task has proven to be challenging. An underlying question is always the direction of causality, as it is difficult to determine the extent to which previous exacerbations of disease activity are taxing the patient's emotional system and therefore provoking future exacerbations of disease coupled with emotional distress. In spite of adjusting for prior disease activity, this remains an important confounding factor in the literature. Other

important limitations in the current literature which drive some of the inconclusive findings have to do with small sample sizes, which in turn restrict differentiation of the following important groups within the IBD population: 1) UC vs. CD and 2) relapse vs. remission. The current literature has also been unclear or inconclusive with regard to behavioral factors that may be mediating or confounding results (e.g., smoking), or the psychiatric history of patients enrolled in studies. Other studies have also been limited by the lack of control groups. Some limitations in the literature have to do with the significant variation in the psychological measures used (particularly with regard to anxiety/stress) as well as the disease outcomes measured. Despite ongoing difficulties in conducting this research, we have enough evidence to suggest the continued importance of understanding the role that psychological variables play on disease status in IBD populations.

## MEDICAL ILLNESS AND HEALTH CARE UTILIZATION

As a chronic illness with relatively normal life expectancy and intermittent flare-ups, care of IBD patients tends to span a lifetime. In a health care environment that is increasingly taxed by the rising costs brought about by chronic illnesses, a premium has been placed on understanding the characteristics of such populations as well as the factors that contribute to increased health care utilization.

In the United States alone, the direct cost of treating IBD (e.g., physician visits, hospitalizations) has been estimated to be $3.1 billion for CD and $2.1 billion for UC annually for adults and children combined (Kappelman et al., 2008). Additionally, research has identified some areas of greater utilization, with some studies concluding that more than 30% of the costs of utilization stem from ambulatory care and over 30% result from inpatient services (Kappelman et al., 2008). Given these findings, our study has focused on both ambulatory as well as inpatient care utilization.

The study of pediatric IBD and health care utilization is particularly important given that this age group accounts for a larger portion of utilization (Kappelman et al., 2011). Many factors can explain the discrepancy, including the higher proportion of cases in childhood, greater costs associated with the first few years after the disease, as well as greater severity of the disease among early-onset patients. However, relatively little is known about the factors that drive utilization among children with the disease.

*Health Care Utilization and Psychological Factors*

Medical utilization and costs are known to be higher among individuals with psychiatric comorbidities. This increase in costs has been reported across the continuum of care, including emergency department visits and length and cost of inpatient hospitalization. In a population-based sample of depressed elderly patients, researchers found cost increases in several areas of health care utilization (Katon, Lin, Russo, & Unutzer, 2003). For instance, total ambulatory costs

for the depressed group were 43-52% higher than those of the non-depressed group, with an average increase of $763.00-$979.00 in charges per patient, per year; inpatient costs were 47-51% higher with increased costs of $1045-1700 per patient annually (Katon, Lin, Russo, & Unutzer, 2003). Among cancer patients, depression has been associated with increased hospital stays and decreased adherence to medical treatments (Pirl & Roth, 1999). In the pediatric literature, the relationship between psychological factors and health care utilization has not been studied as extensively. However, the literature suggests similar outcomes. For example, in a study of youth with insulin-dependent diabetes mellitus, participants with behavioral problems were at increased risk for multiple re-hospitalizations for over a decade later (Charron-Prochownik, Kovacs, Obrosky, & Stiffler, 1994). Similar studies have not been conducted specifically with pediatric IBD populations.

*Ambulatory and Inpatient Care in IBD*

When compared with healthy matched controls, children and adult IBD patients have an additional 21.7 hospitalizations, 20.1 ED visits, and 493 office visits annually, per 100 CD patients (Kappelman et al., 2011). When examining rates per 100 UC patients per year, the rates are slightly lower: 13.3 more hospitalizations, 10.3 more ED visits, and 364 more office visits (Kappelman et al., 2011). In their study published in 2011, Kappelman and colleagues also found health care utilization differences based on demographic variables, including age, sex, and health insurance. For instance, female sex was positively associated with more ED visits and inpatient

hospitalizations; younger age (< 20 years old) was associated with increased use across all services: ED visits, inpatient hospitalizations, and outpatient GI visits; Medicaid insurance (vs. commercial) was associated with more ED visits. Although the literature remains limited, psychiatric comorbidity has been associated with increased health care utilization (Ananthakrishnan et al., 2013).

*Time-To- Medical Care*

Hospital readmission is an important topic in the health care literature, particularly with the increased focus on minimizing hospitalizations and finding the factors that influence re-hospitalization. Relatedly, early readmission has garnered increased attention, as it has been associated at times with preventable processes. For example, research has found a relationship between the quality of inpatient care and early readmission (Ashton et al., 1997). Having a better understanding of the risk factors for readmission would allow providers to address these indicators, and in turn decrease readmissions (or time to readmission), improve care, and also limit economic costs associated with increased or frequent health care utilization.

Survival analysis procedures, which examine time to care, are instrumental in examination of longitudinal data because they allow flexibility in terms of when the patient enters or exits the study. Unlike other statistical procedures, time-to-event survival analysis accounts for the presence of varying time periods throughout the study. To our knowledge, in the adult IBD literature, very few studies have utilized these statistical procedures, and those studies

have looked to determine (1) time to flare-up or (2) relapse post-baseline (Mittermaier et al., 2004; Vidal et al. 2006). With other pediatric populations, however, these statistical procedures have demonstrated important associations between psychological factors and health care utilization. In studies with adolescents with type 1 diabetes, findings show that depressive symptoms are associated with increased risk of hospitalization (Stewart, Rao, Emslie, Klein, & White, 2005). More generally, the adult health psychology literature has revealed important patterns differentiating use of emergency department services and increased hospitalizations. In some studies, ED visits have been linked to acute clinical symptoms while rates of hospitalizations have been associated with factors such as race, age, and education (Adepoju et al., 2014).

## CONCLUSION

Since the 1930s, researchers have been studying the relationship and impact of psychological variables and personality factors on the progression of inflammatory bowel disease. However, as North and colleagues highlighted in their reviews of the literature in the early 1990s, early studies were methodologically flawed, leading to confounding results and false conclusions. Since the 1990s, the IBD research has been mostly cross-sectional and has linked psychological and personality variables with disease progression in IBD patients. Findings from these studies could not be extrapolated to suggest causality given the limitations of the analyses. Within the past decade, prospective studies have focused on teasing out the

relationship between these variables through more methodologically sound studies. Consequently, researchers have been able to establish statistically significant relationships between stress and depressive symptoms in adult IBD populations. Similarly, more studies have begun to establish relationships between personality constructs such as alexithymia and IBD. However, much more research is needed in this area. These studies have focused primarily on adult populations, leaving a large gap in the pediatric IBD population.

The goal of the present study was to advance the literature related to psychosocial variables and health outcomes in the pediatric IBD population. The present study examined the relationship between three psychological variables—alexithymia, depressive symptoms, and stress—as they related prospectively to disease progression in a sample of adolescents with IBD.

## PURPOSE OF STUDY, AIMS, AND HYPOTHESES

The current study sought to determine the extent to which certain psychological variables (i.e., stress, depressive symptoms, and alexithymia) impact health status (as measured by physician-rated disease severity and utilization of non-routine health services) in adolescents with IBD over time.

*Aim 1*

The present study examined the relationship between each of three psychological variables at baseline (i.e., alexithymia, depressive symptoms, and stress) and health status over time as determined by 2 measures of physician-rated disease severity – Physician Global Assessment (PGA) and PUCAI/PCDAI scores. For the purposes of this study, PGA disease severity was conceptualized as a categorical variable, either remission or active disease.

*Hypothesis 1A:* We expected each psychological variable (i.e., alexithymia, depressive symptoms, and stress) to be a significant predictor of PGA over time as measured by any evidence of active disease in the 3 months following baseline.

*Hypothesis 1B*: We expected each psychological variable to be a significant predictor of PGA over time as measured by any evidence of active disease in the 12 months following baseline.

*Hypothesis 1C:* We expected each psychological variable (i.e., alexithymia, depressive symptoms, and stress) to be a significant predictor of PUCAI/PCDAI z-scores in the 3 months following baseline.

*Hypothesis 1D*: We expected each psychological variable to be a significant predictor of PUCAI/PCDAI z-scores in the 12 months following baseline.

*Rationale*: Studies have revealed higher rates of psychiatric difficulties (e.g., depression and anxiety) among adolescents with IBD in comparison to other pediatric populations (Greenley et al., 2010), sometimes with rates as high as 25 percent (Szigethy et al., 2004). Outside the

pediatric IBD literature, in a recent study by Housiaux and colleagues (2010), researchers found a relationship between alexithymia and glycemic control. A few IBD studies have found a temporal association between disease activity and psychological symptoms. For example, a study by Angelopoulos and colleagues (1996) found higher levels of depression and anxiety during the active disease phase of IBD, with symptoms subsiding once the disease reached remission. Similarly, other studies of IBD populations have found associations between worsening disease and parallel changes in psychological concerns (e.g., depression, anxiety), and vice versa (Mikocka-Walus et al., 2007; Mittermaier et al., 2004). In a study done in the adult IBD population by Mardini and colleagues (2004), findings revealed a strong positive relationship between depression and Crohn's disease activity (CDAI scores) when measured simultaneously or 8 to 12 weeks later. However, most of the studies conducted to date have included adult populations, and additional studies with pediatric populations are necessary.

*Aim 2*

The present study examined the relationship between each psychological variable (i.e., alexithymia, depressive symptoms, and stress) at baseline and health care utilization (i.e., GI clinic visits, emergency department use, and nights hospitalized) over time.

*Hypothesis 2A*: We expected each psychological variable (i.e., alexithymia, depressive symptoms, stress) to be a significant predictor of health care utilization in the 3 months following baseline.

*Aim 2B:* We expected each psychological variable (i.e., alexithymia, depressive symptoms, stress) to be a significant predictor of health care utilization in the 12 months following baseline.

*Rationale 2*: Many previous investigators have focused on physiological markers of disease activity as a primary health status outcome variable. However, as the concepts of wellness and illness have broadened, these definitions have come to include indicators of functionality, impairment, as well as 'illness burden.' Important indicators that have emerged in this literature are non-routine health services, such as clinic visits, hospitalizations, and ED visits, which are particularly salient in these times of rising health care costs. Although several recent studies in pediatric IBD have examined the relationship between psychological factors (e.g., depression, anxiety) and time to relapse (Mittermaier et al., 2004), the literature has not examined closely the relationship between psychological factors and whether these factors predict health care utilization. However, there is evidence of a significant relationship between these factors in other literature (e.g., type 1 diabetes literature). For example, it is known that depression is a strong predictor of hospitalization among adults with diabetes (Rosenthal, Fajardo, Gilmore, Morley, and Naliboff, 1998). Among youth, behavioral concerns have been linked to likelihood of multiple hospitalizations longitudinally (Kovacs, Charron-Prochownik, & Obrosky, 1995).

*Aim 3*

The present study examined the relationship between each psychological variable at baseline (i.e., alexithymia, depressive symptoms, and stress) and time-to-ED visit and time-to-hospitalization following baseline.

*Hypothesis 3*: We expected each psychological variable (i.e., alexithymia, depressive symptoms, and stress) to be a significant predictor of (1) time to first ED visit post-baseline and (2) time to first hospitalization post-baseline.

*Rationale*: Survival analysis procedures (Cox regression analysis) are particularly helpful for examination of longitudinal data in which participants have been allowed entry into the study at various times and for which end of the study time also affords variability (e.g., some participants have moved away prior to 1 year post-baseline). Unlike other statistical procedures that require exclusion of participants whose data is not complete for the "full" study period, time-to-event survival analysis adjusts for the presence of varying time periods throughout the study. To our knowledge, in the adult IBD literature, very few studies have utilized these statistical procedures, and those studies have looked to determine (1) time to flare-up or (2) relapse post-baseline (Mittermaier et al., 2004; Vidal et al. 2006). In the pediatric literature with other chronic illness populations, however, these statistical procedures have demonstrated important associations between psychological factors and health care utilization. For example, in studies with adolescents with type 1 diabetes, findings show that depressive symptoms are associated with increased risk of hospitalization (Stewart, Rao, Emslie, Klein, & White, 2005). More

generally, the adult health psychology literature has revealed important patterns differentiating use of emergency department services and increased hospitalizations. In some studies, ED visits have been linked to acute clinical symptoms while rates of hospitalizations have been associated with factors such as race, age, and education (Adepoju et al., 2014). When we consider sociocultural and socioeconomic factors, studies with Latino populations have demonstrated that Latinos have a propensity to postpone their time to medical visits until critical care is required (Galarraga, 2010).

# CHAPTER THREE
# Methodology

## PARTICIPANTS

The current study was a single measure, within-subject design of adolescents with IBD treated at Children's Medical Center (CMC). The participants included 89 adolescents between the ages of 13 years, 0 months and 17 years, 11 months. Of the larger group of participants, 62 had already completed baseline data as part of a previous study (Crowley, 2012) and an additional 27 adolescents with IBD were recruited and enrolled in the study. An a priori power analysis revealed that a total sample size of 89 adolescent participants would be necessary to detect a medium effect size ($f^2 = .15$) and a power of .85 with $\alpha = .05$ to conduct multiple linear regressions. Studies examining the relationship between psychological variables and health outcomes in other disorders, for example type 1 diabetes, have yielded significant associations with similar and smaller samples (i.e., n = 45, Housiaux, Luminet, Van Broeck, & Dorchy, 2010; n = 64, Luminet, de Timary, Buysschaert, & Luts, 2006). All procedures were conducted in accordance with the guidelines of UT Southwestern Medical School's (UTSW) Institutional Review Board, which is responsible for research at UTSW and CMC.

### Inclusion Criteria

1. Adolescent had to be an active patient at CMC's Gastroenterology (GI) clinic and have a diagnosis of IBD.

2. Primary caregiver was willing to complete demographic study forms related to adolescent participant.
3. Adolescent was proficient in English while primary caregiver could have been primarily English- or Spanish-speaking.
4. Absence of developmental or serious mental health disorder that would have interfered with the ability to complete measures by the caregivers and the adolescents.
5. No history of traumatic brain injury, stroke, neurological disorder, or other significant medical condition (e.g., epilepsy, cancer, cystic fibrosis).

## MEASURES

### Clinician Completed Forms

*Comprehensive Medical Chart Review Form*

Medical records were reviewed to obtain relevant demographic and clinical information related to health status and health care service utilization for up to 12 months prior to baseline and 12 months post-baseline. Demographic data (e.g., sex, date of birth, insurance type) was documented along with relevant clinical and medical information: date of diagnosis, age at diagnosis, time since diagnosis (in months), type of diagnosis (i.e., UC or CD), type and date of IBD-related surgeries, Remicade treatment (yes/no), lab results, health care utilization information (outlined in more detail below). For each outpatient GI clinic visit, ratings on the

Physician Global Assessment (PGA) of disease status and PUCAI/PCDAI calculations were also documented when available. Information was documented in the pre-baseline and post-baseline comprehensive chart review forms. More information about our health outcome variables of interest, and the way in which they were operationalized, are included below.

