HHS Public Access

Author manuscript

J Nurs Scholarsh. Author manuscript; available in PMC 2019 September 01.

Published in final edited form as:

J Nurs Scholarsh. 2018 September ; 50(5): 473–481. doi:10.1111/jnu.12409.

Longitudinal Changes in Symptom Cluster Membership in Inflammatory Bowel Disease

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Abstract

Purpose—To describe changes in symptom cluster membership over 1 year and to examine which demographic and clinical factors predict changes in symptom cluster membership among adults with inflammatory bowel disease.

Design—A retrospective longitudinal study of the Crohn's & Colitis Foundation of America Partners Cohort from 2012 to 2015.

Methods—We measured symptoms of pain interference, fatigue, sleep disturbance, depression, and anxiety. We used latent transition analysis to describe changes in symptom cluster membership (baseline, 6 months, and 12 months) and multinomial regressions to examine factors associated with symptom cluster membership transition.

Findings—Four groups were identified (N = 5,296): high symptom burden (32.3%–35.3%), low symptom burden (24.2%–27.1%), physical symptoms (19.0%–20.9%; pain, fatigue, sleep disturbance), and psychological symptoms (20.0%–21.5%; depression, anxiety). The probability of staying in the same group was .814 to .905. Moving from active disease into remission was associated with moving from the high burden to low burden and psychological symptom groups.

Conclusions—Symptom cluster membership was quite stable over 1 year. Research is needed to understand the underlying etiology of symptom clusters better and to develop interventions to reduce symptom burden in this vulnerable population.

Clinical Relevance—Careful consideration of symptom management options should be done with patients to select options that are effective and potentially target multiple symptoms.

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Keywords

Inflammatory bowel disease; latent transition analysis; PROMIS; symptom burden; symptom clusters; symptoms

Inflammatory bowel disease (IBD) primarily includes Crohn's disease and ulcerative colitis and follows an unpredictable path of active disease and remission. About 1.4 million people in the United States and 2.2 million people in Europe have IBD (Molodecky et al., 2012). People with IBD face a high symptom burden (Farrell & Savage, 2010), and disease-related symptoms consistently rank among the most distressing aspects of IBD (Stjernman, Tysk, Almer, Strom, & Hjortswang, 2010). Symptoms in people with IBD are associated with reduced quality of life, decreased leisure activities (Ghosh & Mitchell, 2007), and reduced work productivity (Haapamaki, Turunen, Roine, Farkkila, & Arkkila, 2009). Also, 40% to 60% of people report no symptomatic benefit from the current treatment options (Katz, 2007). Since the majority of individuals with IBD are diagnosed before the age of 40 years (Vind et al., 2006), understanding symptoms is essential because they negatively impact life activities, including obtaining education, career training, and family building and rearing (Devlen et al., 2014).

IBD is a chronic disease associated with unpredictable remissions and exacerbations, which may contribute to the trajectory of symptoms, but little is known about the longitudinal changes of symptom membership or the factors that may contribute to the symptom trajectory. Although symptoms often occur in clusters, the majority of longitudinal studies in IBD explored changes in fatigue severity (Banovic, Gilibert, & Cosnes, 2010; Graff et al., 2013; van Langenberg & Gibson, 2014). Understanding symptom clusters (two or more symptoms that occur together and are related; Fan, Filipczak, & Chow, 2007) is vital because symptoms in IBD do not occur in isolation (Conley, Proctor, Jeon, Sandler, & Redeker, 2017). Also, symptom cluster groups may differ in longitudinal data compared with cross-sectional data (Landau et al., 2016), and information on the trajectory of symptom clusters over time is needed to guide the types and timing of symptom management interventions and to help identify people at highest risk for excessive and sustained symptom burden. Using latent class analysis on cross-sectional data, we previously identified four empirically determined symptom cluster membership groups among adults with IBD: high symptom burden group (pain fatigue, sleep disturbance depression, and anxiety; 38.1%), low symptom burden group (25.6%), physical symptom group (pain interference, fatigue, and sleep disturbance; 22.1%), and psychological symptom group (depression and anxiety; 14.2%) (Conley et al., 2017). To extend this line of work, we used the same data set to describe changes in symptom cluster membership. The purpose of this study was to describe changes in symptom cluster membership over 1 year and to examine the extent to which demographic and clinical factors predict changes in symptom cluster membership among adults with IBD.

