HHS Public Access

Author manuscript

Res Nurs Health. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Res Nurs Health. 2017 October ; 40(5): 424–434. doi:10.1002/nur.21813.

Symptom Clusters in Adults with Inflammatory Bowel Disease

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Abstract

Symptoms (pain, fatigue, sleep disturbance, depression, and anxiety) in inflammatory bowel disease (IBD) are associated with reduced quality of life. Understanding how IBD symptoms cluster and the clinical and demographic factors associated with symptom clusters will enable focused development of symptom management interventions. The study purposes were to (a) identify symptom cluster membership among adults with IBD and (b) examine associations between demographic (age, gender, race/ethnicity, and education) and clinical factors (smoking status, time since diagnosis, medication type, IBD type, disease activity) and membership in specific symptom cluster groups. We conducted a retrospective study of data from the Crohn's and Colitis Foundation of America's Partners Cohort and used Patient Reported Outcome Measurement Information System (PROMIS) measures to measure pain interference, fatigue, sleep disturbance, anxiety, and depression. The sample included 5,296 participants with IBD (mean age 44, 72% female). In latent class analysis, four groups of participants were identified based on symptoms: "low symptom burden" (26% of sample), "high symptom burden" (38%), "physical symptoms" (22%), and "psychological symptoms" (14%). In multinomial regression, female gender, smoking, corticosteroids, Crohn's disease, and active disease state were associated with membership in the high symptom burden group. Additional research is needed to test interventions that may be effective at reducing symptom burden for individuals with IBD.

Keywords

inflammatory bowel disease; symptom clusters; symptoms; PROMIS; latent class analysis

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Inflammatory bowel disease (IBD) primarily includes Crohn's disease and ulcerative colitis, afflicts 1.4 million people in the United States, and has increasing incidence rates worldwide (Molodecky et al., 2012). IBD follows an unpredictable course associated with periods of

active disease and remission and can lead to complications that lead to the escalation of therapy, hospitalization, and surgery (Loftus, 2004).

IBD is associated with many signs and symptoms, including diarrhea, fever, reduced appetite, weight loss, pain, and fatigue. The most prevalent and distressing symptoms experienced by people with IBD are pain, fatigue, sleep disturbance, depression, and anxiety. Between 58.7% and 85.5% of people with IBD experience pain (Ghosh & Mitchell, 2007; Haapamaki, Turunen, Roine, Farkkila, & Arkkila, 2008; Haapamaki, Turunen, Roine, Farkkila, & Arkkila, 2009; Horvath et al., 2012; Magro et al., 2009); 41–48% experience fatigue (van Langenberg & Gibson, 2010), 49%-77% experience sleep disturbance (Graff et al., 2011); 25%-61% report depressive symptoms (Guthrie et al., 2002; Magro et al., 2009; Vidal et al., 2008; Zhang et al., 2013); and 31%-44% report anxiety (Guthrie et al., 2002; Vidal et al., 2008).

People with IBD rate symptoms as major concerns and perceive symptoms to be more distressing than fecal incontinence and the potential development of colon cancer (Czuber-Dochan, Dibley, Terry, Ream, & Norton, 2012; de Rooy et al., 2001; Stjernman, Tysk, Almer, Strom, & Hjortswang, 2010). People with IBD are often embarrassed by symptoms that affect career plans and restrict social life (Devlen et al., 2014). Symptom burden contributes to decreased work productivity (Haapamaki et al., 2009; Magro et al., 2009), decreased ability to participate in leisure activities (Ghosh & Mitchell, 2007; Haapamaki et al., 2009), and reduced quality of life (Ghosh & Mitchell, 2007; Haapamaki et al., 2008).

Symptoms are more common during periods of active disease, but they frequently persist during remission (Ghosh & Mitchell, 2007; Graff et al., 2011; Kurina, Goldacre, Yeates, & Gill, 2001; van Langenberg & Gibson, 2010), a time when intestinal inflammation and the associated fever, rectal bleeding, abnormal stool frequency, and fecal urgency are resolved (Panaccione, Colombel, Louis, Peyrin-Biroulet, & Sandborn, 2013; Travis et al., 2011). Even during remission, symptoms continue to rank as a top disease-related concern in IBD (Keeton, Mikocka-Walus, & Andrews, 2015).