*Physician Global Assessment (PGA)*

PGA is a categorical physician-rated assessment of disease activity in the past week. Based on the findings of their interview and physical exam, physicians indicate whether patients are experiencing quiescent, mild, moderate, or severe disease activity. To standardize the PGA classification, definitions for these categories were developed by the International Council of Nurses (ICN) and made available to providers. Classification into one of the four categories is based on the following factors: abdominal pain, diarrhea, bloody stools, fatigue, activity levels, fistula, weight loss, abdominal mass (tenderness), toxic appearance, and lab tests. Quiescent disease reflected minimal or no symptoms secondary to IBD in the past week; mild disease consisted of mild recurring or persistent symptoms; moderate disease consisted of moderate (or combination of mild and moderate) recurring or persistent symptoms; and severe disease consisted of severe (or a combination of moderate and severe) recurring or persistent symptoms.

For the purposes of this study, the variable PGA was further categorized into remission and active disease; the latter category was comprised of mild, moderate, and severe disease activity ratings. PGA assessment over time consisted of tracking any changes in disease status

(i.e., constant remission = 0 while any flare-up = 1) over the course of 3 months and 12 months post-baseline. For instance, if a patient experienced even one flare-up of disease (i.e., mild, moderate, or severe disease) over the specified time period, the PGA assessment over that entire period was categorized as "1" for the purposes of this study.

*Pediatric Ulcerative Colitis Activity Index (PUCAI)*

The PUCAI was developed to assess disease severity in patients with ulcerative colitis. It is the sum of the following 6 sub-scores, with lower scores reflecting less disease activity: abdominal pain (0 to 10 points), rectal bleeding (0 to 30 points), stool consistency of most stools (0 to 10 points), number of stools per 24 hours (0 to 15 points), nocturnal stools (any episode causing wakening; 0 to 10 points), and activity level (0 to 10 points). It is important to note that no laboratory studies are included in the score, therefore the score does not reflect inflammation. Scores on the PUCAI range from 0 to 85, with a score of < 10 indicating remission, 10 – 34 indicating mild disease, 35 - 64 indicating moderate disease, and 65 - 85 indicating severe disease.

*Pediatric Crohn's Disease Activity Index (PCDAI)*

The PCDAI was developed to assess disease severity in patients with Crohn's disease. The PCDAI is comprised of both objective findings (i.e., laboratory parameters, physical examination, height velocity) as well as subjective information (e.g., self-report of abdominal

pain, stool composition). More specifically, it is the sum of the following sub-scores: abdominal pain (0 -10), stools/bleeding (0 -10), functioning/well-being (0 – 10), HCT lab score (0- 5), ESR lab score (0 -5), albumin lab score (0 – 10), weight (0 -10), height velocity (0 -10), abdominal exam (0 -10), perirectal disease (0 – 10), EIM (0 -10). When all the individual elements are summed, clinicians are able to obtain a total score (i.e., 0 - 100), with higher scores indicating more active disease. The cut-offs are as follows: $\leq$ 10 equals inactive disease, 11 – 30 equals mild disease, and >30 indicates moderate-severe disease.

Both the PUCAI and PCDAI are continuous scores of physician-rated disease severity. The original raw scores on the PCDAI and PUCAI underwent an additional transformation since the rating system varies by IBD subgroup. For the purposes of this study, scores on both PCDAI and PUCAI assessments were converted to z-scores to interpret and compare findings. More specifically, mean and standard deviations were calculated separately for the PCDAI and PUCAI subgroups, and individual z-score values were derived from those calculations and used for subsequent analyses.

*Health Care Utilization Variables*

1. GI outpatient clinic visits - Total number of visits to CMC's GI clinic over the course of 3 months and 12 months post-baseline and pre-baseline. The baseline clinic visit was factored into the post-baseline clinic visits.

2. ED visits – Total number of visits to CMC'S Emergency Department over the course of 3 months and 12 months post-baseline and pre-baseline.

3. Nights Hospitalized – Total number of nights hospitalized at CMC for GI-related concerns over the course of 3 months and 12 months post-baseline and pre-baseline.

4. Time-to-ED-visit – Time to first ED visit post-baseline (in days).

5. Time-to-Hospitalization – Time to first hospitalization at CMC post-baseline (in days).

**Primary Caregiver Completed Form**

*Baseline Caregiver Form*

Primary caregivers completed a six-page demographic and clinical history questionnaire outlining the child's psychological, educational, and medical history. The questionnaire included questions about the patient's home environment, the family's educational history, and parent's employment history. Pertinent demographic information collected about patients and families included: sex, age, race, ethnicity, and household income. Relevant clinical information about patients included: grade in school, academic performance, preferred language, diagnosis of learning disability (yes/no), diagnosis of mental health disorder (yes/no), and history of mental health service use (yes/no). The specific question about mental health use by child asked, "Has your child received any mental health services within the last 3 months?" For all yes/no questions, caregivers were given the opportunity to specify the applicable condition. Caregivers who endorsed mental health services use by their child, could select from the following options

to indicate which type(s) of services had been used: counseling, inpatient program, group therapy, medication, day treatment, and/or other; they could select more than one choice. For the section concerning demographics of the primary and secondary caregivers, the following information was collected: age, marital status, level of education completed, employment status, occupation, household income, and religious affiliation.

**Adolescent Completed Measures**

*Adolescent Minor Stress Inventory (AMSI)*

This inventory, which includes 72 self-report items, is intended to assess minor stress levels in adolescents over the previous 2 weeks (Ames et al., 2005). It was developed for use with both clinical and research populations. With regard to content, it contains three subscales: a minor stress subscale, a "Fake-good" validity subscale, and a "Fake-bad" subscale. The minor stress subscale is further divided into seven content areas: education-related functioning, work (at home and outside), financial matters, family functioning, health, social confidence, and social functioning. Of the 72 total items on the stress subscale, research has shown that 24 items do not load on any factor. As a result, and consistent with recommendations from other research, an abbreviated version of the questionnaire was used in this study, excluding those items (Salafia & Lemer, 2012). This version contains 5 subscales: relationships (10 items), family (6 items), financial (6 items), education (6 items), and performance (20 items). The internal reliability (Cronbach's alpha) for the five subscales ranges from .79 to .93. The inventory is intended for

children between the ages of 13 and 17 and requires a minimum reading grade level of 3.9. It includes statements such as, “My parents punished me” (family), “I argued with a friend” (relationship), and “I did not have enough spending money” (financial). Scores range from 0-5 on a Likert scale, and greater rates of endorsement will correspond with higher levels of perceived stress. The normative mean for this inventory is 85.3 with a standard deviation of 51.89 (Salafia and Lemer, 2012).

It is important to note a primary limitation of the AMSI. The sample used to validate this instrument was composed primarily of adolescents of Caucasian ethnicity that attended the Mayo Clinic in Rochester, Minnesota. As a result, it is difficult to know whether results are generalizable to adolescents from other geographical areas or from diverse backgrounds. This is an important challenge that should be kept in mind while conducting this study, as it likely impacted scores obtained for children belonging to diverse ethnic, and racial backgrounds.

*Children’s Depression Inventory - 2*

The Children’s Depression Inventory 2 (CDI-2; Kovacs, 2010) is the most widely used self-report instrument for assessing depression in children in a wide range of settings, from schools to pediatric centers. It measures cognitive, affective, and behavioral symptoms of depression over the past 2 weeks in children from 7 to 17 years of age. The inventory is composed of 28 items, with the option of choosing from 1 of 3 statements on each item. It requires a second-grade reading level and can take between 15 and 20 minutes to complete. The

instrument has established reliability and validity, with an internal consistency ranging from .71 to .89. The CDI-2 was normed using a representative sample of the U.S. population. The normative sample included children from 26 states and it matched the general population in age and sex, as well as the racial/ethnic distribution based on the 2000 U.S. Census. The CDI-2 recommended raw score cutoff for clinical significance is 14 for the full-length self-report.

*Life Events Checklist for Adolescents*

The Life Events Checklist (LEC; Johnson & McCutcheon, 1980) is a self-report measure designed to assess negative life events over the past 12 months. It consists of a list of 46 events likely to be experienced by adolescents. Given that 7 of the items are not developmentally appropriate for the age sample in this study, they were omitted; this abbreviated version of the LEC has been used previously in research with children and adolescents (Jackson & Frick, 1998). In completing the checklist, children rate their experiences as either negative or positive, and then endorse the effect of the event on their lives on a 4-point scale. The test-retest correlation for positive life event scores was .69 while that for the negative life events was .72 (Brand & Johnson, 1982). The normative mean is 13.7 with a standard deviation of 9.6 for the complete version of the measure (Brand & Johnson, 1982).

*Toronto Alexithymia Scale – 12 (TAS-12)*

The twenty-item Toronto Alexithymia Scale (Bagby, Parker, & Taylor, 1994) is the most commonly used measure of alexithymia (Taylor, 2004). An abbreviated form, the TAS-12, has also been proposed for use with younger populations (Sokkinen, Kaltiala-Heino, Ranta, Haataja, & Joukamaa, 2007). As Parker et al. (2010) point out, it is difficult to compare and apply the same standards used with the TAS-20 to younger populations when no definitive proof exists that the structure and quality of responses between these two populations match. According to the existing literature assessing the TAS-20 with younger populations, the psychometric properties of the instrument "become progressively worse with younger age of the respondents" (Parker et al., 2010). In this same study by Parker et al. (2010), the Externally-Oriented Thinking (EOT) subscale was not reliable for adolescents of any age, complicating the use of the full version of the TAS-20 with younger populations. Authors hypothesized that such lack of reliability may have been related to the higher level of complexity and readability necessary for this subtest (estimated to be 8$^{th}$ or 9$^{th}$ grade), while the Difficulty Identifying Feelings (DIF) and Difficulty Describing Feelings (DDF) were estimated to be around a fifth or sixth grade reading level. The third scale (EOT) also proved unreliable when measured in a previous study with adolescents (Rieffe et al., 2006). A recent study by Heaven et al. (2010) which examined the TAS-12 found that excluding the EOT sub-scale from the TAS-12 measure and calculating the alexithymia score using only the DIF and DDF subscales, "demonstrated excellent internal consistency" (p. 224) with a Cronbach's alpha of 0.87. Given that the DIF and DDF scales have

proven to be adequate and reliable for use with younger populations (Heaven et al., 2010), only these two were used for analyses of adolescent alexithymia in the current study. Normative mean is 31.50 with a standard deviation of 8.64 (Parker et al., 2010).

## PROCEDURES

### Participant Recruitment

Prior to participant recruitment, necessary IRB approval was obtained from UT Southwestern. Information about every study participant's next routine clinic visit was obtained through the GI patient schedules at CMC, and participants were approached at the clinic. These routine visits typically take place every three months. Recruitment and enrollment were ongoing. To determine eligibility, information about incoming clinic patients was obtained from the clinic patient database on a weekly basis. Patients who met criteria were approached during the upcoming clinic visit.

As part of the recruitment process, primary caregivers and their adolescents were informed about study procedures and processes. Informed consent/assent was obtained from both the adolescent and parent following established IRB guidelines. Upon approaching families, the researcher provided the adolescent and caregiver with a complete description of the study as approved by the UTSW IRB. This description included details about the study's purpose, procedures, potential benefits, and potential risks. They were also be made aware that their participation was completely voluntary and that they could withdraw at any point during the

study. Following this process, if patients and their caregivers wished to participate, they were asked to provide written, informed consent/assent and complete the Health Insurance Portability and Accountability Act (HIPAA) Release document, which permits the use of the adolescent's protected health information for study purposes. Copies of the consent and HIPAA release forms were provided for the adolescent and caregiver, CMC Medical Records, and the GI clinic at CMC.

**Data Collection**

Following consent and assent procedures participants were enrolled in the study and began their participation during that same clinic visit. Primary caregivers completed the Baseline Caregiver form. Adolescents completed the following forms: (1) AMSI; (2) CDI-2; (3) IMPACT-III; (4) LEC; and the (5) TAS-12.

The researcher(s) responsible for conducting the study visits were trained in the administration and scoring of all the measures. Immediately following completion of the forms, the researcher screened the CDI-2 for items related to suicidality. A total of 9 participants had clinically-elevated scores on the CDI-2. When an adolescent endorsed suicidality on Item 8 of the CDI-2, steps were taken to ensure the safety of the patient. First, endorsement of Item 8 was discussed in more detail with the adolescent in order to assess current risk. From the pool of 35 new participants recruited for the study since 2013, all the adolescents who endorsed suicidal ideation reported having suicidal ideation in the past, not at the time of the study visit. Whether

the adolescent endorsed past suicidal ideation or severe depressive symptoms with no suicidality, the clinic psychologist was contacted and a decision was made as to what procedure may be most beneficial for the patient. In all instances, the study coordinator verified that the patient either (1) was currently receiving counseling or had previously received counseling services to address the depressive symptoms and/or suicidal ideation, or 2) had referral information for counseling resources in the community. Patients who were not already connected with counseling services were scheduled to return to the GI clinic for a visit with the GI Psychology at CMC.

**Data Management**

As part of this study, it was necessary to access and use protected health information to identify potential participants and collect data. Data collected from medical records were kept in a locked cabinet, in a locked research office, with access limited to study personnel. To maintain confidentiality, a non-identifiable code was assigned to each participant. This code eliminated any direct link between specific names and the extracted information. A key to the coding system was stored separately from the data in a locked storage cabinet, in a locked research office, with access limited to study personnel. The key to the coding system will be destroyed at the end of the study. No identifiable information such as name, date of birth, address, phone number, social security number, or medical record number of subjects was directly linked to data collected. Only individuals who had received HIPAA and Human Subjects Protection training and who

were listed on the IRB for the study reviewed the charts and identifiable patient information. The electronic database was password protected.

Data was managed using Microsoft Excel and then transferred to the SPSS Version 22 for statistical analysis. Data quality control procedures ensured the quality and accuracy of the data collected by re-checking information on the number of GI outpatient visits, ED visits, and hospitalizations post-baseline for the newly recruited subgroup of 34 study participants (36.17% of the total sample).

CHAPTER FOUR
Results

## PRELIMINARY CONSIDERATIONS

### *Preliminary Power Analyses*

An *a priori* power analysis was conducted to determine the parameters necessary for sufficient confidence in statistical findings. It was determined that a total sample size of 89 participants would be necessary to obtain a medium effect size ($f^2 = .15$) and a power of .85 with $\alpha = .05$ when conducting multiple linear regressions.

### *Sample Size*

*Enrollment*. A total of 35 new participants were recruited and enrolled in the present study, adding to an existing pool of 63 adolescents previously recruited for a related study. Of the 35 newly- recruited participants, one was subsequently excluded from all analyses soon after enrollment, as he presented with significant medical complications that violated this study's inclusion criteria.

*3-month analyses.* The total sample size was reduced from 97 to 94, as 3 participants were lost to follow-up prior to 3 months, which is the shortest period of time analyzed in this longitudinal study. Hence, n = 94 is the largest sample size that will appear in any of the analyses reported hereafter.

*12-month analyses.* Ten participants were excluded for these analyses, as these participants were also lost to follow-up at some point during the course of 1 year and therefore

their data was incomplete for analyses. It is also important to note that the newly recruited subgroup of 34 participants was excluded from all of the 12-month data analyses, as not enough time had lapsed since baseline. Hence, n = 53 is the largest sample size that will appear in any of the 12-month data analyses reported hereafter.