Methods

Design

We conducted a retrospective analysis of longitudinal data from the Crohn's & Colitis Foundation of America (CCFA) Partners Cohort, a sample of adults with self-reported IBD.

Participants and Sampling

The CCFA Partners Cohort is an online group recruited via the CCFA email roster, snowball sampling, and paid advertisement. Surveys were sent via email link to participants every 6 months. A full description of the cohort (Long et al., 2012), and the cross-sectional symptom cluster data (Conley et al., 2017), are reported elsewhere. The institutional review board at the University of North Carolina–Chapel Hill approved the CCFA Partners Cohort study.

The details of the sample were reported previously (Conley et al., 2017). Surveys were collected from 2012 to 2015. We included participants at least 18 years of age who self-reported a diagnosis IBD (Crohn's disease, or ulcerative colitis/indeterminate colitis). The diagnosis of IBD was validated by medical record review in 97% of the validation sample (n = 184) (Randell et al., 2014). We excluded people with ostomies or j-pouches due to not being able to assess disease activity. We excluded participants who did not complete at least one symptom measure on the baseline survey. Power analysis is not standardized for latent transition analysis (LTA); however, 100 to 300 people are needed to have a well-identified model and to prevent small cell counts (Collins & Lanza, 2010; Wurpts & Geiser, 2014). Thus, our sample size of 5,296 was adequate.

Variables and Measures

Demographic and clinical characteristics—Demographic variables included age, race or ethnicity, and gender. Clinical variables included smoking status, duration of IBD (years), age at diagnosis, current IBD medications, IBD type, and disease activity. The Simple Clinical Colitis Activity Index (SCCAI; Thia, Loftus, et al., 2011; Walmsley, Ayres, Pounder, & Allan, 1998), and the Short Crohn's Disease Activity Index (SCDAI; Thia, Faubion, et al., 2011) were used to measure self-reported disease activity. Scores of ≤2 on the SCCAI and <150 on the SCDAI defined remission. These indices elicit responses about stool frequency, blood in stool, fever, extraintestinal manifestations, and overall health, and are reliable, valid, and responsive to disease activity changes (Thia, Faubion, et al., 2011; Thia, Loftus, et al., 2011; Walmsley et al., 1998).

Symptoms—Symptoms were measured at baseline and at 6 and 12 months. Patient Reported Outcomes Measurement Information System (PROMIS) four question short-forms were used to measure the severity of pain interference (Amtmann et al., 2010), fatigue (Cella et al., 2010), sleep disturbance (Yu et al., 2011), depression (Teresi et al., 2009), and anxiety (Pilkonis et al., 2011). PROMIS measures are unidimensional and were developed using item-response theory (Cella et al., 2010). All PROMIS measures used a 7-day recall period.

PROMIS measure scores are normalized based on the general population. Scores are reported as t-scores with a mean of 50 and 10-point standard deviations. We dichotomized

the t-scores to run the LTA model. A cut-off t-score of ?50 was used to indicate a symptom as this score indicates the presence of a clinically significant symptom (Cella et al., 2014).

Statistical Analysis

We used SAS 9.4 with a PROC LCA/LTA add-on from the Methodology Center at Pennsylvania State (Lanza, Dziak, Huang, Wagner, & Collins, 2015) to analyze the data. Frequencies, means, and standard deviations were performed to describe the data. We used LTA, a longitudinal extension of latent class analysis, to empirically determine longitudinal symptom clusters and explore changes in symptom cluster membership over time (Lanza & Collins, 2008). LTA identifies unobserved subgroups in heterogeneous populations in longitudinal data (Lanza, Collins, Lemmon, & Schafer, 2007). LTA provides an estimation of the probability of transition over time in latent classes from one time to the next (Lanza & Collins, 2008).