Although past research conducted with people who have IBD focused on single symptoms, symptoms co-occur. For example, depression and anxiety were associated with pain (Schirbel et al., 2010), and sleep disturbance was associated with fatigue, depression, anxiety and abdominal pain (Ananthakrishnan, Long, Martin, Sandler, & Kappelman, 2013; Banovic, Gilibert, & Cosnes, 2010; Banovic, Gilibert, Jebrane, & Cosnes, 2012; Benhayon et al., 2013; Graff et al., 2013; Jelsness-Jorgensen, Bernklev, Henriksen, Torp, & Moum, 2011). In other chronic inflammatory conditions, such as heart disease and cancer, symptoms occur in clusters (Aktas, Walsh, & Rybicki, 2010; Dodd, Miaskowski, & Lee, 2004; Fan, Filipczak, & Chow, 2007), defined as two or more related symptoms that co-occur (Fan et al., 2007). However, little is known about symptom clusters among people with IBD or the demographic and clinical factors that may be associated with symptom clusters.

Demographic factors associated with individual symptoms in IBD include younger age (Bager et al., 2012) and female gender (Larsson, Loof, Ronnblom, & Nordin, 2008;

Romberg-Camps et al., 2010). Although the potential associations between race and ethnicity and symptoms have not been examined in people with IBD, differences in racial and ethnic group members' perceptions of IBD may influence symptom reporting. For example, these may include differences in attributing disease activity to stress and in informing their support network about their diagnosis (Finlay, Basu, & Sellin, 2006). Education level is not associated with fatigue (Czuber-Dochan, Ream, & Norton, 2013), but higher educational attainment is associated with depression in IBD (Fuller-Thomson & Sulman, 2006).

Evidence on links between clinical factors and symptoms is mixed. Longer disease duration and Crohn's disease (compared to ulcerative colitis; Guthrie et al., 2002) are associated with increased symptoms (Mussell, Bocker, Nagel, & Singer, 2004). In contrast to people who have ulcerative colitis, people who smoke and have Crohn's disease may experience fewer symptoms (Mahid, Minor, Soto, Hornung, & Galandiuk, 2006; Parkes, Whelan, & Lindsay, 2014). IBD medications are associated with both increased and decreased symptoms (Haapamaki et al., 2009; Louis et al., 2013). While remission status is associated with reduced symptoms, symptoms can persist during remission (Keeton et al., 2015).

Improved understanding of the nature of symptom clusters and their clinical and demographic correlates is needed to support future interventions focused on managing symptom clusters. This is crucial because treating single symptoms (e.g., depression) may not improve other related symptoms (e.g., sleep disturbance or fatigue; Morrow et al., 2003; Taylor, Walters, Vittengl, Krebaum, & Jarrett, 2010). Understanding modifiable and non-modifiable risk factors for symptom clusters will also assist in targeting future interventions.

Purpose

The purposes of this study were to (a) identify symptom cluster membership groups (for symptoms of pain, fatigue, sleep disturbance, depression and anxiety) among adults with IBD and (b) examine the associations between demographic (age, gender, race/ethnicity, and education) and clinical factors (smoking status, time since diagnosis, medication type, disease activity) and membership in specific symptom clusters.

Methods

Design

We conducted a retrospective analysis of cross-sectional data obtained from the Crohn's and Colitis Foundation of America (CCFA) Partners Cohort that includes adults who had self-reported IBD and responded to a web-based survey. The CCFA Partners began in 2011 and has ongoing enrollment. It includes participants from all 50 United States, multiple US territories, and several additional countries. Data are collected via an internet survey every 6 months. Full details of the cohort and the data collection methods are reported elsewhere (Long et al., 2012). The University of North Carolina Chapel Hill institutional review board (IRB) approved the original study, and all participants provided written informed consent. The IRB at Yale University determined that the present analysis was exempt due to the use of de-identified data.

Sample

The CCFA Partners Cohort included 14,314 participants. Participants were 18 years of age or older and had self-reported diagnoses of IBD (Crohn's disease or ulcerative colitis/ indeterminate colitis). In a validation study of 184 CCFA Partners participants, 97% of the self-reported IBD diagnoses were confirmed by a physician (Randall et al., 2013). We excluded participants who had ostomies or j-pouches because the clinical disease activity indices were not created to assess disease activity after these surgical alterations.