*Loss of Data*. Data on depressive symptoms were not included for 3 additional participants, as one declined to complete the CDI-2 and two others failed to complete the measure fully. Data on stress of major life events was not included for 2 participants due to serious questions about the validity of the completed measures. Data on alexithymia was available for all 94 participants. Some of the data on physician-rated disease severity measures (i.e., PGA and PGA/PUCAI) were also missing, as some of the information could not be found in the medical note or the medical record lacked sufficient data to calculate full scores (i.e., PUCAI/PCDAI values). For the PGA, data was available on 54 participants over the course of 3 months and on 43 participants (out of 53 possible) over the course of 12 months. Forty-three participants had available PUCAI/PCDAI z-scores over the course of 3 months and 39 scores (out of 53) were available over the course of 12 months.

Given these preliminary difficulties with the availability of complete follow-up data, some of the analyses reported in this study are underpowered, limiting the confidence in our findings. Specifically, the results reported from logistic regression equations are underpowered and should be interpreted with caution. Long (1997) suggests that "it is risky to use …samples smaller than 100, while samples over 500 seem adequate." Post-hoc statistical power calculations

were not completed, as these tend to "have limited value due to the incorrect assumption that the sample effect size represents the population effect size" (Sullivan & Feinn, 2012).

## PRELIMINARY ANALYSES

Preliminary analyses involved examination of the data for violations of normality and other statistical assumptions. Specific procedures used included P-P plots, histograms, examinations of data skewness and kurtosis, and frequency tables. Data transformations and truncations were performed to address problematic discrepancies in normality with 3 month and 12 month samples (discussed below). When conducting logistic regressions, each analysis was preceded by checks to ensure low multicollinearity and to ensure proper treatment of outliers; the concern about sample size has been addressed above.

*3-month & 12-month data*. In examining the data over the 3 months post-baseline, two of the three psychological variables – stress and depressive symptoms – showed a significant positive skew (3.34 and 2.26, respectively). In the case of the stress variable, a Log 10 transformation was performed to achieve normality. For the depressive symptoms variable, 5 outliers were truncated to match the next highest raw score within range (i.e., 19), which was sufficient to normalize the sample. The 12-month data was analyzed separately on all the independent and dependent variables of interest, and it mirrored the normality issues of the 3-month data with regard to the stress and depression variables. The same measures were taken to normalize the 12-month data (i.e., conducting Log 10 transformations and truncation of the

depression variable). Data was analyzed using truncated and un-truncated CDI-2 values to assess impact on results. Truncated scores were used in analyses involving Aims 1 and 2, while un-truncated scores were used for Aim 3 analyses only.

*Exploring Differences by IBD Subtype*

The entire IBD sample was analyzed by IBD subtype (i.e., Crohn's disease vs. ulcerative colitis) on demographic and clinical variables of interest to detect any significant group differences that would prevent both subtypes from being analyzed together. Independent *t*-tests were conducted to analyze continuous variables while categorical variables were examined using chi-square analyses. No significant between-group differences were found on health outcome variables or the 3 psychological variables included in this study. IBD diagnosis was not significantly associated with demographic variables (i.e., age, sex, race, ethnicity). Given that IBD diagnosis was not found to be significantly associated with the primary variables of interest in this study, subsequent analyses of data combined both groups. Tables 1-7 include a complete list of results.

*Correlations Between Variables of Interest*

Our three psychological variables of interest – alexithymia, depressive symptoms, and stress – demonstrated statistically significant correlations (at the $p < .01$ level) with each other (refer to Table 31).

Correlations were also conducted between all potential predictor variables of interest (i.e., demographic, clinical), our three psychological variables, and outcome variables (i.e., physician-rated disease severity variables and health care utilization variables; refer to Tables 8-11 for correlational matrices).

Notably, depressive symptoms and stress were both significantly and inversely correlated with reported household income ($p < .01$). In other words, higher household income was associated with less stress and fewer depressive symptoms. Both depressive symptoms and stress were also correlated with reported history of mental health service use ($p < .05$), and directionality indicated that endorsement of past mental health service use was associated with worse depressive symptoms and more stress.

Results also indicated associations between our outcome variables and demographic/clinical variables. For instance, higher (worse) PUCAI/PCDAI z-scores over the course of 3 months were associated with older age at baseline. Over the course of 12 months, higher (worse) PUCAI/PCDAI z-scores were associated with non-white race. Over the course of 3 months post-baseline, an increasing number of ED visits was associated with the female sex and older age at baseline. For all tests conducted in this study, the level of significance was set *at* $p < .05$ unless otherwise specified.

## DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

*Demographics*

The complete sample (n = 94) included adolescents ages 13.03 to 17.93. The demographics of the 3-month and 12-month samples were very similar, but given the notable differences in sample sizes (i.e., 94 vs. 53) between the two groups, information was provided for both (refer to Tables 1 and 2). To ensure Chi-square analyses could be run validly with sufficient numbers of participants in each cell, several variables were re-grouped prior to analyses. Race was divided into 2 categories – White and Other; insurance was classified as either commercial or public; caregiver education level was reduced to only four categories: no high school graduation, high school graduation or GED, some college or vocational training, or bachelor degree or higher.

*Clinical Characteristics*

Health Status. At the time of baseline, 62 (72.9%) participants were in remission as determined by the Physician Global Assessment (PGA) classification. Over the course of 1 year, the number of ED visits was $N = .49$; number of nights hospitalized $N = 2.47$; the number of GI clinic visits $N = 3.76$ (refer to Tables 3 and 4).

Psychological Variables. At the time of baseline, 18 (19.1%) participants endorsed alexithymic traits; a total of 9 (9.6%) participants reported depressive symptoms in the clinical

range, and stress levels ranged from 0 to 60 (which included 3 outliers: 60, 29, 24), and $M = 6.24$ (8.47) prior to transformation (refer to Tables 5-7).

A total of 15 participants reported a history of mental health service use within the 3 months prior to baseline. Of those, 8 (8.5%) reported counseling alone, 1 (1.1%) reported medication use alone, 4 (4.3%) reported receiving both counseling and medications, and 2 (2.1%) reported receiving inpatient psychiatric services, medication, and counseling services.

## HYPOTHESES TESTING

*Aim 1. The present study examined the relationship between each of three psychological variables at baseline (i.e., alexithymia, depressive symptoms, and stress) and health status over time as determined by two physician-rated disease severity ratings (i.e., PGA and PUCAI/PCDAI scores).*

A total of 6 separate logistic regression equations were conducted for hypotheses 1A and 1B (3 equations for each). When conducting analyses using logistic regressions, examination of the odds ratio variable has been deemed to be a useful way to assess effect size (Breaugh, 2002). Recent studies utilizing logistic regressions to assess the relationship between maternal depression and health care utilization have also treated odds ratio as a measure of effect size (Clayton et al., 2013). Relevant odds ratio information as well as significant associations with PGA data is included in Tables 11 and 12. The data included in those tables informed the choice of covariates used in the various equations in hypotheses 1A and 1B.

*Hypothesis 1A: We expected each psychological variable (i.e., alexithymia, depressive symptoms, and stress) to be a significant predictor of physician-rated disease severity as measured by PGA over the course of 3 months following baseline.*

Each continuous psychological variable (i.e., alexithymia, depressive symptoms, and stress) was entered into a logistic regression as the independent variable. The dependent variable for each equation was PGA score, dichotomized to indicate remission or active disease over the 3-month follow-up and 12-month follow-up periods. In addition to the psychological variable, insurance type and pre-baseline PGA scores (3 months) were entered simultaneously as predictor variables. Given that no demographic or clinical variables were significantly associated with PGA status at 3 months post-baseline, insurance was chosen as a control demographic variable based on the literature. For example, other studies have included type of insurance as a covariate in analyses including psychological factors as independent variables and PGA as the dependent variable (Ryan et al., 2013).

Psychological variables were not found to be significant predictors of disease status over the course of 3 months post-baseline. Results revealed that none of the three overall models were significant ($p > .05$), indicating that the models were unable to distinguish between respondents whose disease status was in remission or active disease over the course of 3 months after baseline (refer to Tables 13-15 for 3 equations).

*Hypothesis 1B: We expected each psychological variable (i.e., alexithymia, depressive symptoms, and stress) to be a significant predictor of physician-rated disease severity as measured by the PGA over the course of 12 months following baseline.*

Each continuous psychological variable (i.e., alexithymia, depressive symptoms, and stress) was entered into a logistic regression as the independent variable with the PGA over 12 months post-baseline as the dependent variable. Ethnicity (i.e., Hispanic or Non-Hispanic) and pre-baseline PGA scores (i.e., PGA scores 12 months prior to baseline) were entered simultaneously as predictor variables. Ethnicity was chosen as a predictor variable due to its significant correlation with PGA when considering disease status over the course of 12 months. In a chi-square test, PGA and ethnicity were significantly correlated when using the Fisher's Exact Test, which demonstrated a significant relationship, $p = .03$; effect size was in the medium range, *phi* = -.34. The Fisher's Exact Test was used to correct for cells that were not sufficiently populated in the chi-square test (refer to Table 11).

Results revealed that the overall models including alexithymia and depressive symptoms were not significant. Only the full model containing the psychological variable stress as a predictor variable was statistically significant, $\chi^2$ (3, $n = 36$) = 8.23, $p < .05$, indicating that the model was able to distinguish between participants whose disease status was in remission and those whose disease was active. This specific model as a whole explained between 20.4% (Cox and Snell R Square) and 28.4% (Nagelkerke R Squared) of the variance in disease status and correctly classified 66.7% of cases. None of the independent variables, however, made a unique

contribution to the model at the significance level established for this study ($p < .05$). Despite individual non-significance, the stress variable revealed an odds ratio of 4.43. This indicates that respondents who reported higher stress levels were over four times more likely to experience active disease status at some point over the course of 12 months post-baseline. It is important to highlight, however, that for the purposes of conducting logistic regressions, our study was statistically underpowered, particularly when considering 12-month data (Long, 1997; refer to Tables 16-18).

Prior to conducting the analyses for hypotheses 1C and 1D below, an a priori analysis was conducted to determine the sample size necessary to obtain a medium effect size ($f^2 = .15$) and a power of .80 with $\alpha = .05$ when conducting multiple linear regressions. Output parameters indicated that a total sample size of 77 participants would be necessary, suggesting that the analyses to be conducted for hypothesis 1C would be sufficiently powered while the analyses for hypothesis 1D would be underpowered. A total of 6 linear regression equations were conducted for hypotheses 1C and 1D.

*Hypothesis 1C: We expected each psychological variable (i.e., alexithymia, depressive symptoms, and stress) to be a significant predictor of physician-rated disease severity as measured by the PUCAI/PCDAI z-scores over the course of 3 months following baseline.*

Each continuous psychological variable (i.e., alexithymia, depressive symptoms, and stress) was entered into a separate linear regression as the independent variable with the z-scores

for PUCAI and PCDAI markers as the dependent variable for each equation. Age at baseline and 3-month pre-baseline PUCAI/PCDAI z-scores were entered simultaneously as predictor variables. Age at baseline was selected as a covariate as it was significantly correlated ($r = .37$) with PUCAI/PCDAI z-scores over the course of 3 months post-baseline. Pre-baseline PUCAI/PCDAI scores were entered in the equation to control for disease variance. Results revealed that none of the three overall models were significant ($p > .05$), indicating that our psychological variables were not predictive of disease status as measured by the PUCAI and PCDAI z-scores (refer to Table 19).

*Hypothesis 1D: We expected each psychological variable (i.e., alexithymia, depressive symptoms, and stress) to be a significant predictor of physician-rated disease severity as measured by the PUCAI/PCDAI z-scores over the course of 12 months following baseline.*

Each continuous psychological variable (i.e., alexithymia, depressive symptoms, and stress) was entered into a linear regression as the independent variable with the z-scores for PUCAI and PCDAI at 12 months as the dependent variables. Race and 12-month pre-baseline PUCAI/PCDAI z-scores were entered simultaneously as predictor variables. Race was selected as a covariate as it was significantly correlated ($r = .32$) with PUCAI/PCDAI z-scores over the course of 12 months post-baseline. Results revealed that all three overall models were significant ($p > .01$). However, only the control variable pre-baseline PUCAI/PCDAI was statistically significant in each equation: *beta* = .54, $p < .01$ in equation with alexithymia; *beta* = .52, $p < .01$

in equation with depressive symptoms; *beta* = .55, $p < .01$ in equation with stress (refer to Table 20). Once again, it is important to highlight that 12-month analyses conducted were statistically underpowered.

## Aim 2

*Aim 2: The present study will examine the relationship between each psychological variable (i.e., alexithymia, depressive symptoms, and stress) at baseline and health care utilization (i.e., GI clinic visits, emergency department use, and nights hospitalized) over time.*

Before conducting regression analyses, Pearson correlations and point-biserial correlations were conducted to evaluate the relationship between health care utilization variables and other variables of interest (see Tables 9 and 10). First, Pearson correlations were conducted to assess the relationship between baseline scores on psychological measures and the following longitudinal health care utilization variables: (1) number of GI clinic visits, (2) number of ED visits, and (3) number of nights hospitalized. While all of these correlations were non-significant, stress of major life events approximated a significant correlation with number of ED visits over the course of 12 months, $r(53) = .27$, $p = .054$. Importantly, an a priori power analysis showed that a total sample size of 84 participants would have been necessary to obtain power of .80 with $\alpha = .05$ when conducting correlations with a bivariate normal model for the 12-month data analyses. Therefore, the preliminary correlational analyses for the 12-month data in Aim 2 were underpowered.

Point-biserial correlation analyses were completed to assess the relationship between demographic variables and health care utilization variables of interest (see Table 9). An a priori power analysis showed that a total sample size of 82 participants would be necessary to expect results with power of .80, $\alpha = .05$, and a medium effect size (.30) when conducting point-biserial correlations. From the point-biserial correlations conducted for this aim, only one revealed a statistically significant association. Sex and the number of ED visits over the course of 3 months post-baseline was significant, with adolescent girls having greater number of ED visits over that period of time, $r(94) = -.21$, $p = .046$. Correlations between clinical variables and outcome variables revealed that age at baseline was significantly correlated with number of ED visits over the course of 3 months post-baseline, with older age associated with increased number of ED visits over the 3 month period.

*Hypothesis 2A: We expected each psychological variable (i.e., stress, depressive symptoms, alexithymia) to be a significant predictor of health care utilization at 3-month follow-up in adolescents with IBD.*

A total of 9 negative binomial regression (with log link) equations were conducted to assess the relationship between each of our 3 psychological variables and the 3 health care utilization outcome variables (i.e., number of GI visits, number of ED visits, and number of nights hospitalized) over the course of 3 months.

*GI visits*. Given that no demographic or clinical variables were significantly associated with the number of GI visits at 3 months post-baseline, insurance was chosen as a predictor variable based on the literature. Psychological variables were not found to be significant predictors of the number of GI visits over the course of 3 months post-baseline. Results revealed that none of the three overall models were statistically significant ($p > .05$). For alexithymia, $\chi^2$ (3, $n = 92$) = 1.63, $p = .65$; for depressive symptoms, $\chi^2$ (3, $n = 90$) = 1.71 $p = .64$; and for stress, $\chi^2$ (3, $n = 90$) = 1.23, $p = .75$ (refer to Tables 21-23).

