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Disease Activity, Behavioral Dysfunction, and Health-related Quality of Life in Adolescents with Inflammatory Bowel Disease

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Abstract

Background—Approximately 20-25% of all IBD cases have an onset in childhood or adolescence. Beyond disease severity, little is known regarding determinants of health-related quality of life (HRQOL) in this population. This study aimed to identify behavioral correlates of HRQOL and examine behavioral/emotional dysfunction (e.g., internalizing/externalizing symptoms) as the mechanism through which disease severity impacts HRQOL.

Methods—62 adolescents ($M = 15.47$ years, $SD = 1.42$) with IBD (79% Crohn's disease) and their parents were recruited from one of two pediatric IBD specialty clinics located in the Midwest or Northeast region of the United States. Participants completed a demographic questionnaire, the Youth Self-Report version of the Child Behavior Checklist, and the IMPACT-III. Disease severity was calculated for Crohn's disease and ulcerative colitis using standardized measures.

Results—Greater disease severity, externalizing symptoms, and internalizing symptoms were all independently associated with lower HRQOL. Furthermore, internalizing symptoms partially mediated the relationship between disease activity and HRQOL, reducing the effect of disease severity on HRQOL from 22% to 9% in the mediation model. A Sobel test examining the significance of the indirect effect of disease severity on HRQOL via behavioral dysfunction was marginally non-significant ($p = .053$).

Conclusions—Non-disease specific variables (e.g., behavioral dysfunction) play an important role in impacting HRQOL. Behavioral dysfunction serves as the mechanism through which disease severity partially impacts HRQOL. Continued research to identify other predictors of HRQOL in pediatric IBD will greatly enhance our future ability to design interventions to improve HRQOL and maximize health outcomes.

Keywords

Inflammatory Bowel Disease; Adolescents; Quality of Life; Behavioral Dysfunction

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Crohn's disease and ulcerative colitis (collectively known as inflammatory bowel disease; IBD) are chronic conditions characterized by uncontrolled intestinal inflammation and periods of disease activity and remission.¹ An estimated 20-25% of all IBD cases have an onset in childhood or adolescence,²⁻³ with a median age at diagnosis of 15 years and an incidence of 71 per 100,000.⁴ Children and adolescents with IBD must often deal with unpredictable, unpleasant, and potentially embarrassing gastrointestinal symptoms (e.g., abdominal pain, diarrhea, rectal bleeding) in addition to treatment-related side-effects and burden.¹ Though treatment of IBD varies by individual case presentation, regimens are often complex and may consist of multiple medication doses per day, dietary modifications, and, in some cases, surgical intervention.⁵ Though the goal of medical treatment is to minimize symptom activity and disease-related complications, it is clear that IBD and its treatment impact many areas of patient functioning beyond physical health. As such, there is an increasing need to conceptualize patient health more broadly by incorporating assessments of patient emotional and social well-being into treatment decision making and estimates of health outcome. This is especially true given increased focus on improving long-term patient outcomes.⁶ Health-related quality of life (HRQOL) measures a patient's perception of their health status and the impact of their illness on their physical, social, and emotional functioning.³ Though HRQOL research in the adult IBD literature has been examined extensively,⁷⁻⁸ there is considerably less inferential research on HRQOL in pediatric IBD. In particular, there is scant evidence regarding predictors of HRQOL in pediatric IBD. Thus, little is known about patient factors that are associated with better or worse quality of life outcome in children and adolescents with IBD.

Among the extant research, disease activity has emerged as a consistent predictor of HRQOL in pediatric IBD. Compared to individuals whose symptoms are quiescent or in remission, children/adolescents with greater disease activity report lower levels of HRQOL.^{3, 6} Though this relationship makes intuitive sense as lowered HRQOL may be due in part to the functional impairment of increased gastrointestinal symptoms and perhaps side-effects of more aggressive treatment to control symptoms, this is a unidimensional conceptualization of HRQOL, which is a multidimensional construct. Disease severity accounts for a relatively small proportion of variance in HRQOL in this population³, suggesting that other factors may contribute to HRQOL. Moreover, research examining the mechanisms through which disease activity impacts HRQOL is greatly needed as this is a poorly understood yet important area of research and clinical care. Indeed, because other factors that either improve or worsen HRQOL have not yet been identified,⁹ our ability to design interventions to improve HRQOL and maximize health outcome is limited. Thus, it is imperative that research articulates the relationship between disease activity and HRQOL by examining a broader range of factors related to patient's quality of life.