Power analysis methods have yet to be standardized for latent class analysis (LCA), but LCA experts suggest that 100 to 300 participants are needed to run an LCA model (Collins & Lanza, 2010; Wurpts & Geiser, 2014). The study sample included 5,296 participants; therefore, the sample size was adequate for LCA.

Variables and Measures

Demographic and clinical characteristics—Demographic and clinical characteristics were obtained by self-report. Demographic variables included age, race/ethnicity (non-Hispanic white or other) and gender (male or female). Clinical variables included smoking status (never or current/past), duration of IBD (years), current IBD medications (corticosteroids, 5-ASAs, immunomodulators, biologics), and IBD type (Crohn's disease or ulcerative colitis/indeterminate colitis), and clinical remission (yes/no). Self-reported disease activity indices including the Short Crohn's Disease Activity Index (SCDAI; K. Thia et al., 2011) and the Simple Clinical Colitis Activity Index (SCCAI; K. T. Thia et al., 2011; Walmsley, Ayres, Pounder, & Allan, 1998) were used to differentiate active disease from remission. These clinical indices elicit frequency of bowel movements, the presence of blood in the stool, extra-intestinal manifestations of IBD, and overall health. Scores of < 150 on the Short Crohn's Disease Activity Index (K. Thia et al., 2011) and ≤ 2 on the Simple Clinical Colitis Activity Index (Walmsley et al., 1998) were defined as clinical remission (K. Thia et al., 2011).

Symptoms—Pain interference, fatigue, sleep disturbance, depression, and anxiety were measured with the Patient Reported Outcomes Measurement Information System (PROMIS) from the National Institutes of Health. These symptoms were selected because they are the most common and distressing symptoms experienced by people with IBD (Ananthakrishnan et al., 2013; Banovic et al., 2010; Banovic et al., 2012; Benhayon et al., 2013; Graff et al., 2013; Jelsness-Jorgensen et al., 2011). PROMIS was developed with item-response theory, a method that permits for the reduction of a large number of items into a concise unidimensional measure that is highly reliable, precise, and retains statistical power (Fries, Bruce, & Cella, 2005).

Four-item PROMIS short forms were used to elicit each of the symptoms as occurring over the past 7 days. PROMIS items employ 5-point Likert scales that range from *not at all* to *very much*, with the exception of the pain interference items that include a score of zero for *no pain* in addition to the 5-point Likert scale. PROMIS measures are scored on a normalized *t*-score based on the general population, with 50 as the mean and 10-point standard deviation increments (National Institutes of Health, 2013).

Pain interference: Items elicited responses about how much pain interfered with the ability to work in the home, perform chores, participate in social activities, and do day-to-day activities. This scale is valid compared to the Medical Outcomes Study Short-Form 36 (SF-36) Bodily Pain Scale (Amtmann et al., 2010).

Fatigue: Fatigue items elicit frequency, duration, intensity and interference characteristics (Cella et al., 2010). The fatigue scale is valid and reliable and has comparable performance to the SF-36 vitality scale and the Functional Assessment of Chronic Illness Therapy-Fatigue scale (Cella et al., 2010).

Sleep disturbance: Sleep disturbance items are designed to elicit sleep quality, the extent to which sleep was refreshing, difficulty falling asleep, and sleep problems (National Institutes of Health, 2013). The PROMIS Sleep Disturbance scale is valid compared to the Pittsburgh Sleep Quality Index and is better able to discriminate between levels of sleep disturbance (Yu et al., 2011).

Depression: Depression items elicit frequency of feeling depressed, hopeless, worthless, and helpless (Teresi et al., 2009). The PROMIS depression scale is comparable to legacy depression measures, and the absence of somatic items supports its appropriateness for use in chronic health conditions (Pilkonis et al., 2011).

Anxiety: Anxiety items elicit responses about fear, ability to focus on anything other than anxiety, worries, and feeling of unease (National Institutes of Health, 2013). The anxiety measure is valid compared to legacy anxiety measures (Pilkonis et al., 2011).

Symptom cut-off scores: We dichotomized the symptom scores to indicate presence or absence of the symptom because latent class analysis requires the use of categorical indicator variables. Each of the symptom scores was categorized as present (≥ *t*-score of 50) or absent (<50) because scores of 50 or higher indicate the presence of a clinically significant symptom (Cella et al., 2014; National Institutes of Health, 2013).