*ED visits.* Each psychological variable (i.e., alexithymia, depressive symptoms, and stress) was entered into a negative binomial regression (with log link) equation as the independent variable with the number of ED visits between baseline and 3-month follow-up as the dependent variable. Sex, age at baseline, and pre-baseline number of ED visits (over the 3 months leading up to the baseline visit) were entered as predictor variables. Sex and age at baseline were chosen as covariates given their statistically significant correlation with our outcome variable. After running all three equations, only the overall models including alexithymia and stress as predictor variables were statistically significant. However, only the demographic variable sex emerged as predictive of the number of ED visits over the course of 3 months when entered in equations that included the psychological variables (1) alexithymia and (2) stress. In those two separate equations, sex was the only significant predictor of ED visits, $\chi^2$ (4, $n = 94$) = 10.28, $p < .05$ and $\chi^2$ (4, $n = 92$) = 10.87, $p < .05$, respectively. However, in the equation including depressive symptoms as a predictor variable for number of ED visits, the test

of the full model was no longer significant, with sex no longer making a significant contribution, $\chi^2$ (4, $n$ = 91) = 6.47, $p$ = .17 (see Table 24).

*Nights hospitalized*. Each psychological variable (i.e., alexithymia, depressive symptoms, and stress) was entered as the independent variable with the number of nights hospitalized between baseline and 3 months post-baseline as the dependent variable. Insurance type was also entered as a predictor variable, and number of nights hospitalized over the 3 months prior to baseline was entered as a control variable. In the case of alexithymia and depressive symptoms, results indicated that neither model was significant: $\chi^2$ (3, $n$ = 94) = 5.98, $p$ = .11, and $\chi^2$ (3, $n$ = 91) = 5.97, $p$ = .11, respectively. However, the equation examining the relationship between stress and number of nights hospitalized over a period of 3 months revealed that both the model as well as the individual variable stress were significant, indicating that stress was a significant predictor of nights hospitalized over the course of 3 months, $\chi^2$ (3, $n$ = 92) = 14.16, $p$ < .01. Table 25 includes additional details about each variable in this equation.

Exploratory analysis also revealed that having a reported history of mental health service use predicted the number of nights hospitalized over the course of 3 months post-baseline, $\chi^2$ (3, $n$ = 94) = 12.88, $p$ < .01. As with other equations in this aim, the number of nights hospitalized during the 3 months pre-baseline and type of insurance were included as covariates. In this particular equation, insurance type was also predictive of nights hospitalized. Table 26 includes additional information about this specific equation.

*Hypothesis 2B: We expected each psychological variable (i.e., alexithymia, depressive symptoms, stress) to be a significant predictor of health care utilization over the course of 12 months post-baseline in adolescents with IBD.*

A total of 9 negative binomial regression equations (with log link) were conducted to assess the relationship between our 3 psychological variables and the 3 health care utilization outcome variables of interest (i.e., number of GI visits, number of ED visits, and nights hospitalized) over the course of 12 months.

*GI visits*. Given that no demographic or clinical variables were significantly associated with the number of GI visits at 12 months post-baseline, insurance was chosen as a control demographic variable based on the literature. Psychological variables were not found to be significant predictors of the number of GI visits over the course of 12 months post-baseline. Results revealed that none of the three overall models were statistically significant ($p > .05$). For alexithymia, $\chi^2$ (3, $n = 53$) = 3.25, $p = .35$; for depressive symptoms, $\chi^2$ (3, $n = 53$) = 3.89 $p = .27$; and for stress, $\chi^2$ (3, $n = 53$) = 3.62, $p = .31$.

*ED Visits.* Each psychological variable (i.e., alexithymia, depressive symptoms, and stress) was entered as the independent variable with the number of ED visits between baseline and 12-month follow-up as the dependent variable. Insurance type and pre-baseline number of ED visits (12 months) were entered as predictor variables. Results revealed that none of the three overall models were statistically significant ($p > .05$). For alexithymia, $\chi^2$ (3, $n = 53$) = 5.45, $p =$

.14; for depressive symptoms, $\chi^2$ (3, $n$ = 53) = 6.33, $p$ = .10; for stress, $\chi^2$ (3, $n$ = 53) = 7.72, $p$ = .05.

Exploratory analyses revealed that history of mental health service use was predictive of number of ED visits over the course of 12 months post-baseline while controlling for pre-baseline number of ED visits and including insurance type, $\chi^2$ (3, $n$ = 53) = 10.68, $p$ > .05 (Table 27) or sex.

*Nights hospitalized.* Each psychological variable (i.e., alexithymia, depressive symptoms, and stress) was entered as the independent variable with the number of nights hospitalized between baseline and 12-months as the dependent variable. Insurance type and number of nights hospitalized during the 12 months prior to baseline were entered as predictor variables. Results revealed that all three overall models were statistically significant ($p$ > .001). However, with these specific covariates, none of the psychological variables were predictive of number of nights hospitalized; the variance was accounted for by pre-baseline number of nights hospitalized as well as insurance type. For the equation including alexithymia, $\chi^2$ (3, $n$ = 53) = 20.36, $p$ > .001; for depressive symptoms, $\chi^2$ (3, $n$ = 53) = 19.19 $p$ > .001; and for stress, $\chi^2$ (3, $n$ = 53) = 19.11, $p$ > .001.

In the literature, some studies have established a relationship between the demographic variable sex and hospitalizations; hence, additional analyses were conducted to examine the relationship between psychological variables and nights hospitalized using sex as covariate. All the equations were significant and sex was a predictive variable for each one: $\chi^2$ (3, $n$ = 53) =

17.04, $p > .001$ for alexithymia, $\chi^2$ (3, $n = 53$) = 13.17, $p > .01$ for depressive symptoms, and $\chi^2$ (3, $n = 53$) = 13.81 $p > .01$ for stress. Additionally, alexithymia was a predictive variable for nights hospitalized over the course of 12 months (see Table 30). Although depressive symptoms was not significantly related to nights hospitalized when controlling for sex and pre-baseline nights hospitalized only, when the primary caregiver's educational level was entered into the equation, depressive symptoms became predictive of number of nights hospitalized, $\chi^2$ (6, $n$ = 52) = 27.52, $p > .001$ (see Table 32); this was not the case with other psychological variables, however.

Exploratory analyses revealed that history of mental health service use was predictive of number of nights hospitalized over the course of 12 months post-baseline while controlling for pre-baseline number of ED visits and sex.

## Aim 3

The present study examined the relationship between each psychological variable at baseline (i.e., stress, depressive symptoms, and alexithymia) and time-to-ED visit and time-to-hospitalization following baseline.

*Hypothesis 3*: We expected each psychological variable (i.e., alexithymia, depressive symptoms, stress) to be a significant predictor of (1) time-to first ED visit post-baseline and (2) time-to first hospitalization post-baseline.

Cox regression equations (survival analysis procedures) were performed to examine the relationship between each one of our psychological variables and (1) time-to-ED post-baseline as well as (2) time-to-hospitalization. In all analyses, we controlled for age at diagnosis, time since diagnosis, sex, and insurance type. These covariates were chosen based on statistically significant correlational findings between our psychological variables and clinical and demographic variables of interest (see Table 28) and also based on the literature (Stewart, Rao, Emslie, Klein, & White, 2005).

*Time-to-Hospitalization.* Nineteen participants (20.43% of the total sample) had at least 1 hospitalization between entry in the study and the end of the study period. The first Cox regression equation examined the relationship between alexithymia and time-to-hospitalization. Results showed that the overall equation was not significant, $\chi^2$ (5, $n$ = 93) = 7.63, $p$ = .18. A similar equation with the alexithymia variable dichotomized into alexithymic vs. non-alexithymic results also yielded non-significance (see Figure 1). When examining the relationship between depressive symptoms and hospitalization, the overall equation was significant, $\chi^2$ (5, $n$ = 90) = 11.93, $p$ >.05. Additionally, both depressive symptoms and age at diagnosis were predictive of time to hospitalization (p >.01 and p >.05, respectively; see Table 29). It is important to note that for this analysis, the un-truncated CDI-2 scores were used; truncated CDI-2 scores were not predictive of time-to-hospitalization, suggesting that extremely high scores were particularly influential in the equation. When a similar equation using the

dichotomized depressive symptoms variable (i.e., depressed vs. non-depressed) was performed, results were non-significant. This finding suggests that "subthreshold" levels of depression may be predictive of time to hospitalization, and this variable is better conceptualized in a continuum instead of a dichotomous category (see Figure 2). The equation examining the relationship between stress and time to hospitalization was non-significant, $\chi^2$ (5, $n$ = 91) = 7.28, $p$ = .20

*Time-to-ED*. Twenty-two participants (23.66% of the total sample) had at least 1 ED visit between entry in the study and the end of the study period. The first Cox regression equation examined the relationship between alexithymia and time to first ED visit post-baseline. Results showed that the overall equation was not significant, $\chi^2$ (5, $n$ = 93) = 6.04, $p$ = .30. Similarly, the equation examining the relationship between depressive symptoms and time to first ED visit was non-significant, $\chi^2$ (5, $n$ = 90) = 6.95, $p$ = .22. Equations including the depressive symptoms variable (1) truncated and (2) dichotomized (i.e., depressed vs. non-depressed) did not yield different findings (see Figure 3). The equation examining the relationship between stress and time to first ED visit was also non-significant, $\chi^2$ (5, $n$ = 91) = 7.47, $p$ = .19.

Exploratory analysis revealed a relationship between history of mental health service use and time to first ED visit post-baseline, $\chi^2$ (5, $n$ = 93) = 16.18, $p$ > .01 (see Figure 4). However, a similar relationship was not found between history of mental health service use and time to hospitalization, $\chi^2$ (5, $n$ = 93) = 8.65, $p$ = .12.

# CHAPTER FIVE

# CONCLUSIONS AND RECOMMENDATIONS

## *Overview*

Inflammatory bowel disease (IBD) is a condition characterized by chronic inflammation of the gastrointestinal tract, and associated symptoms have the potential to be unpredictable, burdensome, or embarrassing for adolescents (e.g., abdominal pain, diarrhea, fatigue, significant weight loss). In addition to the emotional tax of the disease on patients, medical treatment of the disease is also financially taxing for the health care system. In the United States, the direct costs of pediatric and adult IBD on health care have been estimated at $3.1 billion for CD and $2.1 billion for UC (Kappelman et al., 2008).

Although a clear association has not been found between psychological difficulties and the development of IBD, a possible relationship between psychological factors and progression of the disease remains a source of ongoing investigation. Further exploration of this relationship is needed in the pediatric literature, as few well-controlled, prospective studies have been conducted to date in this area (Micocka-Walus et al., 2007).

The present study sought to advance the understanding of the relationship between psychological factors and health outcomes in two principal ways: (1) by examining our health outcome variables prospectively, over two time periods, and (2) by conceptualizing health outcomes in terms of both physician-rated disease severity and health care utilization. Our data

supported a relationship between psychological factors and health care utilization, with important demographic and clinical correlates also associated with health care utilization. Results were also indicative of a relationship between physician-rated disease severity outcomes and specific demographic variables (i.e., race and ethnicity). Taken together, these findings support the notion that a complex interplay of biopsychosocial factors influence both physical health and health care utilization.

### *Our Sample*

The majority (72.9%) of our sample was in remission at baseline. In a recent study examining 112 children and adolescents (ages 7-18) with IBD, researchers found that the remission rate, as determined by PGA, was 58.1% (Ryan et al., 2013). General parameters of health care utilization in our study also paralleled findings by Ryan and colleagues (2013), which estimated the number of annual ED visits and GI clinic visits to be .52 and 3.30, respectively (in our study: .49 and 3.76, respectively). In a Canadian study by Longobardi and Bernstein (2006) examining health care utilization among adults and children with IBD (*N* =5485*),* it was determined that 15% of the sample had at least1 inpatient stay over the course of 1 year. In our sample, the percentage was higher, with at least 24.53% of participants having haat least one inpatient stay in the same time frame (13 out of 53 participants). The same study also determined the average number of nights hospitalized in the year to be 15.58; in our study, the average for

those 13 participants who had been hospitalized at some point was lower at 10.08 (SD = 8.06) (Longobardi & Bernstein, 2006).

With regard to psychological factors, 19.1% of our total sample scored above the cut-off score for alexithymia traits. This percentage represents a rate higher than what has previously been reported in the general adolescent population (i.e., 7.3%; Honkalampi et al., 2009). Although no prior studies have examined the rate of alexithymia in adolescents with IBD, a study with an adult IBD population determined the rate to be 35.7% (Porcelli, Zaka, Leoci, Centone, & Taylor, 1995). On the other hand, the rate of clinical depression in our sample (i.e., 9.6%) was lower than expected, as rates of depressive symptoms in pediatric IBD populations have been reported to be as high as 25 percent (Szigethy et al., 2004), and in other reports have ranged widely, from 10% to 73% (Burke et al., 1989; Szajnberg, Krall, Davis, Treem, & Hyams, 1993). Overall, the rate of stress in our sample was low. Some studies have reported that children with IBD do not endorse more perceived stress than healthy children, which may be related to coping styles (Gitlin et al., 1991).

### *Psychological Variables and Disease Status*

Our study explored the relationship between psychological variables and physician-rated disease severity using two separate measures, PGA and PUCAI/PCDAI scores, one categorical and the other one continuous. The inclusion of both measures allowed for the opportunity to explore disease severity in its broader definition (e.g., remission or active disease) as well as the

nuances in variability that can only be detected through a continuous measurement (i.e., PUCAI/PCDAI scores).

Contrary to our hypotheses, psychological variables did not predict physician-rated disease severity over time with either parameter of disease status. Similar to our findings, a recent study by Ryan and colleagues (2013) examining the impact of HRQOL on PGA in a pediatric IBD population also determined that depressive symptoms were not predictive of PGA over the course of 12 months. However, other studies have contradicted these findings. For example, Mardini and colleagues (2004) examined Crohn's disease in adult patients over the course of 2 years and found a strong positive association between depression, anxiety, and disease activity (CDAI). Mittermaier and colleagues (2004) found that, among pediatric IBD patients with inactive disease at baseline, depression levels significantly correlated with the total number of relapses over the course of 18 months. It is difficult to draw direct comparisons between our findings and the larger pediatric IBD literature, however, as studies have varied widely in design. Generally speaking, studies that have been able to detect relationships between psychological variables and disease outcomes over time have separated CD and UC samples; have been able to select participants who are in remission at baseline; have clearly differentiated between disease status groups, or have examined IBD samples with more variability in disease severity, which allows for more detailed comparisons between subgroups. Although our results were likely impacted by a combination of several of these factors mentioned, the fact that our

sample was mostly in remission (72.9%) at the time of baseline likely played a significant role in our findings.

Although our psychological variables were not predictive of physician-rated disease severity scores, some significant associations emerged between our health outcome variables and demographic variables in correlational analyses. Over the course of 12 months post-baseline, PGA significantly differed based on ethnicity. More specifically, all Hispanic patients experienced active disease at some point during the course of the 12 months after baseline while their non-Hispanic counterparts showed an even distribution between those who experienced active disease and those who were consistently in remission during that same time period. However, no predictive associations emerged in subsequent analyses. Recent studies point to differences in IBD subtypes and serologic markers between Hispanic and non-Hispanic populations, which perhaps may account for some of the ethnic discrepancies observed in our own study. For example, in a study by Hattar and colleagues (2012) examining disease characteristics in a pediatric Hispanic population in Texas, researchers found that Hispanics had the highest proportion of patients with UC and IBD-unclassified, and none of the Hispanics in the study had a first-degree relative with IBD. Other studies examining Hispanic IBD populations have noted significant differences in serologic markers among ethnic lines, with all Mexican American patients in one study having positive p-ANCA compared to only 40% of whites (Basu, Lopez, Kulkarni, & Sellin, 2005).