Models with two, three, four, and five latent symptom cluster groups were run and compared to determine which model provided the best fit to the longitudinal data. To determine best model fit, we used the relative model fit statistics of the Akaike information criterion (AIC) and Bayesian information criterion (BIC). The models were then compared, and the model with the lower numbers was selected because lower AIC and BIC indicate better fit. Likelihood ratio G^2 was used to determine absolute model fit and follows a chi-squared distribution pattern (Lanza & Collins, 2008). We also selected a model that was parsimonious and made clinical sense, as is consistent in LTA (Lanza & Collins, 2008). We used the symptoms of pain interference, fatigue, sleep disturbance, depression, and anxiety in our LTA model. The measurement invariance was restricted across time to improve model identification. Full-information maximum likelihood (FIML) was used to handle missing data in the LTA model (Graham, 2009). FIML is the standard imputation method in LTA.

We used multinomial regressions, an extension of logistic regression, to explore associations between age, race or ethnicity, gender, smoking history, disease duration, age at diagnosis, IBD medications at baseline (corticosteroids, immunomodulators, biologics, aminosalicylates), IBD type, baseline remission status, and transition from active disease to remission from baseline to 6 months and symptom cluster membership transition from the baseline high symptom burden group. We used no change in group membership from the high symptom burden group as reference. Significance was set at $p < .05$.

Results

As reported previously (Conley et al., 2017), the cohort included 14,143 participants. We excluded 1,847 participants for having a j-pouch ($n = 569$), ostomy ($n = 789$), both ($n = 160$), or missing this data ($n = 328$). We excluded 7,172 participants for missing symptom data. Our final sample included 5,296 participants. Those excluded had a similar percentage of participants with active disease (39.77% vs. 39.40%), and on average were younger ($M = 42.80$ [$SD = 14.68$] vs. $M = 44.13$ years [$SD = 15.19$] years) and had shorter disease duration ($M = 13.90$ years [$SD = 12.23$] vs. $M = 14.42$ years [$SD = 12.92$]). Table 1 reports the demographic and clinical characteristics of the sample, of whom 72.15% ($n = 3,821$)

were female, and 92.33% (n = 4,599) were non-Hispanic White with a mean age of 44.13 years (*SD* 15.19).

Fit statistics, likelihood ratio G^2, degrees of freedom, AIC, and BIC for each model are reported in Table 3. The models with four or five latent symptom clusters had the best fit. Due to little difference in the interpretation of four or five symptom cluster models, to assure parsimony we selected the four-symptom cluster model. We identified four symptom cluster groups across all time points: high symptom burden group (pain, fatigue, depression, anxiety, and sleep disturbance), low symptom burden group, physical symptom group (pain, fatigue, and sleep disturbance), and psychological symptom group (depression and anxiety). The individual symptom item probabilities for all time points are presented in Table 4.

Transitions Between Symptom Clusters

Overall, symptom cluster group membership remained stable over the year of follow-up. Figure 1 shows the proportion of participants in the four classes at each time point. The proportion of people in each group was largely stable over the year. Participants had probabilities ranging from .814 to .905 of staying in the same symptom cluster group over the year. The probabilities of transitions were the smallest between the physical and psychological symptom groups and between the low and high symptom burden groups (probabilities = .000 to .001). The highest probabilities of transition were between the physical and high symptom burden groups (probabilities = .073 to .115), with similar transition probabilities in both directions (physical to high symptom burden and high symptom burden to physical). See Figure 1 for the transition probabilities between baseline and 6 months and between 6 and 12 months.

Factors Associated With Transition From the High Symptom Burden Group

We examined the associations between and clinical and demographic variables and transitions from the baseline high symptom burden group to all other 6-month symptom groups. We selected the high symptom burden group for further analysis because it was the largest symptom cluster group and comprised the highest level of symptom burden. We did not look at the movement from other groups because of low and zero cell counts due to the lack of movement between symptom cluster groups. Of the 1,936 participants who started in the baseline high symptom burden group, 1,756 (90.56%) stayed in the high symptom burden group at 6 months, 15 (0.77%) moved to the 6-month low symptom burden group, 26 (1.34%) moved to the 6-month physical symptom group, and 80 (4.13%) moved to the 6-month psychological symptom group. All participants missing symptom data on the 6-month survey belonged to the baseline high symptom burden group (n = 59).