Because social and emotional factors are significant aspects of overall HRQOL, behavioral dysfunction may explain a portion of the variance in HRQOL. Behavioral dysfunction refers to both internalizing symptoms (e.g., anxiety, depression) and externalizing symptoms (e.g., aggression, disruptive behavior). Several studies have examined rates of behavioral dysfunction in children with IBD and healthy controls. In general, children with IBD are at greater risk of having problems in emotional and behavioral functioning (Mackner et al., 2006) and are rated by their parents as displaying greater levels of internalizing symptoms (e.g., anxiety, depression) than healthy controls.¹⁰⁻¹¹ Although the relationship between behavioral dysfunction and HRQOL has been documented in other chronic illness groups,¹²⁻¹³ this has not been examined in the pediatric IBD population.

Currently, many gaps exist in the research literature with regard to HRQOL in adolescents with IBD. Disease severity only explains a small portion of the variance in HRQOL and

little is known regarding other factors that may impact HRQOL or the mechanisms through which disease activity impacts HRQOL. Based on research in other pediatric populations, one potential factor that may increase our understanding of HRQOL outcome in IBD is behavioral dysfunction. To this end, the current study was designed to examine the relationship among behavioral dysfunction and disease activity with HRQOL in a sample of adolescents with IBD. Greater behavioral dysfunction and greater disease severity were hypothesized to predict poorer HRQOL. Furthermore, behavioral dysfunction was expected to mediate the relationship between disease activity and HRQOL.

Method

Participants and Procedures

The current study is part of a larger prospective study examining psychological and behavioral factors impacting treatment adherence in adolescents with IBD. Participants were 62 adolescents (ages 13-17) receiving medical care at one of two pediatric IBD specialty clinics located in the Midwest or Northeast region of the United States, and their caregiver. To be eligible for the study, participants had to have a diagnosis of IBD, be between the ages of 13-17, and be currently prescribed 5-aminosalicylic acid (5-ASA) and/or 6-mercaptopurine (6-MP)/azathioprine. Participants were excluded if they had a neurocognitive disorder (e.g., mental retardation), a comorbid chronic illness, or were unable to complete the questionnaires due to limited English fluency. Prescription of biologic agents was not an exclusion criterion. Additionally, participants prescribed greater than 1mg/kg/day of corticosteroid treatment were excluded due to higher risk of behavioral and psychiatric side-effects.¹⁴⁻¹⁵

A total of 83 eligible participants were approached for the study. Thirteen declined participation, citing lack of time, lack of interest, and not wanting to have their blood drawn as their primary reasons for refusal. An additional 8 participants had incomplete data and were excluded, resulting in the final sample of 62 adolescents. Potential participants were recruited while in private patient exam rooms or via telephone following clinic appointments, and consent/assent were obtained prior to all data collection. Parents and adolescents were instructed to complete their questionnaires independently and each family was given \$25 for their participation in the study. This study was approved by the governing Institutional Review Board at each recruitment site.

Measures

Demographic questionnaire—To obtain family demographic information regarding annual income, caregiver marital status and child age, race, gender, caregivers completed a brief questionnaire designed for this study.

Child Behavior Checklist Youth Self-Report—The Youth Self-Report (YSR)¹⁶ is a well-validated 113-item self-report measure designed to obtain information on the behavioral and emotional functioning of adolescents. Using a 3-item Likert scale, youth are asked to rate the frequency with which they experience various problem behaviors/symptoms over the past six months. Answers are computer scored according to norms specific to participant age and gender and are then grouped across 8 subscale scores and two broad measures of functioning: Internalizing and Externalizing symptoms. The Internalizing syndrome scale is comprised of the social withdrawal, somatic complaints, and anxiety/depression scales. The Externalizing syndrome scale is comprised of the delinquent behavior and aggressive behavior scales. In the current study, the Internalizing and Externalizing scales of the YSR were used as measures of behavioral dysfunction.

IMPACT-III questionnaire—The IMPACT-III³ is a 35-item self-report measure that assesses quality of life in children and adolescents with inflammatory bowel disease. Children indicate on a 5-point Likert scale the extent to which they are bothered by specific aspects of their health condition. Possible scores range from 35 to 175, with higher scores suggesting better quality of life. In a recent factor analysis conducted by Perrin and colleagues,⁶ the IMPACT-III was found to have four factors with good to excellent reliability: general well-being and symptoms, emotional functioning, social interaction, and body image. In the current study, these scales were summed to obtain a total HRQOL score. Reliability for the current sample was good ($\alpha = .94$).