In addition to the relationship between PGA and ethnicity over the course of 12 months post-baseline, our study also revealed a significant association between PUCAI/PCDAI z-scores and race over the course of 12 months. Non-White race was associated with worse PUCAI/PCDAI z-scores, although these differences did not have predictive power over time. However, other studies have not found similar associations between race and disease activity in their samples (Ghazi et al., 2014). The fact that both measures of physician-rated disease severity in our study (i.e., PGA and PUCAI/PCDAI) revealed a correlation between disease status and race/ethnicity suggests an underlying relationship that perhaps would have become more apparent in our analyses had our equations been sufficiently powered. Unfortunately, our only findings in this area are correlational, and directionality or possible mechanisms underlying the relationship cannot be discerned and would be difficult to pursue further given the limited sample size.

Our study also suggested a relationship between younger age at baseline and worse disease status as determined by PUCAI/PCDAI scores over the course of 3 months after baseline. This finding corroborates the general pediatric IBD literature, which has found a relationship between younger age and worse disease status (Kappelman et al., 2011). Our findings also suggest that even in the context of a tight age group range (i.e., all adolescents), age can be an important factor in disease status. In turn, these associations impact rates of health care utilization in our society. For instance, the study by Kappelman and colleagues (2011) examining health care use among IBD patients and non-IBD matched controls revealed that utilization by

IBD patients varied not only by age (with younger patients using more services), but also by sex (females using more services) and insurance type, with a larger number of patients with non-commercial insurance using ED services.

## *Psychological Variables and Health Care Utilization in IBD*

The Behavioral Model of Health Services Use, a conceptual model, was developed and adjusted over the years by R. M. Andersen. The model was designed with the goal of explaining the complex dynamic relationship between contextual characteristics, individual characteristics, and health behavior factors that lead to health care utilization. Among the predisposing contextual and individual characteristics that influence health care use are demographic, social, and belief factors; health behaviors (e.g., personal health practices) have also been shown to impact health care service utilization. It is important to keep in mind that these "individual" factors do not operate in a vacuum; in fact, they may be cumulative, interdependent, and bidirectional, as we were able to glean from the relationship between disease status and demographic variables.

### *Health care utilization over the course of 3 months*

Over the course of 3 months after baseline, only our psychological variable stress was associated with health care utilization, showing that it was predictive of the number of nights

hospitalized, with increasing levels of stress predicting more nights in the hospital. Biopsychosocial variables may be associated with this finding. From the literature, we know that stress can have a direct physiological impact on health. Stress is associated with elevated lipids, elevated blood pressure, increased hormonal activity, and decreased immunity. In children with IBD who are already hospitalized, any of these effects may lead to lengthier hospitalizations. Models of stress and disease (Taylor, 2008) also suggest that stress impacts health habits (e.g., decreased nutrition, decreased sleep) and health-related behaviors (e.g., decreased compliance with treatment, increased delay in seeking care), which in turn complicates hospitalizations and delays resolution of underlying IBD problems during those hospitalizations.

In our study, we did not find a relationship between stress and number of nights hospitalized over the course of 12 months. This finding is particularly surprising in the context of our stress measure used, the Life Events Checklist, which assesses stress of major life events (e.g., parents' divorce, death in family); it is not likely that these stressors would subside or become less impactful in a matter of a few months, yet no association emerged between this type of stress and nights hospitalized over the course of 12 months. Two possible and feasible reasons for the lack of associations between our stress variable and nights hospitalized include (1) the overall low levels of stress reported and/or (2) issues of statistical power.

For instance, lack of association raises the question as to the mechanisms through which stress has an effect on health status. Our findings suggest that the acute effects of stress may be attenuated over time, as the physiological response is followed by habituation, as is the case with

low-level stressors (Taylor, 2008). It would be interesting to see whether the study of stress over a period of time longer than 1 year may yield different health outcome findings once again; it would perhaps suggest a process of initial arousal, followed by habituation, and perhaps subsequent relapse similar to what happens in chronic stress and its relationship with cardiovascular disorders later in life.

In addition to the impact on the physiological system, stress has also been found to impact the appraisal of environmental demands and allocation of personal resources to address the environmental demands, as Monroe (2008) highlights in his review of the stress literature. Negative appraisal of a given situation may lead to increased perceived stress, negative emotions, and ultimately physiological arousal and possible health behaviors that increase the negative repercussions of an already fragile system, causing a prolonged hospitalization.

In this study, a caregiver's report of mental health service use by child was also predictive of number of nights hospitalized over the course of 3 months post-baseline. Although a non-specific, dichotomous (yes/no) marker of past mental health use, significant associations between this variable and health outcomes would suggest a more insidious effect of prior mental health difficulties on prospective medical health and functioning.

*Health care utilization over the course of 12 months*

Over the course of 12 months, both alexithymia and depressive symptoms emerged as predictive of nights hospitalized, possibly suggesting a different mechanism by which these psychological factors may impact longer-term health care utilization.

According to a well-known researcher in the study of alexithymia, "among the various emotion-related constructs that have been associated with health and disease, alexithymia has the longest history" (Taylor, 2004). Several pathways have been hypothesized in the relationship between alexithymia and disease: (1) alexithymia leading to organic disease through physiological means; (2) alexithymia leading to illness behavior; (3) physical illness leading to alexithymia; and/or (4) alexithymia and physical illness surfacing from sociocultural or organic factors (Lumley, Stettner, & Wehmer, 1996). In the literature, alexithymia has been linked to tonic sympathetic hyperarousal, somatosensory amplification, and unhealthy behaviors (e.g., substance abuse, eating disorders). One interesting study found that individuals with alexithymia demonstrated increased tension before a stressor, while the non-alexithymic group demonstrated increased tension after the stressor (Papciak, Feuerstein, & Spiegel, 1985). In the context of our study, the increased affective dysregulation caused by alexithymia, along with the physiological dysregulation that it provokes or intensifies, and the related unhealthy behaviors, may provide a perfect storm for patients who are already medically vulnerable. In other words, the environmental and physical disruptions that follow an inpatient hospitalization may be exacerbated or prolonged by further emotional and physical decompensation from a patient who

will likely not have the necessary coping skills to address the stressors (e.g., due to emotional dysregulation and poor appraisal of stressors).

Similarly to alexithymia, increasing depressive symptoms were also associated with an increased number of nights hospitalized. However, it is important to note that depression did not show significance when entered in equations with both sex and insurance type as covariates; it only emerged as a significant variable when entered in the equation with the following variables: (1) sex and (2) caregiver's highest grade completed in school. Despite the distinction that developed between insurance type and caregiver's highest grade completed in school when entered as covariates in this particular equation, these two variables were nonetheless significantly correlated in our study. This discrepancy in relation to depressive symptoms raises the question of how the primary caregiver's education (in our study, usually the mother) may be impacting functioning in children with IBD. We may hypothesize that the impact may be related to socioeconomic factors and/or other parental factors that may be related or directly impacted by education level (e.g., coping, stress) We know from the literature that maternal psychological factors (i.e., depression) impacts health care utilization among youth with diabetes (Clayton et al., 2013), and similar mechanisms and interactions may be underlying the relationships we are observing here, although we are unable to test these hypotheses further given the data we have available.

To our knowledge, to date, no studies have looked at the relationship between depression in children and adolescents with IBD and hospitalizations. However, based on other literature

examining the relationship between psychological variables and health care utilization, we may be able to hypothesize mechanisms by which this relationship between increased depressive symptoms and increased health care use has emerged. One way is that depressive symptoms impact health-promoting behaviors, including adherence to medical regimens. Poor adherence to medical treatment has been observed across several medical diagnoses. For instance, in a meta-analysis conducted by DiMatteo and colleagues (2000) several years ago, findings revealed that depressed patients had three times greater chances of being noncompliant with recommendations made by their medical teams. Depression in cancer populations has also been associated with decreased adherence to medical treatments (Pirl & Roth, 1999). In the adult IBD literature more specifically, a significant association exists between depression and lower remission rates and decreased time to retreatment with infliximab treatment in adult populations (Persoons et al., 2005). In turn, these behaviors may contribute to worsened medical condition and increased number of nights hospitalized.

In addition to the impact that health behaviors may have on physical disability, we also know that depression is also related to functionality and perception of functionality. For example, depression and anxiety have also been associated with greater rates of reported physical symptoms without clear organic etiology (Katon, Sullivan, & Walker, 2001). In the adult IBD literature specifically, a pilot study looking at 40 IBD patients' current psychiatric disorders revealed that psychiatric difficulties (e.g., depression) were associated with increased functional disability, and treatment for depression decreased functional disability (Walker, Gelfand,

Gelfand, Creed, & Katon, 1996). Therefore, both perceptions and certain health behaviors may contribute to the relationship we have noted in our study between depression and increased number of nights hospitalized.

Research has also noted a relationship between ethnicity and health care use, with individuals of Hispanic origin delaying care until they require critical care (Galarraga, 2010). In our study, we did not find this relationship. However, insurance type was predictive of nights hospitalized over the course of 12 months.

### *Time To Health Care Utilization*

In addition to looking at health care utilization over time, our study also sought to examine the relationship between our three psychological variables of interest and time-to-medical care. With this particular aim, we expected that psychological variables (i.e., stress, depressive symptoms, and alexithymia) would significantly predict (1) time to first hospitalization post-baseline and (2) time to first ED visit post-baseline.

In our study, depressive symptoms emerged as predictive of shorter time to hospitalization. Importantly, this association was only present when we entered the un-truncated depressive symptom scores. This finding suggests that extreme values (highly elevated depression) added significant predictive value to our model, over and above what elevated scores had contributed before. This finding follows in line with research conducted by Stewart and colleagues (2005), which found that depressive symptoms predicted hospitalizations for

adolescents with type 1 diabetes mellitus. Depressive symptoms scores were also entered as dichotomous variables (i.e., depressed and non-depressed) into regression equations, which yielded no significant associations. For this reason, our findings also highlight the importance of "subthreshold" manifestations of depression, which may still contribute to worse health outcomes in this population (Lewinsohn, Solomon, Seeley, & Zeiss, 2000). In sum, our findings suggest that both extreme elevations in depressive symptoms as well as "sub-threshold" manifestations may influence time-to-hospitalization in this population, confirming previous findings that suggest that depressive symptoms are best conceptualized on a continuum (Lewinsohn et al.,2000).

In addition to the predictive value of depressive symptoms, older age at the time of diagnosis was significantly associated with shorter time-to-hospitalization. Our findings are contrary to studies of childhood diabetes mellitus, which have found a relationship between younger age at onset of diabetes mellitus and an increased risk of early re-hospitalization (Charron-Prochownik, Kovacs, Obrosky, & Stiffler, 1994). However, our findings make sense in the context of our adolescent population when considering the influence of this variable from a developmental perspective. For instance, older age at diagnosis in IBD may involve a process of greater adjustment to illness that may not be deemed as pronounced or disruptive in a younger population. Given that our findings do stand in contrast to studies such as Kappelmanand colleagues' (2011), which reported greater health care utilization among younger patients, it would be important to explore the possibility that perhaps the mechanisms underlying shorter-

time-to-hospitalization may differen from service use such as time hospitalized, number of ED visits, or outpatient clinic visits.

## Limitations

Several limitations should be considered in the context of the present study. The primary limitations are the sample size and limited power, clinical and medical characteristics of this sample, as well as limitations of our measurements. One of the most significant limitations is related to our sample size. A priori calculations indicated that a sample size of 89 participants or more would be adequate to conduct the analyses initially outlined, and recruitment targets were based on this goal. Changes following an overview of the data identified problems with the actual sample size available. For instance, the longitudinal aspect of this study created unforeseen limitations stemming from the reduced availability of follow-up data. Loss to follow-up was due to multiple reasons, including participants leaving this pediatric clinic to enroll in adult care (i.e., our sample only looked at adolescents) and participants moving to other locations or seeking care elsewhere.

Our sample size, from the onset, limited the possibilities that we had to look at our data in ways that would have more meaningful or preferable, based on the literature. For example, the literature suggests that analyzing disease groups by disease status (e.g., mild, moderate, remission) is effective in elucidating differences in this population that may otherwise by

obscured by combining them. Unfortunately, given the sample size and the characteristics of our specific sample, this was not a possibility. Furthermore, the literature suggests separating IBD samples into UC and CD, which have yielded significant disparities between the groups. However, in our study, no meaningful differences were observed between the groups even when we analyzed the data for discrepancies. However, it is unclear whether a larger sample size may have yielded different results.

Another critical limitation of our study was its characteristics with regard to the medical and psychological conditions. Our sample revealed very few differences in disease status as assessed with the physician-rated disease severity measure, PGA. In fact, most of our sample was in remission at baseline and overall variability was minimal. As a result, analyses had to be conducted by dividing the sample into remission and active disease. These characteristics suggest that our sample (1) was, overall, physically healthy with regard to their disease severity at the time of baseline, and that (2) lack of variability may have also contributed to the lack of significant differences or findings between the groups.

With regard to the psychological characteristics of our particular population, participants endorsed levels of depressive symptoms and stress that were comparable or lower than in normative samples. In sum, the overall healthy emotional state of our sample makes it more challenging to study the impact of psychological variables on health status over time.

The longitudinal nature of our study, in addition to presenting difficulties in terms of loss to follow-up, also may present challenges with regard to the time durations studied. That is, our

study is one of the few in the pediatric IBD literature that looks at the relationship between psychological variables and health status over time. As a result, the theoretical research is unclear about the lengths of time that are necessary to determine meaningful relationships between our variables of interest. Although our research was able to study two relatively distant time periods (i.e., 3 months and 12 months), it is unclear whether a longer period of time may have contributed to more statistically meaningful findings with regard to our hypotheses.

## Directions for Future Research

Our study offers insight into characteristics and certain dynamics involving adolescents with IBD that can help guide future research. For instance, expansion of this study may involve increasing the sample size. A greater number of participants would help to eliminate many of the limitations of this study surrounding lack of statistical power. With a larger sample, it would be possible to conduct the necessary statistical analyses with sufficient statistical power to detect meaningful differences between the groups. It would also allow for separation of groups based on clinically meaningful and theory-based grounds (i.e., by disease status), particularly given the longitudinal component of this study.

As mentioned above, dividing study participants into meaningful groups by clinical characteristics or other relevant parameters would be beneficial for a more thorough study of this population. This may include groups by type of illness (CD vs. UC), or time since diagnosis, or

disease status (i.e., remission, mild, moderate, or severe). Separating groups by psychiatric status (i.e., current elevated psychiatric symptoms vs. non-elevated symptoms) would also be beneficial in studying this population.

Extending the longitudinal component of this research study would also lead to greater insight into the factors that affect this population. For instance, as mentioned previously, it is unclear whether extending the time period of this study to longer than 3 months or 1 year may be more conducive to a better understanding of the relationship between psychological variables and health status, as some of the factors being tested here may not become evident over a shorter period of time.

Our study also indicated a significant relationship between our psychological variables and health outcomes. Future research would benefit from re-administration of these measures over time, as doing so may elucidate the relationship between these variables from a longitudinal perspective.

## Clinical Implications

Despite its limitations, the current study has led to a better understanding of the characteristics of and important factors related to adolescents with IBD.