The multinomial regression analysis revealed that age (p = .066), race or ethnicity (p = .421), gender (p = .153), smoking history (p = .130), disease duration (p = .695), age at diagnosis (p = .199), use of corticosteroids at baseline (p = .378), use of immunomodulators at baseline (p = .720), use of biologics at baseline (p = 482), use of aminosalicylates at baseline (p = .369), IBD type (p = .508), and baseline remission status (p = .464) did not predict changes in membership from the high symptom cluster to other symptom cluster groups. Transition from active disease into remission was associated with moving from the

high symptom burden group into the low symptom burden group (odds ratio = 10.76, 95% confidence interval [CI] 3.11–37.24) and from the high symptom burden group into the psychological symptom group (odds ratio = 3.95, 95% CI 1.68–9.31), but was not associated with movement from the high symptom burden group to the physical symptom group (odds ratio = 1.79, 95% CI 0.10–3.21).

Among participants who stayed in the high symptom burden group at baseline and 6 months, 507 (52.16%) had continuously active disease, while 136 (13.99%) transitioned from active disease into remission, 202 (20.78%) stayed in remission, and 127 (13.07%) transitioned from remission to active disease. Only 32 participants who transitioned from active disease into remission changed their symptom cluster membership from the high symptom burden group.

Discussion

Overall symptom cluster group membership was quite stable over a 1-year period among this large IBD cohort. The symptom burden of this sample was quite high, with approximately one third of the sample remaining in the high symptom cluster group and nearly 75% of the sample belonging to a symptom cluster group that contained at least two symptoms. Our findings emphasize that high levels of symptom burden are persistent in this population and underscore the need for healthcare professionals to support these patients to address symptoms.

The majority of people in the baseline high symptom burden group remained in the high symptom burden group at 6 and 12 months, as only about 10% transitioned to a symptom cluster group with fewer symptoms. Moving into remission at 6 months was associated with decreased symptoms, but only 19.05% of participants who transitioned into remission improved their symptom cluster status from the high symptom burden group. These findings are consistent with our previous findings that disease activity does not fully explain symptom cluster membership (Conley et al., 2017). These findings emphasize the need for additional explanations for the persistently high symptom burden. Other possible reasons for persistent symptoms may include elevated cytokines (Illi et al., 2012), dysfunctional cognitions and behavior (Kroenke & Swindle, 2000), and plastic changes in the central nervous system (Apkarian, Hashmi, & Baliki, 2011).

The persistent nature of symptoms in IBD suggests the need for the development of appropriately targeted and timed interventions for the self-management of symptom clusters. Although remission explained some of the changes in symptom burden, these changes were not consistent. This finding is consistent with previous research that found that current IBD treatment does not adequately address symptoms, as 40% to 60% of people report receiving little or no symptom relief (Katz, 2007). Self-management interventions, when used in conjunction with optimal medical therapy, may be useful in managing multiple symptoms and improving quality of life and may extend remission (Conley & Redeker, 2016). Additional research is needed to examine the efficacy of behavioral interventions in reducing symptoms.

Future studies should also be conducted to evaluate the biobehavioral mechanisms for symptom clusters among people with IBD. Understanding the etiology of symptom clusters allows for early identification and more targeted treatment of people at high risk for experiencing a high symptom burden (Miaskowski & Aouizerat, 2012). A potential pathway to study the etiology of persistent symptoms clusters is the microbiota–gut–brain axis, which has bidirectional communication between the brain, digestive tract, and the microbiota and has been linked to the symptoms of pain, depression, and anxiety as well as IBD pathogenesis (Montiel-Castro, Gonzalez-Cervantes, Bravo-Ruiseco, & Pacheco-Lopez, 2013).