Pediatric Crohn's Disease Activity Index—The Pediatric Crohn's Disease Activity Index (PCDAI)¹⁷ is a reliable and valid eight-item measure designed to assess disease activity in patients with Crohn's Disease. In determining a rating of disease activity, the PCDAI takes into account patient history and the following laboratory data: complete blood count (CBC), erythrocyte sedimentation rate (ESR), and albumin. For those patients who did not receive laboratory testing as part of their regular medical care or who did not have recent laboratory data (within past month) available, a CBC, ESR, and albumin were conducted as part of the study. Higher scores on the PCDAI are suggestive of greater disease activity. Scores range from 0-100, with ≤ 10 indicating inactive disease, 11-30 indicating mild disease, and > 30 indicating moderate-to-severe disease activity¹⁸. Reliability for the current sample was good ($\alpha = .83$).

Lichtiger Colitis Activity Index—The Lichtiger Colitis Activity Index (LCAI)¹⁹ is an 8-item measure designed to assess disease activity in patients with ulcerative colitis across 8 symptoms: daily stool frequency, nocturnal diarrhea, visible blood in stool, fecal incontinence, abdominal pain or cramping, general well-being, abdominal tenderness, and need for anti-diarrheal medication. Scores on the LCAI range from zero to 21, with higher scores indicating greater disease activity (i.e., ≤ 2 = quiescent disease; < 10 = a response to therapy; ≥ 10 = active disease and no response to therapy)²⁰. Reliability for the current sample was good ($\alpha = .81$).

Statistical Analyses

All analyses were conducted with SPSS 17.0 software. Descriptive statistics (mean, standard deviation, skewness, kurtosis) were run to confirm normal distribution of the data. Bivariate Pearson correlation coefficients were calculated to examine the relationships between demographic variables (e.g., child age, family income), disease activity, behavioral dysfunction, and quality of life. Hypothesized mediating relationships were examined according to the steps outlined by Baron and Kenny.²¹ In order for a variable to serve as a full mediator, the following conditions must be met via three separate multiple regression analyses: 1) the independent variable (disease activity) must be associated with the dependent variable (quality of life); 2) the independent variable must be associated with the proposed mediator (behavioral dysfunction), 3) the proposed mediator must be associated with the dependent variable; and 4) when both the independent variable and the proposed mediator are entered into a model predicting the dependent variable, the relationship between the independent variable and the dependent variable (as measured in step 1) is reduced to zero. If this relationship decreases, but is not reduced to zero, partial mediation is indicated. For all models meeting either partial or full mediation criteria, a Sobel test was run to confirm that the indirect effect of the independent variable on the dependent variable via the mediator was significantly different from zero.

Results

Participant Characteristics

There were no significant differences by recruitment site in demographics or the variables of interest. As such, all analyses were conducted on the combined sample. Of the 62 participants in the study, 56.5% ($N = 35$) were male and 43.5% ($N = 27$) were female. Adolescents ranged in age from 13-17 years ($M = 15.47$, $SD = 1.42$). The majority of the sample was Caucasian/White (88.7%), with a smaller percentage identified as African-American/Black (8.1%), Hispanic (1.6%), or Other (1.6%). Caregivers were primarily mothers (88.7%), though fathers (9.7%) and other caregivers (1.6%) were also represented. The majority of caregivers reported being married (88.7%) and the median reported annual family income ranged from \$75,001-\$100,000.

Seventy-nine percent ($N = 49$) of adolescents were diagnosed with Crohn's disease. Among this group, 55.1% had inactive disease, 40.8% had mild disease, and 4.1% had moderate-to-severe disease. Twenty-one percent ($N = 13$) of the sample was diagnosed with ulcerative colitis. The majority of these participants had disease activity in the quiescent range (61.5%), with an additional 30.8% in mild range and responding to therapy, and 7.7% in the active disease and not responding to therapy.