With regard to sample characteristics, this study has demonstrated that despite the inherent difficulties of living with a chronic illness, overall, most adolescents in our particular

sample were well-adjusted emotionally and generally healthy with regard to their disease status. However, despite these indicators of health, patterns emerged that suggest that gradients of psychological distress are predictive of increased health care utilization over time. For instance, our research shows that increasing levels of stress can be predictive of short-term hospital stay. This knowledge can help guide screening protocols and the development of psychological interventions designed to ameliorate symptoms of stress, or help adolescents build coping skills to address ongoing stressors. Our findings in this area clearly speak to the acuity of this relationship, which further alerts clinicians to the importance of prompt interventions to address psychological distress.

Similarly, our study also highlights the impact of alexithymia and depressive symptoms on health care utilization over a much longer period of time, and once again, the importance of addressing symptoms that are "subthreshold," as these also impact long-term health. It informs clinicians about the importance of intervening before psychological symptoms even reach clinical levels. For example, cognitive-behavioral therapy has been proven to be effective in treating depressive symptoms in adolescents with IBD (Szigethy et al., 2007). Other innovative techniques, such as hypnosis, have also been shown to be effective in treatment of symptoms in children with IBD (Shaoul, Sukhotnik, & Mogilner, 2009). The tools learned in therapy may help decrease negative affect, increase positive affect, and improve coping.

Another noteworthy finding from our study was the significant relationship between a parent-reported history of mental health services for the child and several measures of health care

utilization over time (i.e., ED visits over a 12-month period and nights hospitalized over 3 months and 12 months of time). It suggests that even asking a simple yes/no question about mental health history may be very helpful for understanding a patient's past level of distress and its potential impact on health care utilization.

As our findings suggest, psychological factors, on a continuum, impact health outcomes over time. As a result, psychological measures that tend to focus on clinical levels of emotional instability or distress (i.e., CDI-2) may not always allow clinicians to detect subthreshold difficulties that are still critical in the wellbeing of the patient. Instead, measures that rely less on cut-offs but instead captures the nature of the symptoms, cognitions, and functionality, may be most appropriate.

TABLES

Table 1
*Descriptive Data: Independent t, $\chi^2$, Fisher's tests by IBD subtype*

| | Total (n = 94) | CD (n = 58) | UC (n = 36) | | |
|---|---|---|---|---|---|
| Variable | *M* (SD) or *n* (%) | *M* (SD) or *n* (%) | *M* (SD) or *n* (%) | *t*, df | $\chi^2$, df |
| Age at baseline | 15.45 (1.45) | 15.43 (1.51) | 15.49 (1.36) | -.19, 92 | |
| Sex (%) | | | | | .03, 1 |
| Female | 46 (48.9) | 28 (48.3) | 18 (50.0) | | |
| Male | 48 (51.1) | 30 (51.7) | 18 (50.0) | | |
| Race (%) | | | | | .69, 2 |
| African American | 18 (19.1) | 11 (19.0) | 7 (19.4) | | |
| Caucasian | 66 (70.2) | 42 (72.4) | 24 (66.7) | | |
| Other | 10 (10.6) | 5 (8.6) | 5 (13.9) | | |
| Ethnicity | | | | | .53, 1 |
| Hispanic /Latino | 15 (16.0) | 8 (13.8) | 7 (19.4) | | |
| Not Hispanic/Latino | 79 (84.0) | 50 (86.2) | 29 (80.6) | | |

Note. None of the results reported in this table were significant.

Table 2

*12-Month Sample Descriptive Data: Independent t and $\chi^2$ tests by IBD subtype*

| | Total (n = 53) | CD (n = 34) | UC (n = 19) | | |
|---|---|---|---|---|---|
| Variable | *M* (SD) or *n* (%) | *M* (SD) or *n* (%) | *M* (SD) or *n* (%) | t, df | $\chi^2$, df |
| Age at baseline | 15.44 (1.25) | 15.35 (1.37) | 15.59 (.99) | -.65, 51 | |
| Sex (%) | | | | | .27, 1 |
| Female | 22 (41.5) | 15 (44.1) | 7 (36.8) | | |
| Male | 31 (58.5) | 19 (55.9) | 12 (63.2) | | |
| Race (%) | | | | | .26[a] |
| African American | 9 (17.0) | 4 (11.8) | 5 (26.3) | | |
| Caucasian | 40 (75.5) | 27 (79.4) | 13 (68.4) | | |
| Other | 4 (7.5) | *3 (8.8)* | *1 (5.3)* | | |
| Ethnicity | | | | | 1.0[b] |
| Hispanic /Latino | 9 (17.0) | 6 (17.6) | 3 (15.8) | | |
| Not Hispanic/Latino | 44 (83.0) | 28 (82.4) | 16 (84.2) | | |

Note. None of the results reported in this table were significant.

[a] Three cells had an expected count of less than 5, yet a Fisher's exact test could not be used because the cells are 3 X 2. Therefore, a chi-square test was conducted using on the race categories of Caucasian and African American (leaving out *n* =4 for Other in the comparison). With this calculation, 1 cell had an expected count less than 5 and a Fisher's exact test was used with a 2-sided significance of .26 (reflected in the table).

[b] Fisher's exact test used because cell(s) had expected count less than 5.

Table 3
*Descriptive Medical Data with Summary Statistics by IBD Subtype*

| | Total (n = 94) | CD (n = 58) | UC (n = 36) | | |
|---|---|---|---|---|---|
| Variable | *M* (SD) or *n* (%) | *M* (SD) or *n* (%) | *M* (SD) or *n* (%) | t, df | $\chi^2$, df |
| Illness duration (months) | 29.73 (26.44) | 32.66 (26.83) | 25.03 (25.47) | 1.37, 92 | |
| Physician's Global Assessment (PGA) Remission at Baseline (%) [b] | 62 (72.94) | 38 (73.10) | 24 (66.67) | | .97, 1 |
| Outpatient Clinic Visits - 3 months post-baseline | 1.50 (.85) | 1.60 (.92) | 1.33 (.72) | .14, 92 | |
| ED visits - 3 months post-baseline | .18 (.05) | .21 (.52) | .14 (.42) | .51, 92 | |

*Note*. None of the results reported in this table were significant.
[a] Postbaseline outpatient clinic visits *include* the baseline visit.
[b] N = 85 because 9 PGA values are missing at baseline.

Table 4
*12-Month Data: Descriptive Medical Data with Summary Statistics by IBD Subtype*

| | Total (n = 53) | CD (n = 34) | UC (n = 19) | | |
|---|---|---|---|---|---|
| Variable | *M* (SD) or *n* (%) | *M* (SD) or *n* (%) | *M* (SD) or *n* (%) | t, df | $\chi^2$, df |
| Illness duration (months) | 32.90 (27.19) | 37.83 (27.86) | 24.07 (24.18) | 1.80, 51 | |
| PGA Remission at Baseline (%) [a] | 34 (75.56) | 21 (75.0) | 13 (76.5) | | 1.00 [c] |
| Outpatient Clinic Visits in 12 months post-baseline | 3.76 (2.91) [b] | 3.94 (3.50) | 3.42 (1.39) | .62, 51 | |
| ED visits in 12 months post-baseline | .49 (.91) | .50 (.96) | .47 (.84) | .92, 51 | |

*Note*. None of the results reported in this table were significant.
[a] N = 45 due to 8 participants missing PGA values at baseline.
[b] Postbaseline outpatient clinic visits *include* the baseline visit.
[c] Fisher's exact Test used because 1 cell had less than the expected count of 5.

Table 5

*Normative and Sample Information for Psychological Variables of Interest*

| Measure | Cut-Off Score | Normative M (SD) | Sample M (SD) | Sample Range | Above cut-off n (%) |
|---|---|---|---|---|---|
| Alexithymia (TAS – 12) [a] | ≥ 37 = high alexithymia | 31.50 (8.64)[b] | 26.95 (10.22) | 12 - 55 | 18 (19.1) |
| Stress of Major Life Events (LEC) [c] | | | 6.24 (8.47) | 0 - 60 | |
| Depressive Symptoms (CDI-2; raw scores) [e] | ≥ 20 = elevated; females<br>≥ 16 = elevated; males | | 7.78 (7.17) | 0 - 45 | 9 (9.6) |

*Note.* In the above table, non-transformed and non-truncated means and standard deviations were reported for stress of major life events and depressive symptoms (respectively) in order to make comparisons with the normative population. [a] Heaven et al., 2010; [b] Parker et al., 2010; [c] Johnson & McCutcheon, 1980; [e] Kovacs, 2010.

Table 6

*Psychological Variables with Summary Statistics for Independent t tests by IBD Subtype*

| | CD | UC | | |
|---|---|---|---|---|
| Measure | *M* (*s*) | *M* (*s*) | *t, df* | Sig. |
| Alexithymia - 12 | 26.07 (9.70) | 28.36 (11.02) | -1.06, 92 | .29 |
| Stress of Major Life Events (LEC) [+] | 6.54 (9.41) | 5.78 (6.86) | .42, 90 | .69 |
| Depressive Symptoms (CDI-2; raw scores) * | 7.89 (6.47) | 7.61 (8.22) | .18, 89 | .86 |

Note. None of the reported results in this table were significant.
Total *n* = 94, CD *n* = 58, and UC *n* = 36.
[+] Total *n* = 92, CD *n* = 56, and UC *n* = 36.
* Total *n* = 91, CD *n* = 55, and UC *n* = 36.

Table 7
*12-Month Data: Psychological Variables with Summary Statistics for Independent t tests by IBD Subtype*

| Measure | CD M (SD) | UC M (SD) | *t, df* | Sig. |
|---|---|---|---|---|
| Alexithymia – 12 | 26.88 (9.77) | 28.21 (11.75) | -.44, 51 | .66 |
| Stress of Major Life Events (LEC) | 6.03 (6.55) | 5.74 (7.39) | .15, 51 | .88 |
| Depressive Symptoms (CDI-2; raw scores) | 8.71 (7.49) | 8.26 (10.42) | .18, 51 | .86 |

Note. None of the reported results in this table were significant.
Total $n = 53$, CD $n = 34$, and UC $n = 19$.

Table 8

*Correlations Between Demographic and Clinical Variables and Psychological Variables*

| Variables of Interest | Alexithymia | Depressive Symptoms | Stress |
|---|---|---|---|
| Sex | - .09 (94) | - .13 (91) | - .12 (92) |
| Race | .10 (94) | .10 (91) | .16 (92) |
| Ethnicity | - .01 (94) | - .02 (91) | - .15 (92) |
| Household Income | - .09 (92) | - .28 (90)** | - .38 (90)** |
| Insurance | .02 (94) | .08 (91) | .21 (92)* |
| Age at baseline | .05 (94) | .02 (91) | - .01 (92) |
| Time from Diagnosis | - .07 (94) | - .05 (91) | - .13 (92) |
| Age at diagnosis | .09 (94) | .05 (91) | .11 (92) |
| Hx of mental health services use (yes/no) | - .17(94) | - .27 (91)* | - .25 (92)* |
| Caregiver Highest Academic degree | - .003 (93) | - .05 (90) | - .11 (91) |

Table 9

*Correlations Between Demographic Variables and Health Outcome Measures*

| Variables | PUCAI/PCDAI Baseline Z scores | PUCAI/PCDAI 3 mos Z scores | PUCAI/PCDAI 12 mos Z scores | GI Visits 3 mos | GI Visits 12 mos | ED Visits 3 mos | ED Visits 12 mos | Nights Hospitalized 3 mos | Nights Hospitalized 12 mos |
|---|---|---|---|---|---|---|---|---|---|
| Sex | - .08 (70) | - .01 (43) | - .03 39) | - .05 (94) | - .05 (53) | -.21 (94)* | - .09 (53) | .07 (94) | .08 (53) |
| Race | .11 (70) | .08 (43) | .32 (39)* | .11 (94) | .003 (53) | - .003 (94) | .03 (53) | - .06 (94) | .04 (53) |
| Ethnicity | - .02 (70) | .24 (43) | .09 (39) | .12 (94) | .05 (53) | - .02 (94) | .19 (53) | - .16 (94) | .14 (53) |
| Age at baseline | .16 (70) | .37 (43)* | - .07 (39) | - .03 (94) | - .21(53) | .21 (94)* | .03 (53) | .03 (94) | .06 (53) |
| Household Income | - .17 (68) | .02 (41) | .09 (38) | .00 (92) | - .02 (52) | .001 (92) | .00 (52) | - .04 (92) | .21 (52) |
| Insurance | .04 (70) | - .20 (43) | .13 (39) | - .03 (93) | .02 (53) | .06 (94) | .01 (53) | .04 (94) | - .18 (53) |
| Parent level of education | .01 (69) | .05 (42) | .10 (38) | - .03 (94) | - .06 (52) | .01 (93) | .01 (52) | - .08 (93) | .11 (52) |
| Time from diagnosis | - .05 (70) | .11 (43) | .02 (39) | - .02 (94) | - .14 (53) | - .03 (94) | - .12 (52) | - .04 (94) | - .09 (53) |
| Age at diagnosis | .13 (70) | .11 (43) | - .06 39) | - .002 (94) | .02 (53) | .15 (94) | .12 (53) | .05 (94) | .11 (53) |

Table 10
*Correlations Between Psychological Variables and Health Outcome Measures*

| | Baseline PGA[a] (*n*) | PUCAI/PCDAI Baseline (*n*) | PUCAI/PCDAI 3mos (*n*) | PUCAI/PCDAI 12mos (*n*) | GI visits 3 mos (*n*) | GI visits 12 mos (*n*) | ED visits 3 mos (*n*) | ED visits 12 mos (*n*) | Total Nights Hospitalized 3mos (*n*) | Total Nights Hospitalized 12 mos (*n*) |
|---|---|---|---|---|---|---|---|---|---|---|
| Alexithymia | -.01 (85) | .05 (70) | .14 (43) | .07 (39) | -.16 (94) | -.05 (53) | .04 (94) | -.08 (53) | - .05 (94) | - .19 (53) |
| Depressive symptoms | .05 (82) | .19 (68) | -.11 (41) | - .04 (39) | .06 (91) | .17 (53) | -.004 (91) | .12 (53) | -.05 (91) | - .04 (53) |
| Stress of Major Life Events | .05 (83) | .19 (70) | .10 (42) | .03 (53) | -.07 (92) | .16 (53) | .11 (92) | .27 (53) | .10 (92) | .03 (53) |

*Note:* None of the reported results are significant.
[a] Point-biserial correlation used
* $p < .05$

Table 11

*Demographic Characteristics Associated with PGA Remission and Non-remission Status at Baseline, 3mos, and 12mos*

| *Baseline* | | | |
|---|---|---|---|
| **Characteristic** | Remitted (*n* = 62) | Non-remitted (*n* = 23) | $\chi^2$ |
| **Sex** | | | .08 |
| **Female** | 31 (70.5%) | 13 (29.5%) | |
| **Male** | 31 (75.6%) | 10 (24.4%) | |
| **Race** | | | 5.06[c] |
| **White** | 43 (72.9%) | 16 (27.1%) | |
| **African American** | 10 (58.8%) | 7 (41.2%) | |
| **Other** | 9 (100.0%) | 0 (0.0%) | |
| **Ethnicity** | | | .73 [a] |
| **Hispanic** | 8 (66.7%) | 4 (33.3%) | |
| **Non-Hispanic** | 54 (74.0%) | 19 (26.0%) | |

| *3 months* | | | |
|---|---|---|---|
| **Characteristic** | Remitted (*n* = 28) | Non-remitted (*n* = 26) | $\chi^2$ |
| **Sex** | | | 1.19 |
| **Female** | 16 (59.3%) | 11 (40.7%) | |
| **Male** | 12 (44.4%) | 15 (55.6%) | |
| **Race** | | | 2.70 |
| **White** | 17 (48.6%) | 18 (51.4%) | |
| **African American** | 6 (46.2%) | 7 (53.8%) | |
| **Other** | 5 (83.3%) | 1 (16.7%) | |
| **Ethnicity** | | | .01 [a] |
| **Hispanic** | 4 (50.0%) | 4 (50.0%) | |
| **Non-Hispanic** | 24 (52.2%) | 22 (47.8%) | |

| *12 months* | | | |
|---|---|---|---|
| **Characteristic** | Remitted (*n* = 18) | Non-remitted (*n* = 25) | $\chi^2$ |
| **Sex** | | | 0.15 |
| **Female** | 9 (45.0%) | 11 (55.0%) | |
| **Male** | 9 (39.1%) | 14 (60.9%) | |
| **Race** | | | 2.32 |
| **White** | 14 (45.2%) | 17 (54.8%) | |
| **African American** | 2 (22.2%) | 7 (77.8%) | |
| **Other** | 2 (66.7%) | 1 (33.3%) | |
| **Ethnicity** | | | 5.02*[ab] |
| **Hispanic** | 0 (0.0%) | 6 (100%) | |
| **Non-Hispanic** | 18 (48.6%) | 19 (51.4%) | |

[a] Fisher's exact test used.