Statistical Analysis

Data were described using distributions, means, medians, standard deviations, and frequencies as appropriate. We compared individual symptoms and disease activity using chi-square analysis and used latent class analysis (LCA), a clustering approach that classifies subgroups of people into mutually exclusive and exhaustive groups based on the presence or absence of a characteristic, to determine symptom cluster membership (Lanza, Collins, Lemmon, & Schafer, 2007; Vermunt & Magidson, 2004). We used SAS 9.4 with the *PROC LCA & LTA* (Lanza, Dziak, Huang, Wagner, & Collins, 2015) add-on for SAS from the Methodology Center at Pennsylvania State to conduct the analysis. Significance was set at $p < .05$.

There are two conceptual views of symptom clusters: the grouping of variables (variable-oriented) and the grouping of people (person-oriented; Maliski, Kwan, Elashoff, & Litwin, 2008). Variable-oriented approaches, such as factor analysis, focus on identifying relationships between variables, and researchers assume that these relationships are stable

across the population. Person-oriented approaches, such as latent class and cluster analyses, are used to identify subgroups of people who exhibit similar patterns of characteristics. Common person-oriented clustering methods include latent class and cluster analysis (Bergman & Trost, 2006; Collins & Lanza, 2010; Conley, 2016). The person-oriented approach is particularly useful in uncovering subgroups in heterogeneous populations because the structure of the variables does not have to remain constant across the population (Magnusson, 2003). Because people with IBD are a heterogeneous population, we used LCA to identify symptom cluster group membership.

The symptoms of pain interference, fatigue, depression, anxiety, and sleep disturbance were categorical indicator variables in the LCA model. We ran models with one, two, three, four, and five classes because these were the number of plausible groups, given the use of five symptom variables. To determine the optimal fit of latent classes with our data, model fit statistics were the Akaike information criterion (AIC; Akaike, 1987), and the Bayesian information criterion (BIC; Schwartz, 1978). AIC and BIC are both relative fit statistics; therefore, no single number indicates best fit. Model fit is determined relative to other models, and lower numbers indicate better fit. We also reported goodness of fit G^2 fit statistic, an absolute model fit statistic that does not take the other models into consideration. The goodness of fit G^2 fit statistic follows a chi-square distribution. As is standard with LCA, we also took into account parsimony and interpretability when selecting the final model.

To interpret the final model, we used class prevalences and item-response probabilities. Latent class prevalences provide the proportion of people belonging to each class. Item-response probabilities reflect the probability that a group will endorse a particular response. Item-response probabilities range from 0 to 1, and larger numbers indicate a higher probability of a symptom occurring within a particular group (Collins & Lanza, 2010).

To explore the associations between demographic (age, gender, race/ethnicity, education level) and clinical characteristics (smoking status, time since diagnosis, IBD medications, IBD type, disease activity) and symptom cluster membership, multinomial regression with backward selection using a logit link function was used. Multinomial regression is similar to logistic regression but allows for multiple categorical non-ordered outcomes. All demographic and clinical factors were added into the model, and characteristics that were not statistically significantly linked with a symptom cluster membership group were removed one at a time. Variables for which the 95% confidence intervals contained 1 in all of the symptom cluster groups were removed to ensure we had a parsimonious model. The low symptom burden group was the reference group for comparison with the other symptom groups.

Missing data in the LCA model were handled with full-information maximum likelihood (FIML), an imputation method often used in latent class analysis and structural equation modeling. FIML imposes no bias for data missing completely or missing at random and can be used with categorical indicator variables (Enders & Bandalos, 2001). FIML is superior to case-wise deletion, even when data are not missing at random (Graham, 2009). Due to the

limitations of FIML, we excluded cases with missing covariate data, to mirror the approach used in structural equation modeling (Collins & Lanza, 2010).

Results

The original CCFA Partners sample included 14,314 participants. We excluded 1,846 who had j-pouches or ostomies or who did not indicate presence or absence of either. We used symptom data from the second CCFA survey (administered between 2012 and 2015) because pain interference was not included in the baseline survey. We excluded 7,172 participants who did not complete the second survey. The final sample included 5,296 participants. Excluded participants had a similar percentage with active disease (39.77% vs. 39.40%). However, they were, on average, younger (M = 42.80 [SD = 14.68] vs. M = 44.13 years [SD = 15.19] years) and had shorter disease duration in years (M = 13.90 [SD = 12.23] vs. M = 14.42 years [SD = 12.92]) than included participants. Less than 10% of data were missing for the final sample. Therefore, there was low risk of bias due to missing data (Bennett, 2001).