Intercorrelations

There was no relationship between demographic variables and disease activity, behavioral dysfunction, or quality of life. Skewness and kurtosis estimates for all predictor and outcome variables were within acceptable limits (e.g., less than 2), indicating normal data distribution. Out of a possible range of 33 to 175, mean quality of life for the entire sample was 137.24 ($SD = 18.63$). Table 1 presents the intercorrelations among disease activity, behavioral dysfunction (YSR internalizing and externalizing scores), and HRQOL. Correlations among disease activity, internalizing symptoms, and HRQOL were small to moderate. Because externalizing symptoms were not related to disease activity, it could not serve as a mediator and was excluded from further analyses.

Regression Analyses

Three separate multiple regressions were run according to the steps outlined by Baron and Kenny²¹ to examine the potential role of internalizing symptoms as a mediator in the relationship between disease activity and quality of life. Disease activity was significantly associated with both quality of life ($\beta = -.45$, $p < .001$, $R^2 = .20$) and internalizing symptoms ($\beta = .25$; $p < .05$; $R^2 = .06$), meeting the first two criteria for mediation. When regressing the dependent variable (quality of life) on both the mediator (internalizing symptoms) and the independent variable (disease activity), internalizing symptoms were significantly associated with quality of life ($\beta = -.59$, $p < .001$), meeting the third criteria for mediation. The inclusion of internalizing symptoms in this final model reduced the effects of disease activity from 20% to 9% ($\beta = -.30$, $p < .01$), meeting criteria for partial mediation (Figure 1). A Sobel test to determine if the indirect effect of disease activity on quality of life via internalizing problems was significantly different from zero, was marginally non-significant (Sobel = -1.94 , $p = .053$).

Discussion

The current study expands our understanding of factors associated with HRQOL in adolescents with IBD through the examination of demographic, physiological, and behavioral factors as correlates of HRQOL. Though demographic factors were not associated with HRQOL, important relationships between disease severity, behavioral

dysfunction, and HRQOL were found. Consistent with prior findings, increased disease severity was associated with lower HRQOL. In addition, higher levels of externalizing symptoms were related to lower HRQOL. One possible explanation for this finding is that increased externalizing symptoms (e.g., aggression, delinquent behavior) may lead to increased negative experiences in school and social settings, which may reduce youth's overall perception of HRQOL. An alternative hypothesis is that externalizing symptoms are a byproduct of adolescent coping with poorer HRQOL. Further investigation of this relationship is needed to understand how externalizing symptoms relate to HRQOL and if this relationship is bidirectional.

Internalizing symptoms emerged as a strong correlate of disease severity and predicted HRQOL. Among an adult IBD sample internalizing symptoms were found to independently contribute to lowered HRQOL.²² To our knowledge, however, this study is the first to report such a relationship in a pediatric population. The emergence of internalizing symptoms as the mechanism through which disease severity partially affects HRQOL adds significantly to our understanding of the disease severity-HRQOL relationship. Increased disease severity may directly impact quality of life through the increased presence of disruptive GI symptoms and the possible need for more aggressive treatment approaches (e.g., surgery, steroid treatment). Our partial mediation model suggests an additional pathway through which disease severity impacts HRQOL. Due to the unpredictable and disruptive nature of their disorder, adolescents with IBD may be more likely to experience internalizing symptoms (e.g., anxiety and depression), especially when their disease is most active and has the greatest potential to impair daily functioning. Increased levels of these internalizing symptoms may lead to further declines in reported HRQOL.

Results from the current study have direct implications for the design of intervention programs to improve HRQOL in adolescents with IBD. Though disease severity is a commonly targeted variable, our results suggest that it is also important to target symptoms of behavioral dysfunction. There is some evidence from the adult IBD literature to suggest that targeting psychiatric morbidity may lead to improvements in HRQOL.²³ Although interventions targeting emotional and behavioral functioning have been reported in other pediatric chronic illness populations, only one psychosocial intervention has been reported in pediatric IBD.²⁴ In this pilot study, adolescents with IBD and comorbid depression received an adapted 12-session cognitive-behavioral intervention. By the end of the intervention, adolescents reported a reduction in depressive symptoms and, although HRQOL was not specifically measured, adolescent perceptions of their general health and physical functioning had improved from pre- to post-treatment. Taken together, these studies provide some evidence to suggest that targeting behavioral symptoms as well as taking steps to improve an adolescent's health status may optimize improvements in HRQOL. Targeting behavioral symptoms may also improve disease activity by either improving medication adherence or by reducing symptoms of fatigue and poor appetite, which are common in certain internalizing disorders but may be mistakenly interpreted as signs of increased disease activity.