Sleep in this population warrants further exploration as both a possible underlying etiology of co-occurring symptoms and as a possible avenue for treatment. In particular, circadian disruption may underline these symptom clusters since experimental disruption of the light–dark and activity–rest rhythms increased colonic inflammation in IBD mouse models (Preuss et al., 2008; Tang, Preuss, Turek, Jakate, & Keshavarzian, 2009), and associations between altered circadian rhythms and symptoms in rheumatoid arthritis (Cutolo et al., 2005) suggest that disrupted activity–rest rhythms contribute to symptoms.

Given the presence of multiple persistent symptoms in IBD, comprehensive symptom assessment is needed in the clinical setting. Clinicians should not assume that symptoms resolve with time. When weighing between symptom treatments, clinicians should consider all the symptoms in the cluster because treating one symptom may worsen or improve another (Thomas et al., 2014). For example, the use of opioids to treat pain may worsen the symptoms of fatigue and sleep disturbance (Dimsdale, Norman, DeJardin, & Wallace, 2007). And the use of cognitive behavioral therapy for insomnia improves sleep, but may also improve symptoms of depression (Luik et al., 2017) and pain (Vitiello, Rybarczyk, Von Korff, & Stepanski, 2009). Careful consideration of symptom treatment options should be done with patients to select symptom management options that are effective and potentially target multiple symptoms.

Significant strengths of this study were the large sample, use of well-validated symptom measures, availability of longitudinal data, and use of empirically determined symptom clusters. However, limitations of the study were primarily due to the use of secondary analysis of an existing data set. Limitations included the characteristics of symptoms, time frames for assessment, limited available clinical data, and limited racial and ethnic diversity.

Use of dichotomized symptom severity scores, as needed to conduct the LTA, may have precluded identifying small changes in symptoms over time. Symptoms also have daily variations that were not elicited in this study. In addition, symptoms are multidimensional but were measured unidimensionally in this study. Repeated-measure self-report studies are subject to panel conditioning, by asking repeated questions the responses change over time. Thus, we may have seen freezing of symptom responses rather than true symptom stability (Kroh, Winter, & Schupp, 2016). Due to the use of an existing data set, we had access only to information on self-reported disease activity and we might have seen more disease activity changes if we had used an objective measurement of disease activity such as endoscopy. Finally, due to the selection bias of this convenience Internet sample, the sample

was overrepresented by non-Hispanic, highly educated, White females (IBD affects males and females equally), which limits the generalizability of our findings. Research is needed to validate these findings in a more diverse sample to determine if these symptom clusters and the persistence of symptoms remain.

We found that symptom cluster membership was overall stable over a 1-year period. Healthcare providers and researchers should not assume that symptoms improve in IBD without intervention. Additional research is needed that explores the biological basis for persistent symptoms in IBD. Due to the severe and persistent nature of symptom clusters identified in this study, the development of empirically validated symptom management interventions is needed.

Acknowledgments

This study was funded in part by grants from the National Institutes of Health to the Yale School of Nursing's T32 in Self and Family Management (T32-NR008346), the Crohn's and Colitis Foundation of America (CCFA), and the Patient Centered Outcomes Research Institute (PCORI).

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Clinical Resources

- Crohn's & Colitis Foundation of America. Facts about IBD. http://www.crohnscolitisfoundation.org/assets/pdfs/updatedibdfactbook.pdf
- Oncology Nursing Society. Symptom assessment tools. https://www.ons.org/assessment-tools