Demographics, Clinical Characteristics, and Symptoms

Table 1 includes the clinical and demographic characteristics of the final sample. The mean age of participants was 44.13 years (SD 15.19, range 18–89 years), and the majority of the sample were female (72.15%) and non-Hispanic white (92.33%). The mean disease duration was 14.42 years (SD = 12.92, range = 0–64 years).

All five symptoms were prevalent, with 54.06% of participants reporting pain interference, 63.14% reporting fatigue, 59.23% reporting sleep disturbance, 49.92% reporting depressive symptoms, and 62.65% reporting anxiety. The prevalence of each symptom and the associations of symptoms with disease activity are reported in Table 2. The majority of participants reported 2 or more symptoms (n = 3,884; 73.33%), while 13.27% (n = 703) reported one symptom, 12.09% (n = 640) reported no symptoms, and 1.20% (n = 69) were missing data on one or more symptoms.

Symptom Clusters

Participants were grouped into four distinct symptom clusters in LCA based on the presence or absence of each of the symptoms. We selected the four-class solution because it had the lowest AIC and BIC statistics and was parsimonious and clinically relevant. The fit indices for all five models are shown in Table 3. The item-response probabilities for each of the four symptom membership groups by symptom are shown in Table 4.

The first group was labeled “low symptom burden” and included 25.59% of the participants. It was characterized by a low probability of experiencing pain, fatigue, sleep disturbance, depression, and anxiety. The second and largest group (38.10% of the sample) was labeled “high symptom burden” and was characterized by a high probability of experiencing pain, fatigue, sleep disturbance, depression, and anxiety. The third group, including 22.09% of participants, was labeled “physical symptoms,” and was characterized by a high probability of experiencing pain, fatigue, and sleep disturbance. The fourth group “psychological

symptoms," was the smallest group at 14.22% and was characterized by a high probability of experiencing anxiety and depression.

Demographic and Clinical Factors Associated with Symptom Cluster Group Membership

In developing the multivariable multinomial regression model, current use of immunomodulators (p = .56), 5-ASA (p = .41), biologics (p = .06), completion of some or all college (p = .06) or graduate school (p = .84) compared to high school education or less, and race/ethnicity (p = .05) were dropped in the above order because they were not statistically associated with membership in any symptom cluster group. Younger age, female gender, smoking history, IBD duration, current use of corticosteroids, IBD type, and active disease status were included in the final model. See Table 5 for the estimated odds ratios with 95% confidence intervals for the associations between the demographic and clinical characteristics and symptom cluster membership.

Older age was associated with a small decrease in odds of membership (based on magnitude of odds ratios as interpreted by Chen, Cohen, and Chen, 2010) in the psychological symptom cluster group. Female gender and smoking history were associated with a small increase in odds of membership in both the high symptom burden and psychological symptom groups. Longer IBD duration was associated with a small decrease in odds of membership the high symptom burden group. Current use of corticosteroids and a diagnosis of Crohn's disease compared to ulcerative colitis/indeterminate colitis were associated with a medium increase in odds of being in the high symptom burden group and the physical symptoms group. Remission was associated with a medium (psychological symptom group) to large decrease in odds (high symptom burden group and physical symptom group) of being in the high symptom burden, physical, and psychological symptom cluster groups.

Discussion

To our knowledge, this study was the first to identify symptom cluster group membership among people with IBD. The findings suggest that symptom burden is high among people with IBD, as demonstrated by the fact that nearly 75% of the sample belonged to a symptom cluster group characterized by at least two symptoms. This result suggests that symptom management may be suboptimal in this population. Although the full implications of the differences between the symptom cluster groups are not known, there is a need to better understand the etiology and consequences of symptom cluster group membership and to consider differences in need for interventions based on symptom cluster group membership. For example, interventions for those with physical versus psychological symptoms are likely to differ. The high symptom cluster burden group may have worse function (e.g., physical function, social function, ability to work) and medical outcomes (e.g. need for surgery, hospitalizations); however, additional research is needed to identify how these outcomes differ with symptom cluster group membership. The clusters found in our study are consistent with previous studies of adults with other common chronic inflammatory conditions, including multiple sclerosis (Shahrbanian, Duquette, Kuspinar, & Mayo, 2015), cancer (Miaskowski et al., 2015), and heart failure (Lee et al., 2010).