The current study has several strengths including the use of well-validated measures to assess disease severity, behavioral dysfunction, and HRQOL, multi-site data collection, and the collection of data from multiple sources. The use of an IBD-specific HRQOL measure is a particular strength over previous research studies that have primarily utilized generic measures of HRQOL. Disease-specific measures have been found to be superior to generic measures as they have fewer ceiling effects and demonstrate more variability in scores, suggesting greater sensitivity to change in HRQOL.²⁵ In addition, the collection of data from multiple sources limits shared method bias. Disease severity ratings were calculated using objective data including laboratory results and symptom frequency.

Nevertheless, this study is not without limitations. First, the cross-sectional nature of this study prohibits the inference of causal relationships. Additionally, though the mediation model presented met criteria for partial mediation according to the guidelines set forth by Baron and Kenny,²¹ the Sobel test was marginally non-significant. Thus, the significance of the indirect effect of disease severity on HRQOL via behavioral dysfunction could not be confirmed. However, this analysis may have been underpowered due to the conservative nature of the Sobel test, which assumes a large sample size.²⁶ The relative homogeneity of the participant sample with regard to race, socioeconomic status, and disease severity is another limitation. Though the current sample is similar in demographic background to other samples previously reported in the literature,²⁷ the extent to which our findings are generalizable to all adolescents with IBD, particularly those from lower socioeconomic status or from an ethnic minority background, is unknown.

Although participant disease severity varied, the majority of the sample was reported to have inactive or mild disease. By nature of its treatment, patients with severe disease may have been underrepresented in our study as they are typically treated in an inpatient setting and our study was conducted with an outpatient sample. Thus, our study captured the typical pattern of functioning of children and adolescents with IBD treated in an outpatient setting. It is unknown to what extent these findings generalize to the smaller percentage of patients with severe disease activity. Future studies utilizing recruitment within an inpatient unit may further articulate factors related to HRQOL that are unique to this subpopulation.

Data collection for the larger longitudinal study from which this cross-sectional data were drawn began prior to the publication of the Pediatric Ulcerative Colitis Activity Index²⁸. Thus, the disease severity measure for ulcerative colitis patients in this study may not be the most rigorously validated measure. The use of two separate measures, each with a different scale, to assess disease severity is another limitation. Though the use of two measures with a different scale was not ideal, this was the best approach to assess disease severity as IBD subtypes (UC vs. CD) differ in symptom presentation and are thus assessed differently with regard to disease severity. Additionally, given that higher scores on both measures were indicative of greater disease severity and regression analyses were used to examine if increases in disease severity corresponded to decreases in HRQOL, methodological issues associated with combining these two measures were minimized. Finally, this study was unable to account for overlap in symptoms (e.g., fatigue and depression) of internalizing disorders and disease activity. One possible solution to this problem would be to remove items on the YSR that overlap with physiological signs of disease activity. However, doing so would greatly compromise the construct validity of the YSR and subsequent study findings.

While the current study improves our understanding of the role of disease severity and behavioral dysfunction in IBD HRQOL, additional research is needed to advance our understanding of how these relationships change over time and in response to intervention. Effort should be made to identify factors related to treatment regimen demands that may be associated with HRQOL. Though the relationship between treatment burden and HRQOL has been documented among patients with cystic fibrosis,²⁹ this relationship has not been examined in children and adolescents with IBD. Additionally, given the chronic, intermittent, and unpredictable nature of IBD, the relationship between illness uncertainty³⁰ and HRQOL is also worthy of investigation, as increased level of illness uncertainty may lead to patient perceptions of lowered social, physical, and emotional functioning. Continued identification of key factors associated with HRQOL will not only improve our understanding of this complex construct, but will also inform the development of intervention programs to improve HRQOL and maximize patient outcomes.

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Figure 1.

Table 1
Intercorrelations for Disease Activity, Behavioral Dysfunction, and Health-related Quality of Life

Measure	1	2	3	4
1. Disease Activity	--			
2. Internalizing Symptoms	.25 [*]	--		
3. Externalizing Symptoms	.12	.54 ^{**}	--	
4. Health-related Quality of Life	-.45 ^{**}	-.67 ^{**}	-.32 [*]	--

*
 $p < .05$.

**
 $p < .001$.