[b] Effect size: *phi* = -.342; p = .03

[c] Fisher's exact test needed but option not available with this 2X3 table.

* $p < .05$

Table 12
*Clinical Characteristics Associated with PGA at 3mos & 12mos*

| | *3 months* | | |
|---|---|---|---|
| **Characteristic** | Remitted (*n* = 28) | Non-remitted (*n* = 26) | Test |
| **Time from diagnosis (mos)** | 30.12 (28.70) | 27.18 (24.69) | 0.40[a] |
| **Age at dx** | 12.72 (2.66) | 13.51(2.79) | -1.07[a] |
| **Endorsed Hx MH Svcs** | 4 (44.4%) | 5 (55.6%) | .24[c] |

| | *12 months* | | |
|---|---|---|---|
| **Characteristic** | Remitted (*n* = 18) | Non-remitted (*n* = 25) | Test |
| **Time from diagnosis (mos)** | 27.39 (20.6) | 30.13 (28.7) | -.35[a] |
| **Age at dx** | 13.12 (1.9) | 12.95 (2.6) | .24[a] |
| **Endorsed Hx MH Svcs** | 4 (40.0%) | 6 (60.0%) | .02[c] |

*Note:* No results in this table were significant

[a] t-test used (*t* value provided)
[b] $\chi^2$ test used ($\chi^2$ value provided)
[c] Fisher's exact test used.

Table 13
*Logistic Regression Analysis of PGA Status Over 3 Months Post-baseline as a Function of Alexithymia*

| | *B* | S.E. | Wald | df | *p* | Odds Ratio | 95% C.I. for Odds Ratio | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| Alexithymia | .04 | .04 | 1.12 | 1 | .29 | 1.04 | .97 | 1.12 |
| Insurance | .10 | .74 | .02 | 1 | .90 | 1.10 | .26 | 4.68 |
| PGA Pre-baseline | .98 | .69 | 2.00 | 1 | .16 | 2.66 | .69 | 10.32 |

*Note.* None of the reported results in this table were significant.

Table 14
*Logistic Regression Analysis of PGA Status Over 3 Months Post-baseline as a Function of Depressive Symptoms*

| | *B* | S.E. | Wald | df | *p* | Odds Ratio | 95% C.I. for Odds Ratio | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| Depressive Symptoms | .05 | .07 | .47 | 1 | .50 | 1.05 | .92 | 1.20 |
| Insurance | .03 | .73 | .001 | 1 | .97 | 1.03 | .25 | 4.26 |
| PGA Pre-baseline | .96 | .69 | 1.97 | 1 | .16 | 2.61 | .68 | 10.02 |

*Note.* None of the reported results in this table were significant.

Table 15
*Logistic Regression Analysis of PGA Status Over 3 Months Post-baseline as a Function of Stress*

| | *B* | S.E. | Wald | df | *p* | Odds Ratio | 95% C.I. for Odds Ratio | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| Stress | 1.08 | .78 | 1.92 | 1 | .17 | 2.96 | .64 | 13.71 |
| Insurance | .09 | .77 | .01 | 1 | .91 | 1.09 | .25 | 4.90 |
| PGA Pre-baseline | .80 | .71 | 1.28 | 1 | .26 | 2.22 | .56 | 8.85 |

*Note.* None of the reported results in this table were significant.

Table 16
*Logistic Regression Analysis of PGA Status Over 12 Months Post-baseline as a Function of Alexithymia*

| | *B* | S.E. | Wald | df | *p* | Odds Ratio | 95% C.I. for Odds Ratio | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| Alexithymia | - .01 | .03 | .04 | 1 | .84 | .99 | .93 | 1.06 |
| Ethnicity | -20.75 | 16317.40 | .00 | 1 | .99 | .00 | .00 | . |
| PGA Pre-baseline | .49 | .78 | .40 | 1 | .53 | 1.63 | .35 | 7.54 |

*Note.* None of the reported results in this table were significant.

Table 17
*Logistic Regression Analysis of PGA Status Over 12 Months Post-baseline as a Function of Depressive Symptoms*

| | *B* | S.E. | Wald | df | *p* | Odds Ratio | 95% C.I. for Odds Ratio | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| Depressive Symptoms | - .02 | .07 | .06 | 1 | .81 | .98 | .86 | 1.13 |
| Ethnicity | -20.77 | 16293.33 | .00 | 1 | .99 | .00 | .00 | . |
| PGA Pre-baseline | .49 | .78 | .41 | 1 | .52 | 1.64 | .36 | 7.49 |

*Note.* None of the reported results in this table were significant.

Table 18
*Logistic Regression Analysis of PGA Status Over 12 Months Post-baseline as a Function of Stress*

| | *B* | S.E. | Wald | df | *p* | Odds Ratio | 95% C.I. for Odds Ratio | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| Stress | 1.49 | 1.00 | 2.2 | 1 | .14 | 4.43 | .62 | 31.60 |
| Ethnicity | -20.57 | 16094.40 | .00 | 1 | .99 | .00 | .00 | . |
| PGA Pre-baseline | -.10 | .87 | .01 | 1 | .91 | .90 | .17 | 4.91 |

*Note.* None of the reported results in this table were significant.

Table 19

*Summary of 3 Separate Linear Regression Analyses for Predicting PUCAI/PCDAI While Controlling for Age at Baseline and 3-Month Pre-baseline PUCAI/PCDAI Values*

| | *PUCAI/PCDAI Scores* | | |
|---|---|---|---|
| | Adjusted $R^2$ | F (3, 43) | $\beta$ |
| Alexithymia | .10 | 2.21 | .09 |
| Depressive Symptoms | .11 | 2.25 | -.10 |
| Stress | .11 | 2.31 | .12 |

*Note.* None of the reported results in this table were significant.

Table 20

*Summary of 3 Separate Linear Regression Analyses for Predicting PUCAI/PCDAI While Controlling for Race and 12-month Pre-baseline PUCAI/PCDAI Values*

| | *PUCAI/PCDAI Scores* | | |
|---|---|---|---|
| | Adjusted $R^2$ | F (3, 39) | $\beta$ |
| Alexithymia | .24 | 4.61 | .02 |
| Depressive Symptoms | .26 | 4.98 | -.14 |
| Stress | .25 | 4.79 | -.09 |

Table 21
*Negative Binomial with Log Link Analysis: GI Visits Over 3 Months Post-baseline as a Function of Alexithymia*

| | | | Hypothesis Test | | |
|---|---|---|---|---|---|
| | *β* | S.E. | Wald Chi-Square | df | *p* |
| Alexithymia | - .01 | .01 | .35 | 1 | .32 |
| Insurance | .04 | .28 | .02 | 1 | .88 |
| GI Visits Pre-baseline | .17 | .15 | 1.27 | 1 | .26 |

*Note.* None of the reported results in this table were significant.

Table 22
*Negative Binomial with Log Link Analysis: GI Visits Over 3 Months Post-baseline as a Function of Depressive Symptoms*

| | | | Hypothesis Test | | |
|---|---|---|---|---|---|
| | *β* | S.E. | Wald Chi-Square | df | *p* |
| Depressive Symptoms | .01 | .03 | .17 | 1 | .68 |
| Insurance | .03 | .29 | .01 | 1 | .93 |
| GI Visits Pre-baseline | .19 | .16 | 1.46 | 1 | .23 |

*Note.* None of the reported results in this table were significant.

Table 23
*Negative Binomial with Log Link Analysis: GI Visits Over 3 Months Post-baseline as a Function of Stress*

| | | | Hypothesis Test | | |
|---|---|---|---|---|---|
| | *β* | S.E. | Wald Chi-Square | df | *p* |
| Stress | -.02 | .30 | .004 | 1 | .95 |
| Insurance | .06 | .30 | .04 | 1 | .85 |
| GI Visits Pre-baseline | .17 | .16 | 1.16 | 1 | .28 |

*Note.* None of the reported results in this table were significant.

Table 24
*Negative Binomial with Log Link Analysis: ED Visits Over 3 Months Post-baseline as a Function of Depressive Symptoms*

| | | | Hypothesis Test | | |
|---|---|---|---|---|---|
| | *β* | S.E. | Wald Chi-Square | df | *p* |
| Depressive Sxs | -.04 | .06 | .34 | 1 | .56 |
| Sex | 1.21 | .67 | 3.29 | 1 | .07 |
| Child Age at Baseline | .37 | .23 | 2.64 | 1 | .10 |
| ED Visits Pre-baseline | .37 | .89 | .17 | 1 | .68 |

*Note.* None of the reported results in this table were significant.

Table 25
*Negative Binomial with Log Link Analysis: Nights Hospitalized Over 3 Months Post-baseline as a Function of Stress*

| | | | Hypothesis Test | | |
|---|---|---|---|---|---|
| | *β* | S.E. | Wald Chi-Square | df | *p* |
| Stress | 1.29 | .47 | 7.52 | 1 | .01 |
| Nights Hospitalized Pre-baseline | .15 | .10 | 2.16 | 1 | .14 |
| Insurance | 1.00 | .51 | 3.80 | 1 | .05 |

Table 26
*Negative Binomial with Log Link Analysis: Nights Hospitalized Over 3 Months Post-baseline as a Function of History of Mental Health Service Use*

| | | | Hypothesis Test | | |
|---|---|---|---|---|---|
| | *β* | S.E. | Wald Chi-Square | df | *p* |
| History of MH Service Use | 1.36 | .44 | 9.52 | 1 | .002 |
| Nights Hospitalized Pre-baseline | .18 | .10 | 3.04 | 1 | .08 |
| Insurance | - .86 | .39 | 4.89 | 1 | .03 |

Table 27

*Negative Binomial with Log Link Analysis: ED visits Over 12 Months Post-baseline as a Function of History of Mental Health Service Use*

| | | | Hypothesis Test | | |
|---|---|---|---|---|---|
| | *B* | S.E. | Wald Chi-Square | df | *p* |
| History of MH Service Use | 1.21 | .53 | 5.18 | 1 | .02 |
| ED Visits Pre-baseline | .59 | .28 | 4.69 | 1 | .03 |
| Insurance | .34 | .56 | .36 | 1 | .55 |

Table 28

*Correlations Between (1) Time to ED Visit and (2) Time to Hospitalization and Other Variables of Interest*

| Variables | Time-to-Hospitalization | Time-to-ED-Visit |
|---|---|---|
| Alexithymia | .05 (94) | .05 (94) |
| Depressive Symptoms | - .02 (91) | - .03 (91) |
| Stress | - .11 (92) | - .10 (92) |
| Parent Educational Level | .04 (93) | - .01 (93) |
| Household Income | - .02 (92) | .04 (92) |
| Race | - .13 (94) | - .15 (94) |
| Sex | .06 (94) | .18 (94) |
| Age at Baseline | - .09 (94) | - .13 (94) |
| Ethnicity | - .08 (94) | - .05 (94) |
| History of MH Svcs Use | - .10 (94) | .05 (94) |
| Insurance | - .05 (94) | - .12 (94) |
| Age at Diagnosis | - .29 (94)** | - .23 (94)* |
| Time from Diagnosis to Baseline | .28 (94)** | .18 (94) |

*Table 29*
*Cox Regression of time to hospitalization as a function of depressive symptoms.*

| | *B* | S.E. | Wald | df | *P* | Odds Ratio | 95% C.I. for Odds Ratio | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| Depressive Symptoms | .076 | .03 | 6.98 | 1 | .008 | 1.079 | 1.02 | 1.14 |
| Sex | .39 | .50 | .60 | 1 | .44 | 1.48 | .55 | 3.95 |
| Insurance | .22 | .52 | .18 | 1 | .67 | 1.25 | .45 | 3.46 |
| Age at Diagnosis | .38 | .18 | 4.44 | 1 | .04 | 1.46 | 1.03 | 2.08 |
| Time Since Diagnosis | .01 | .02 | .64 | 1 | .43 | 1.01 | .98 | 1.05 |

Table 30
*Negative Binomial with Log Link Analysis: Nights Hospitalized Over 12 Months Post-baseline as a Function of Alexithymia While Controlling for Sex*

| | | | Hypothesis Test | | |
|---|---|---|---|---|---|
| | *β* | S.E. | Wald Chi-Square | df | *p* |
| Alexithymia | - .04 | .02 | 4.83 | 1 | .03 |
| Sex | - .82 | .37 | 4.84 | 1 | .03 |
| Nights Hospitalized Pre-baseline | .10 | .05 | 3.92 | 1 | .05 |

Table 31
*Correlations Between Psychological Variables*

| Variables of Interest | Alexithymia | Depressive Symptoms | Stress |
|---|---|---|---|
| Alexithymia | 1 (94) | .58 (91)** | .30 (92)** |
| Depressive Symptoms | .58 (91)** | 1 (91) | .57 (89**) |
| Stress | .30 (92)** | .57 (89)** | 1 (92) |

*Note:* **. Correlation significant at the 0.01 level

Table 32
*Negative Binomial with Log Link Analysis: Nights Hospitalized Over 12 Months Post-baseline as a Function of Depressive Symptoms While Controlling for Caregiver's Educational Level*

| | *β* | S.E. | Hypothesis Test | | |
|---|---|---|---|---|---|
| | | | Wald Chi-Square | df | *p* |
| Depressive Symptoms | .09 | .04 | 4.84 | 1 | .03 |
| Nights Hospitalized Pre-baseline | .27 | .07 | 14.60 | 1 | .00 |
| Sex | -1.70 | .49 | 10.89 | 1 | .001 |
| Highest Grade – Coded 1 | -.56 | .70 | .63 | 1 | .43 |
| Highest Grade - Coded 2 | -1.87 | .66 | 8.04 | 1 | .01 |
| Highest Grade - Coded 3 | .18 | .52 | .12 | 1 | .73 |
| Highest Grade – Coded 4 | .18 | .52 | .12 | 1 | .73 |