Although remission is associated with decreased symptoms, our finding that nearly half of those in remission reported at least one symptom is consistent with previous research conducted with people with IBD (Bielefeldt, Davis, & Binion, 2009; Zhang et al., 2013). Possible reasons for the persistence of symptoms may include sub-clinical inflammation (Berrill, Green, Hood, & Campbell, 2013), comorbid conditions such as rheumatoid arthritis and irritable bowel syndrome (Ansari et al., 2008), or learned behavior (Kattoor et al., 2013), but none of these variables were included in the CCFA Partners surveys. Studies should be conducted to improve understanding of the etiology of symptoms occurring during both active disease and remission and the factors that may differentiate them.

Crohn's disease was associated with membership in the high symptom burden and physical symptom groups. In contrast to our findings, other researchers found no difference in sleep quality or fatigue between people with Crohn's disease and ulcerative colitis (Graff et al., 2011). Our findings suggest that Crohn's disease may be a risk factor for high symptom burden and warrant focused symptom assessment and management. Additional research is needed to explore the reasons for differences in symptom cluster membership that may be modifiable. For example, nutritional status may differ between Crohn's disease and ulcerative colitis and affect the symptom experience (Bryant, Trott, Bartholomeusz, & Andrews, 2013).

Our finding that use of corticosteroids was associated with membership in the high symptom burden and physical symptom groups is consistent with previous findings of strong associations between corticosteroid use and anxiety and depression (Loftus et al., 2011). Our findings suggested people with IBD who took corticosteroids did not experience psychological symptoms alone but also experienced physical symptoms. Although corticosteroids are often used to treat active disease, the association between symptom cluster membership and corticosteroids was not fully explained by remission status, suggesting that any persons with IBD taking prescribed corticosteroids may need symptom management.

Female gender was associated with higher odds of belonging to the high symptom burden and psychological symptom cluster groups compared to the low symptom burden cluster group, even with remission taken into account. This result is consistent with previous IBD research in which females were more likely to have more severe symptoms compared to men (Ananthakrishnan et al., 2013; Bager et al., 2012; Walker et al., 2008). Gender differences may be a result of greater symptom awareness among females, differences in perceptions or reporting rates, or biological differences such as menstrual cycle influences (Barsky, Peekna, & Borus, 2001; Racine et al., 2012). These findings suggest a greater need for symptom management among females, although gender differences need further study.

Smoking history was associated with membership in the high symptom burden and the psychological symptom groups. The relationship between smoking and IBD is complex and somewhat contradictory. For example, smoking is associated with development and worsening of Crohn's disease but protective against development and worsening of ulcerative colitis (Birrenbach & Bocker, 2004; Parkes et al., 2014). In past research, smoking history was associated with anxiety but not depression among people with IBD (Nahon et

al., 2012). In the general population, a history of smoking is related to anxiety and depression, nicotine dependence symptoms and depressive symptoms are often comorbid (Mykletun, Overland, Aaro, Liabo, & Stewart, 2008), and smoking may increase the risk of depression (Boden, Fergusson, & Horwood, 2010). Our findings suggest that former and current smokers need additional symptom screening and symptom treatment, especially for psychological symptoms.

While the odds ratio was small, we were surprised to find that longer IBD duration was associated with decreased odds of membership in the high symptom burden cluster group, even when controlling for remission status and corticosteroid use. Although the reasons need further study, people diagnosed with IBD may go through a period of adjustment and adaptation (McCormick et al., 2012) in which they establish new expectations and meanings regarding health (Cooper, Collier, James, & Hawkey, 2010; Hall, Rubin, Dougall, Hungin, & Neely, 2005) and become accustomed to symptoms. Learning how to adapt to IBD takes time and experience but becomes part of a normal life (Cooper et al., 2010; Hall et al., 2005). Health care providers can provide active support to IBD patients to help define expectations and experiences to assist in this transition.