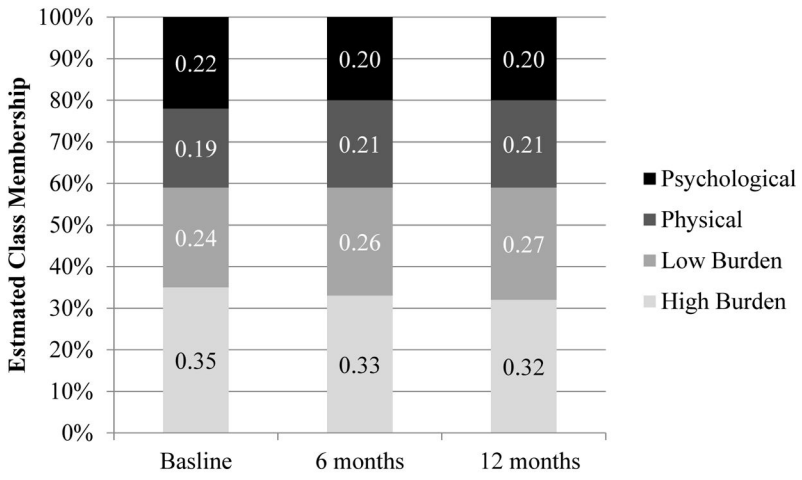

Figure 1.
Estimated proportion of symptom cluster membership at each time point.

Table 1

Baseline Demographic Characteristics

Age, mean years (*SD*)	44.13 (15.19)
Gender, *n* (%)	
Female	3,821 (72.15)
Male	1,475 (27.85)
Race/ethnicity, *n* (%)	
White Non-Hispanic	4,599 (92.33)
Other	382 (7.67)
Missing	315 (5.95)
Education, *n* (%)	
High school or less	369 (6.97)
Some college/college degree	2,934 (55.4)
Graduate School	1,536 (29.00)
Missing	457 (8.62)
Smoking status, *n* (%)	
Never	3,341 (63.09)
Ever	1,947 (37.76)
Current	29 (0.55)
Missing	8 (0.15)
Disease duration, mean years (*SD*)	14.42 (12.92)
Age at diagnosis, mean years (*SD*)	29.70 (13.63)
Medications, *n* (%)	
Aminosalicylates	2,474 (46.71)
Corticosteroids	753 (14.21)
Immunomodulators	1,522 (28.74)
Biologics	1,839 (34.72)
IBD diagnosis, *n* (%)	
Crohn's disease	2,992 (56.50)
Ulcerative colitis	1,803 (34.04)
Missing	501 (9.46)
Disease activity, *n* (%)	
Remission	2,835 (53.53)
Active disease	2,086 (39.39)
Missing	375 (7.08)

Note. Data were reported previously in Conley, S., Proctor, D. D., Jeon, S., Sandler, R. S., & Redeker, N. S. (2017). Symptom clusters in adults with inflammatory bowel disease. *Research in Nursing and Health, 40*(5), 424–434. doi:10.1002/nur.21813

Table 2

Fit Statistics for Fitted LTA Models With Different Numbers of Classes

Number of statuses	Likelihood ratio G^2	Degrees of freedom	AIC	BIC
2	12,702.45	32,752	12,732.45	12,845.06
3	10,941.12	32,738	10,999.12	11,216.83
4	**8,852.75**	**32,720**	**8,946.76**	**9,299.60**
5	8,523.89	32,698	8,661.89	9,179.89

Note. Boldface values indicate the selected model. For AIC and BIC, lower numbers indicate better fit.

AIC = Akaike's information criterion; BIC, Bayesian information criterion; LTA = latent transition analysis.

Table 3

The Probabilities of Having a Symptom at All Times

	Low burden	High burden	Physical	Psychological
Pain	.125	**.907**	**.670**	.319
Fatigue	.116	**.962**	**.774**	.557
Sleep disturbance	.244	**.867**	**.673**	.507
Depression	.024	**.907**	.116	**.689**
Anxiety	.141	**.971**	.292	**.887**

Note. Boldface values indicate symptoms that characterize cluster.

Table 4

Transition Probabilities in Latent Status Memberships From Baseline to 6 Months, and From 6 Months to 12 Months

	Low burden	High burden	Physical	Psychological
Transitions from baseline (rows) to 6 months (columns)				
Low burden	**.905**	.000	.015	.080
High burden	.009	**.868**	.102	.020
Physical	.011	.101	**.882**	.006
Psychological	.102	.031	.009	**.814**
Transitions from 6 months (rows) to 12 months (columns)				
Low burden	**.890**	.006	.027	.078
High burden	.013	**.887**	.073	.026
Physical	.049	.115	**.837**	.000
Psychological	.143	.011	.002	**.845**

Note. Boldface values indicate probability of staying in same symptom cluster.