FIGURES

Figure 1: Cox Regression Equation: Alexithymia and Time-to-Hospitalization

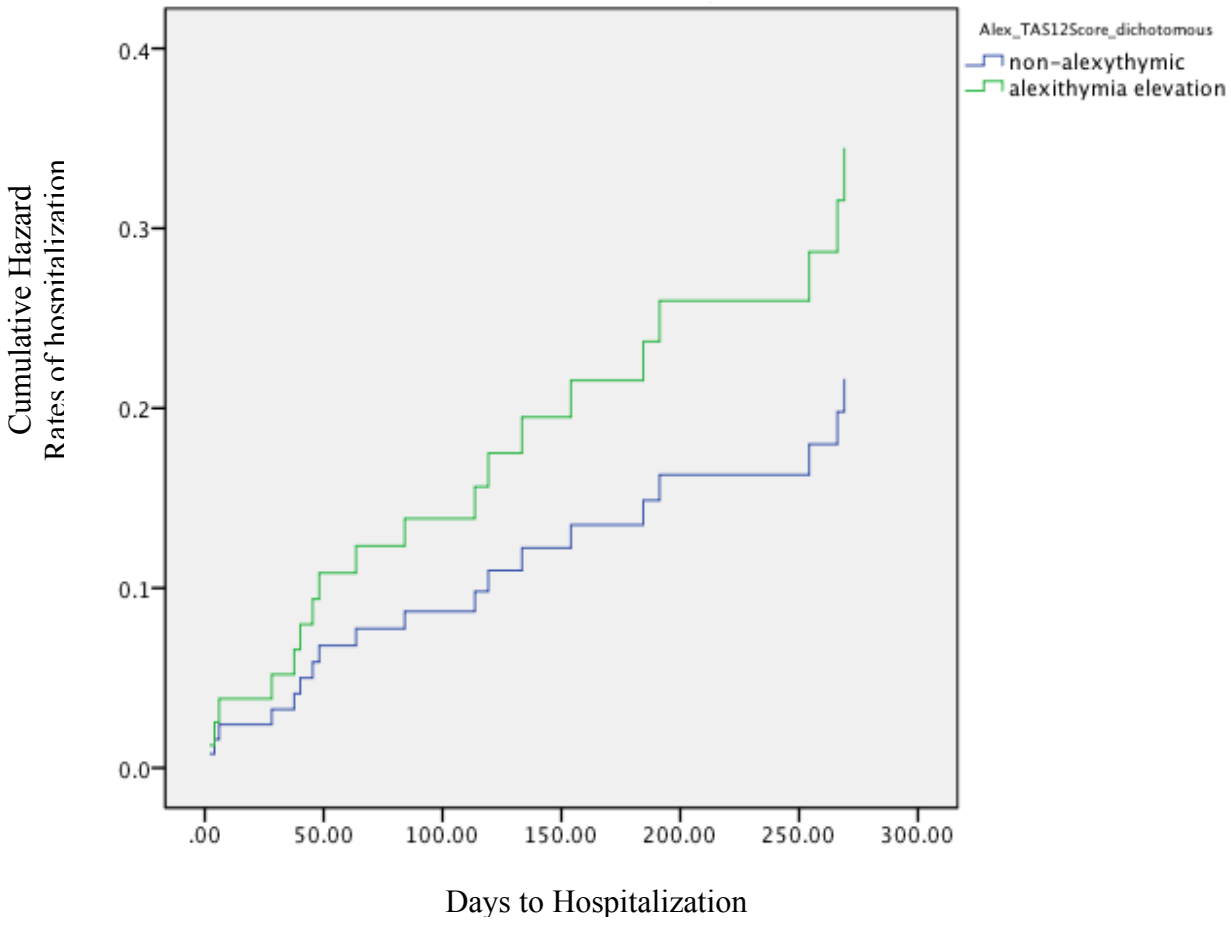


Figure 2: Cox Regression Equation: Depression and Time-to-Hospitalization

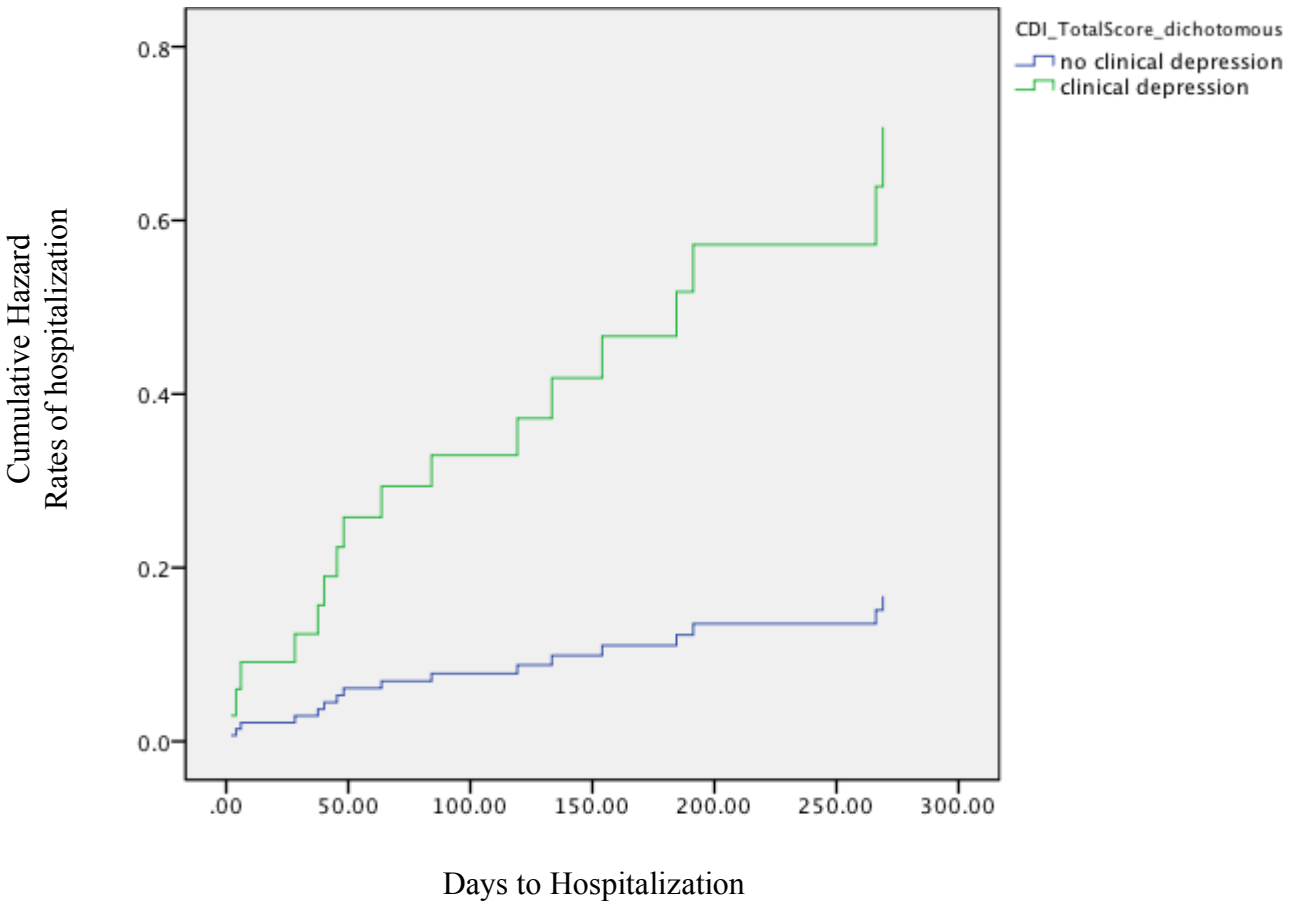


Figure 3: Cox Regression Equation: Depressive Symptoms and Time-to-Hospitalization

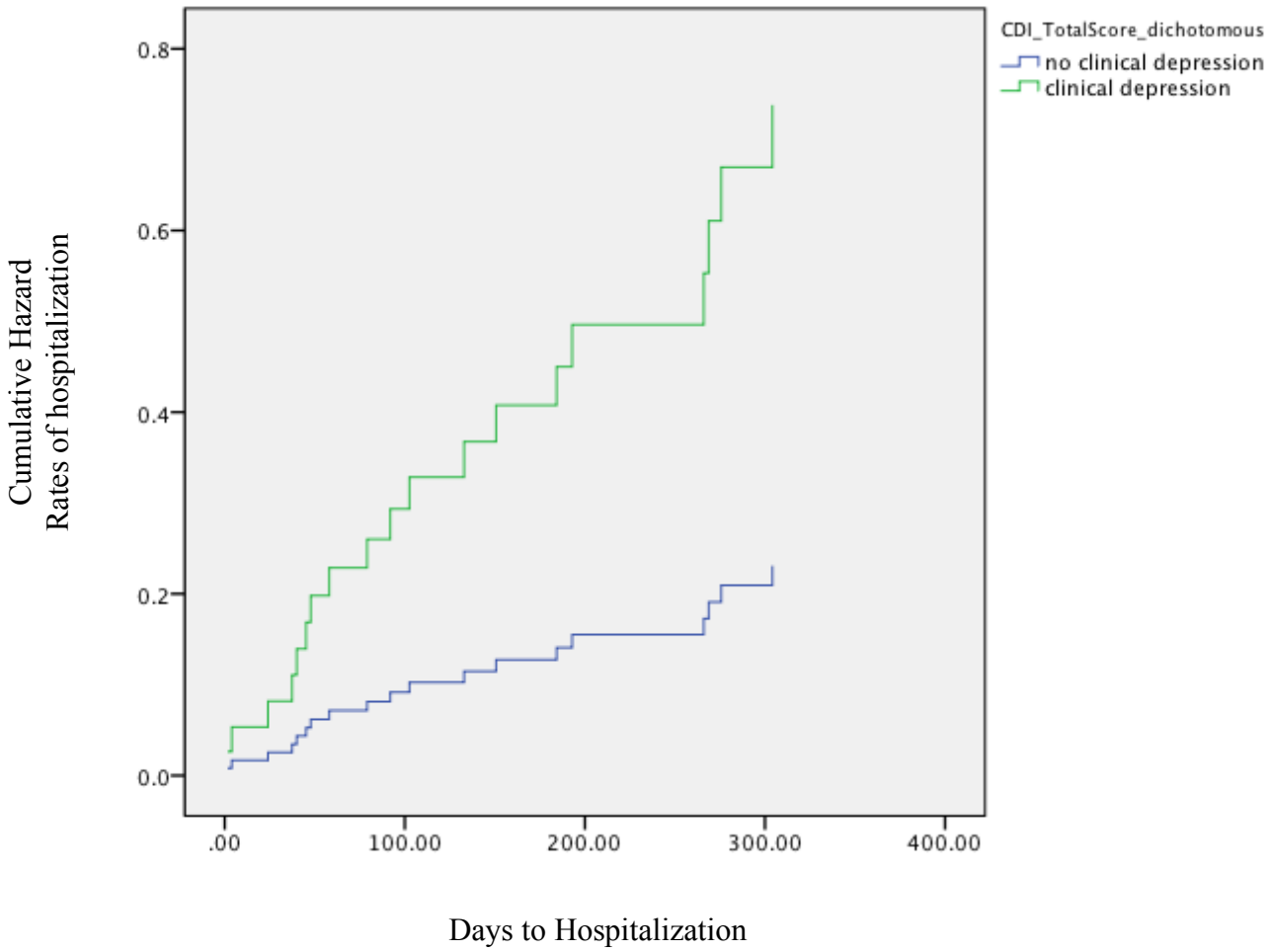
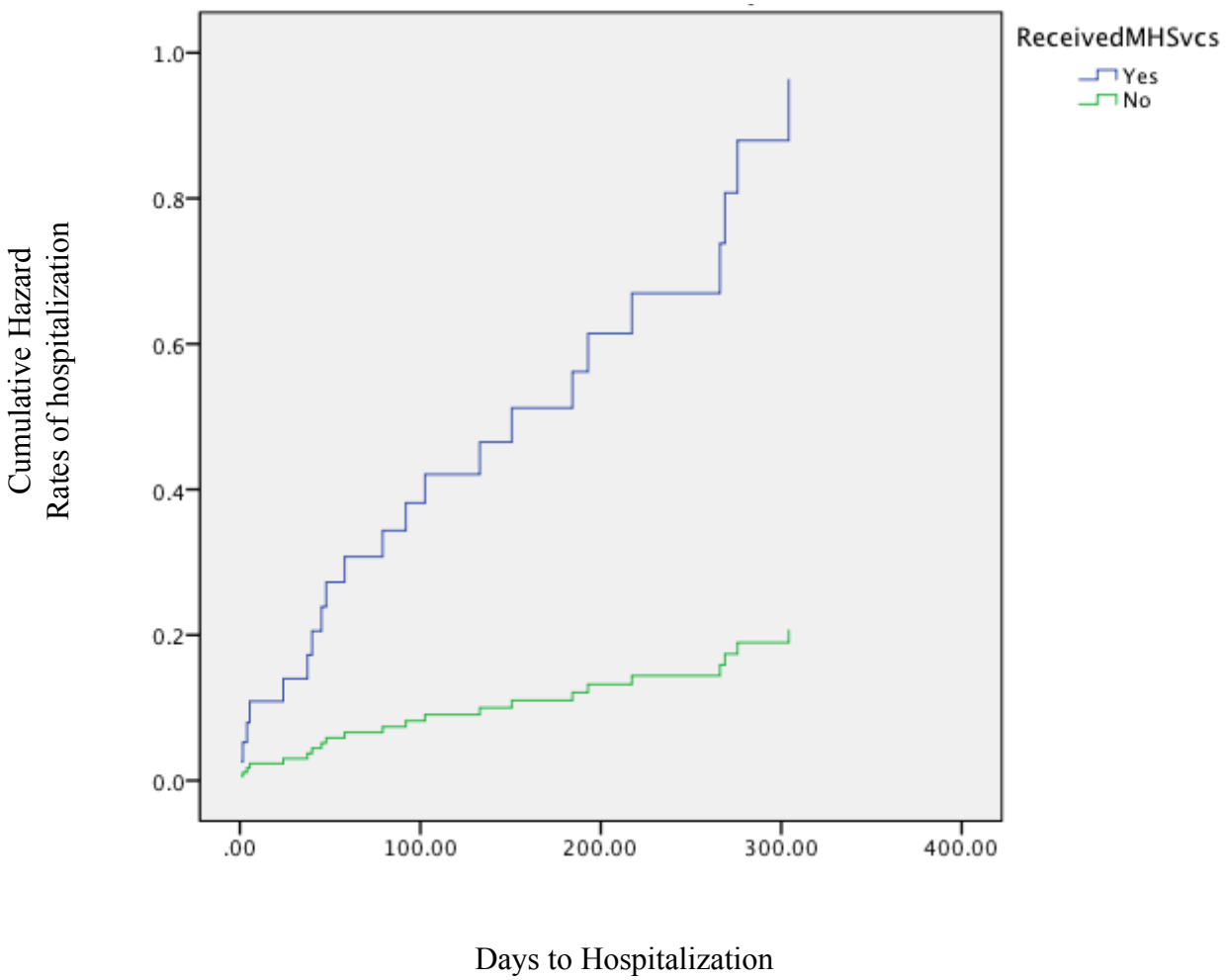


Figure 4: Cox Regression Equation: History of Mental Health Services and Time-to-Hospitalization



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