Implications for Future Research

The etiology of symptom clusters in IBD is unknown. Researchers suggested that symptom clusters in cancer may have a common biological mechanism, including inflammatory cytokines (Cleeland et al., 2003; Illi et al., 2012), hypothalamus-pituitary-adrenal axis (HPA) dysfunction (Kim, Barsevick, Fang, & Miaskowski, 2012; Thornton, Andersen, & Blakely, 2010), dysfunctional cognitions and behaviors (Kroenke & Swindle, 2000), and catastrophizing cognitions (Somers et al., 2009). It is possible that similar mechanisms are responsible for symptoms in people with IBD, a condition that is also inflammatory in nature. There is a need for evaluation of the associations of symptom clusters with biomarkers, such as cytokines (Miaskowski & Aouizerat, 2012), fecal calprotectin (Vieira et al., 2009) and omics (e.g., inflammatory genes; Illi et al., 2012). This research will increase understanding of the etiology of symptom clusters.

Because symptoms are associated with decreased ability to work and participate in social activities, further research is needed to understand better the full impact of symptom cluster membership on multiple domains of quality of life, including ability to work, and social functioning and health care utilization and costs. These studies will support understanding of the consequences of symptom burden. Subsequent research can follow to determine the effects of interventions to improve symptom burden.

Strengths and Limitations

This study has several strengths, including the use of a well-characterized cohort and a statistically robust method that is well-suited for secondary data analysis of symptom clusters (Magidson & Vermunt, 2003). The large sample enabled us to conduct a well-identified LCA model, including consideration of several covariates. Use of validated and standardized symptom measures will allow comparison of the results with those of other studies in which these measures were used.

Limitations of this study were the unidimensional nature of the PROMIS measures and the need to dichotomize the symptoms to use LCA. Therefore, we cannot infer severity of single symptoms, frequency, or symptom-associated distress. Reliance on secondary analysis precluded knowledge of participant characteristics that were not collected in the surveys, such as participants' disease location (e.g., ileum, rectum) or use of non-IBD medications (e.g., hypnotics, antidepressants). Another limitation is that diarrhea and fecal incontinence were not included as indicator variables in this study. Diarrhea and fecal incontinence are the predominant signs (objective indicators) of IBD. Diarrhea is a primary indicator in the disease activity indices that were used as a covariate but cannot be teased out of the disease activity indices, as they were not measured consistently between Crohn's disease and ulcerative colitis. Future research is needed to further explore the significance of these signs in IBD. Last, although the use of the internet for data collection allowed a broad geographic representation, it may have limited the racial and ethnic diversity of the sample, which had an overrepresentation of highly educated, non-Hispanic white females. Therefore, the results cannot be generalized to groups that were underrepresented in this cohort.

Conclusion

People with IBD experience high symptom burden. Younger age, female gender, current or past smoking, IBD duration, current use of corticosteroids, Crohn's disease, and remission status were associated with symptom burden. Future research will focus on biomarkers and genetic factors associated with symptom clusters and on the impact of symptom clusters on work and social functioning, health care resource utilization, and costs of health care. In the meantime, healthcare providers should assess for the presence of symptom clusters and offer symptom management where needed.

Acknowledgments

This study was funded in part by grants from the National Institutes of Health to the Yale School of Nursing T32 in Self and Family Management (NINR T32NR008346), the Crohn's and Colitis Foundation of America (CCFA), and the Patient Centered Outcomes Research Institute (PCORI).

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Table 1

Demographic and Clinical Characteristics of the Sample (*N*=5926)

	M	SD	n	%
Age (years)	44.13	15.19		
Gender				
Female			3821	72.15
Male			1475	27.85
Missing			0	0.00
Race/Ethnicity				
White Non-Hispanic			4599	92.33
Other			382	7.67
Missing			315	5.95
Education n (%)				
High school or less			369	6.97
Some college/college degree			2934	55.40
Graduate School			1536	29.00
Missing			457	8.62
Smoking Status				
Never			3341	63.09
Ever			1631	30.80
Current			316	5.97
Missing			8	0.15
Disease Duration (years)	14.42	12.92		
IBD Diagnosis				
Crohn’s disease			2992	56.50
Ulcerative Colitis			1803	34.04
Missing			501	9.46
Medications				
5-ASAs			2474	46.71
Corticosteroids			753	14.21
Immunomodulators			1522	28.74
Biologics			1839	34.72
Disease Activity				
Remission			2835	53.53
Active Disease			2086	39.40
Missing			375	7.08

Note: IBD=inflammatory bowel disease, 5-ASAs=5-aminosalicyclic acids.

Table 2

Comparison of Symptom Reports on Disease Activity (n = 5296)

Symptom	Total Sample	Active Disease (*n*=2086, 39.4%)	Remission[a] (*n* = 2825, 53.3%)
	***n* (%)**	***n* (%)**	***n* (%)**
Pain			
Yes	2863 (54.06)	1659 (31.33)	999 (18.9)
No	2372 (44.79)	405 (7.65)	1819 (34.35)
Fatigue			
Yes	3344 (63.14)	1745 (32.95)	1355 (25.58)
No	1928 (36.40)	332 (6.27)	1470 (27.76)
Sleep Disturbance			
Yes	3137 (59.23)	1540 (29.08)	1374 (25.94)
No	2101 (39.67)	527 (9.95)	1442 (27.23)
Depression			
Yes	2644 (49.92)	1411 (26.64)	1032 (19.49)
No	2647 (49.98)	674 (12.73)	1799 (33.97)
Anxiety			
Yes	3318 (62.65)	1591 (30.04)	1478 (27.91)
No	1976 (37.31)	494 (9.33)	1356 (25.60)

Note. Due to missing data, percentages do not add up to 100%. All group comparisons $p<001$ in chi-square tests.

[a]Scores of <150 on the Short Crohn's Disease Activity Index and ≤ 2 on the Simple Clinical Colitis Activity Index were defined as clinical remission.

Table 3

Latent Class Fit Statistics for One to Five Latent Classes of Symptoms

Number of Latent Classes	Log-Likelihood	G^2	*df*	AIC	BIC
1	−17759.89	5206.58	26	5216.58	5249.45
2	−15499.39	685.57	20	707.57	779.89
3	−15280.48	247.75	14	281.75	393.52
4[a]	−15160.26	7.31	8	53.31	204.52
5	−15157.84	2.46	2	60.46	251.13

Note. AIC, Akaike information criterion; BIC, Bayesian information criterion

[a]The 4-class solution was selected because AIC and BIC were lowest.

Table 4

Prevalence of Class Membership and Response Probabilities in Four-Class Model of Symptom Clusters (N = 5296)

	Low Symptom Burden	High Symptom Burden	Physical Symptoms	Psychological Symptoms
Prevalence	n = 1355, 25.59%	n = 2018, 38.10%	n = 1170, 22.09%	n = 753, 14.22%
Pain	.12	**.86**	**.66**	.32
Fatigue	.13	**.96**	**.78**	.46
Depression	.04	**.90**	.23	**.69**
Anxiety	.18	**1.00**	.27	**1.00**
Sleep Disturbance	.24	**.84**	**.70**	.45

Note. **Bold font** indicates symptoms that characterize each class.

Table 5

Demographic and Clinical Factors Associated with Symptom Cluster Group Membership (n = 4544)

	High Symptom Burden		Physical Symptoms		Psychological Symptoms	
	Odds Ratio	**(95% CI)**	**Odds Ratio**	**(95% CI)**	**Odds Ratio**	**(95% CI)**
Age	0.99	(0.98, 1.00)	1.02	(1.00, 1.03)	**0.99**	**(0.98, 0.99)**
Female	**2.46**	**(1.29, 2.27)**	0.85	(0.59, 1.23)	**1.33**	**(1.05, 1.66)**
Ever Smoker	**1.71**	**(1.30, 2.24)**	0.87	(0.62, 1.22)	**1.32**	**(1.05, 1.66)**
IBD duration (years)	**0.98**	**(0.97, 0.99)**	0.99	(0.97, 1.00)	1.00	(0.99, 1.01)
Corticosteroids (yes/no)	**3.99**	**(2.66, 5.99)**	**3.37**	**(2.09, 5.40)**	1.51	(1.00, 2.27)
Crohn's Disease	**5.69**	**(3.81, 8.50)**	**6.33**	**(4.00, 10.11)**	1.08	(0.86, 1.36)
Remission	**0.11**	**(0.01, 0.02)**	**0.03**	**(0.02, 0.04)**	**0.23**	**(0.16, 0.38)**

Note. Results of multinomial regression analysis using backwards selection with symptom cluster membership as the outcome. Low symptom burden group was used a reference group. **Bold font** indicates significant association.

Res Nurs Health. Author manuscript; available in PMC 2018 October 01.